Cover sheet

Title of the project
A validation study of the NightOwl PAT-based home sleep apnea test.

Protocol identifier and date
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Protocol amendments
1

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Purpose and background

Scientific objectives
The objective of this study is to evaluate the performance of a miniaturized sleep apnea test, called NightOwl. The system consists of a sensor placed on the fingertip and a cloud-based analytics software. The sensor acquires accelerometer and photoplethysmographic data. The software derives actigraphy from the former, and blood oxygen saturation and peripheral arterial tone (PAT), among other features, from the latter. In order to assess NightOwl's performance, we will compare the respiratory event index (REI), defined as the number of respiratory events per hour of sleep, derived by the NightOwl system, to the AHI obtained from manual analysis of the polysomnography (PSG), which is the gold standard for sleep apnea diagnosis. We will also compare the total sleep time (TST) derived by both systems. This study will be performed in a sleep lab environment.

As of March 2017, the new clinical practice guideline for diagnostic testing for adult sleep apnea of the American Academy of Sleep Medicine (AASM) for the first time formulates a strong recommendation that both polysomnography (PSG) and home sleep apnea testing (HSAT) are appropriate diagnostic testing options for uncomplicated adult patients who are at increased risk of moderate to severe sleep apnea.[1]
Collop et al.[2] performed a comprehensive analysis of the evidence for HSAT devices to diagnose obstructive sleep apnea (OSA) in out-of-center settings. The authors concluded that testing devices that analyze changes in peripheral arterial tone (PAT) in combination with actigraphy and blood oxygen saturation (SpO2) are adequate to diagnose OSA in patient populations with a high pre-test probability.
In this study, we wish to assess the performance of a system for the diagnosis of OSA that measures and analyzes the abovementioned parameters, called NightOwl. The system consists of a small sensor device which is placed on the fingertip and a cloud-based analytics platform. An illustration of the NightOwl sensor can be found in Figure 1.

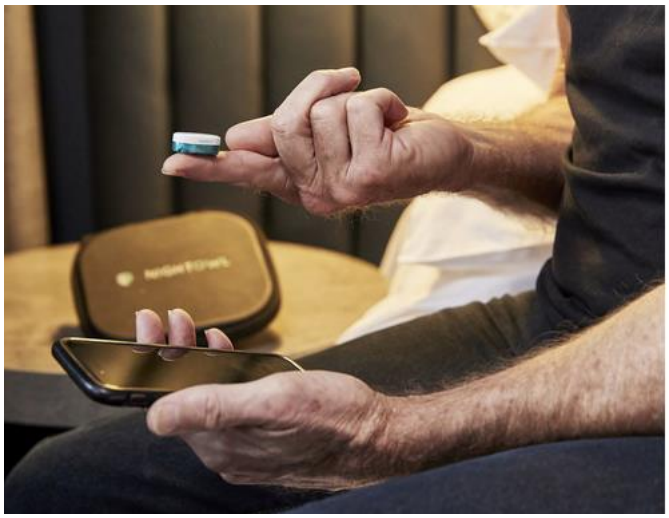

Figure 1: A photograph of the NightOwl sensor positioned on the index finger (source: https://www.resmed.com.au/sleep-apnea/sleep-study)

It is designed to be self-applied and initiated by the patient by attaching the sensor to the fingertip by means of an adhesive patch.

Justification for involving humans
In order to investigate whether the NightOwl achieves adequate performance in deriving the REI, we need to apply it to subjects that are undergoing a simultaneous polysomnography study, which is the gold standard for sleep apnea diagnosis.

Subjects

Number of subjects
100

Gender of subjects
No gender specific bias will be introduced in recruitment, such that the subject sample will approximate the gender distribution of subjects admitted to a sleep clinic for an overnight PSG. From previous clinical trials, we expect the gender distribution to be approximately 60% male and 40% female. We do not exclude pregnant women from participating in the study since we

want to represent this population in our subject pool. As justified below, the NightOwl sensor poses negligible risk for the subject, pregnant or otherwise.

Subjects age
We aim to include subjects from the age of 13 and older. The American Academy of Sleep Medicine (AASM), which is the leading guideline body in sleep medicine, recommends using the adult criteria for the scoring of respiratory events for young adolescents of at least 13 years of age. The AASM recognized that this recommendation would provide the underserved adolescent population greater access to sleep studies. Hence in order to represent the full age range of subjects for which the adult scoring rules apply, and for which we want to validate our device, we aim to include subjects of 13 years of age and older.

Racial and Ethnic Origin
We aim to include sufficient enrollment of persons of diverse racial and ethnic backgrounds. We will not stratify the subject population on a racial or ethnical basis but will assume that the subjects population without stratification will represent subjects of a diverse racial/ethnic background because of the significant subject pool size.

Inclusion criteria
Subjects with an indication for an in-lab polysomnography

Exclusion criteria
Intellectually disabled people
People younger than 13 years of age.

Vulnerable Subjects:
Children aged 13 or older will not be excluded (rationale provided in the *Subjects age* paragraph). Explicit consent of the parents will be required before inclusion.
Pregnant women will not be excluded (rationale in the *Gender of subjects* paragraph).

Methods and procedures

Overview of study design and procedures
The study is open-blind and non-randomized.

During the PSG night:

- Eligible patients will be invited to participate in the study and will be presented with the ICF.
- If the ICF is accepted, the patient will undergo the scheduled in-lab PSG, in which the NightOwl sensor will be included.

During each study night, the following flowchart will be followed:

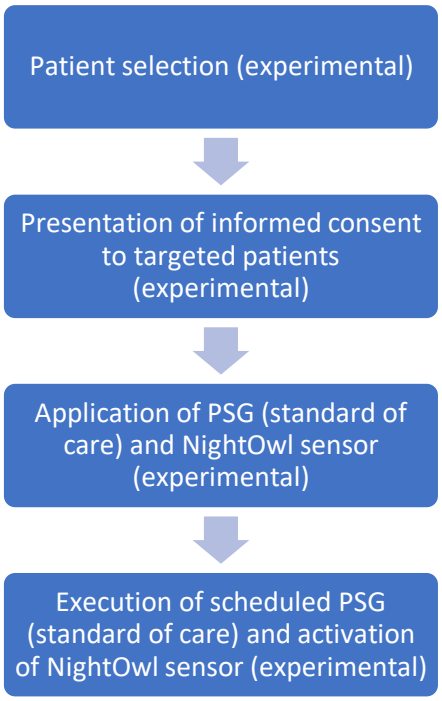

Figure 2 - Flowchart of study. Experimental signifies procedures that are performed exclusively for research purposes.

Frequency and duration

We aim to include between 10 and 19 subjects every study night. Each patient has one night of recording.

Precautions

No procedures, situations, or materials are deemed hazardous; hence no specific precautions are to be exercised. See NightOwl Product Risk Analysis (attached)

Sample collection

Data of the PSG and NightOwl will be collected throughout the entire duration of the overnight PSG study.

Detailed procedure for each study night

For every patient scheduled for an overnight in-lab PSG, the clinical personnel in charge of administering the PSG will assess whether the patient is eligible for inclusion (does not violate the exclusion criteria) to the study (the patient passes the inclusion criteria since he/she has been scheduled for a PSG). Every eligible patient will be presented with the ICF. The patient can at all time ask for clarifications on the content of the ICF and will be provided with sufficient time to read the entire form. Upon signing of the ICF, the patient will be included in the study. For subjects aged under 22, parental consent is required.

For each subject included during a particular night, the age, gender, height, and weight will be collected. Additionally, we will ask the subject for a self-report of his/her race and ethnicity. The following options will be provided:

Ethnicity Data Standard

Are you Hispanic, Latino/a, or of Spanish origin? (One or more categories may be selected)

a. ____No, not of Hispanic, Latino/a, or Spanish origin
b. ____Yes, Mexican, Mexican American, Chicano/a
c. ____Yes, Puerto Rican
d. ____Yes, Cuban
e. ____Yes, Another Hispanic, Latino/a or Spanish origin

These categories roll up to the Hispanic or Latino category of the OMB standard

Race Data Standard

What is your race? (One or more categories may be selected)

a. ____White
b. ____Black or African American
c. ____American Indian or Alaska Native

These categories are part of the current OMB standard

d. ____Asian Indian
e. ____Chinese
f. ____ Filipino
g. ____Japanese
h. ____Korean
i. ____ Vietnamese
j. ____ Other Asian

These categories roll up to the Asian category of the OMB standard

k. ____Native Hawaiian
l. ____ Guamanian or Chamorro
m. ___ Samoan
n. ____Other Pacific Islander

These categories roll-up to the Native Hawaiian or Other Pacific Islander category of the OMB standard

Table 1: Self-reported options for Ethnicity and Race

The NightOwl sensor will be attached to the middle finger of the hand on which the pulse oximeter of the PSG is applied by means of a disposable adhesive fingerwrap. The NightOwl sensor will be switched on and connected to a smartphone on which the NightOwl Companion App is installed. The NightOwl Companion App continuously acquires the raw sensor data from the NightOwl Sensor and stores this data on its internal memory. After starting the acquisition of the NightOwl sensor data via the NightOwl Companion App, the PSG recording can be started.

When the personnel press the 'Wake up' button in the NightOwl Companion App at the end of the PSG study, the data will be uploaded to a secure cloud server in which the raw NightOwl Sensor data is stored and on which the NightOwl Software, which analyses the data, is deployed.

After pressing the 'Wake up' button in the NightOwl Companion App, the PSG equipment and NightOwl sensor will be detached from the subject. The NightOwl Sensor will be disinfected and cleaned. The following disinfectants can be used on the sensor:

- Mikrozid
- Clorox
- Lysol
- Cavicide
- 70% Ethyl alcohol or isopropyl alcohol (IPA)

Details of acquired dataset for each subject

Throughout the study, the following data will be collected for each included subject:

- Polysomnographic data (EDF format), by means of export from the sleep clinics' PSG software
- Respiratory events and sleep stages annotated by the sleep technician (EDF, TXT, or CSV format), by means of export from the sleep clinics' PSG software
- NightOwl sensor data, by means of export from the NightOwl database:
    - red and infrared PPG from finger (CSV)
    - accelerometry from finger (CSV)
- Subject's age, gender, weight, height, self-reported ethnicity, and self-reported race will be collected right before administering the PSG.

Potential risks

Risk Category

The NightOwl sensor has been tested against IEC 60601-1 (Medical Device Electrical Safety) and IEC 60601-1-2 (Medical Device Electromagnetic Compatibility) standards. It is a low voltage device that contains an accelerometer and an optical sensor such as would be found in a traditional pulse oximeter. In the FDA guidance document "Pulse Oximeters - Premarket Notification Submissions [510(k)s]" it is stated that generally, FDA believes pulse oximeters addressed by this guidance document are non-significant risk devices.

The Product Risk Analysis, conducted in accordance with ISO14971:2012; Application of Risk Management to Medical Devices, is attached. There are no residual risks that considered to be unacceptable.

Hence, risk of the research is considered **minimal**. the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Potential Risk and protection against such risk

A non-serious risk for cytotoxicity or skin irritation caused by the sensor material being in continuous contact with the fingertip for the overnight recording could be identified. However, this risk is deemed negligible since the sensor enclosure material passed ISO10993-1 compliant tests for cytotoxicity and Direct Primary Skin Irritation.

A risk for discomfort of the subject caused by the tight application of the NightOwl sensor to the finger exists. In order to mitigate this risk, the subject will be explicitly encouraged to either contact the clinical personnel to reapply the sensor more loosely or to detach the sensor from the finger.

Potential Benefit

There is no potential benefit for individual subjects

Subject identification, recruitment, and consent/assent

For every patient scheduled for an overnight in-lab PSG, the clinical personnel in charge of administering the PSG will assess whether the patient is eligible for inclusion (does not violate the exclusion criteria) to the study (the patient passes the inclusion criteria since he/she has been scheduled for a PSG). Every eligible patient will be presented with the ICF. The patient can at

all time ask for clarifications on the content of the ICF and will be provided with sufficient time to read the entire form. The protocol will be discussed with the subject, all questions will be answered. The subject will explicitly be asked if all content was clear.
Upon signing of the ICF, the patient will be included in the study. For patients aged under 22, parental consent is required and both parent and child will be asked if all content was clear. The consent forms will be stored. All ICFs will be entered into the IRB's storage system in unlocked word form.

The subject will incur no extra cost as a result of participating in the study.

Compensation of subjects
The subjects will receive no payment for participating in the study

DATA AND CONFIDENTIALTIY

HIPAA Compliance
This study will be conducted in full accordance the HIPAA privacy rule. Any episodes of non-compliance will be documented. The investigators will perform the study in accordance with this protocol and will obtain consent (unless a HIPAA waiver of Consent is granted) and will report unexpected problems in accordance with institutional regulatory committee. Collection of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study. The principal investigator overseeing the conduct of this study and the research personnel will comply with the applicable federal, state, and local regulations governing clinical research and the protection of human research subjects.

Study analysis
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Two main performance analyses will be performed:

- The evaluation of the Pearson correlation between the REI and TST estimate obtained from the NightOwl and the AHI and TST determined from the PSG;
- The evaluation of the agreement between patient categorization (into sleep apnea severity categories) obtained by the NightOwl and those obtained by the manual analysis of the PSG.

In order to establish an external benchmark to which the NightOwl and PSG analysis could be compared, the codified PSG data will be transferred to Younes Medical Technologies Ltd. (YMT), the corporation behind the Michele Sleep Scoring System (MSSS) developed by Dr. M. Younes. Malhotra et al.[3] confirmed that the MSSS, complemented with manual editing, standardizes PSG scoring results within and across sleep centers. Using such external benchmark, the impact of inter-scorer variability of current and future reports on NightOwl's performance metrics is reduced.

Data Storage and Confidentiality
The data will be stored in a cloud storage system (Google drive with activated Google Vault) protected by password, which is only known by the Principal Investigator and Sponsor. Google Vault is SSAE 16, SOC 2 audited, and ISO 27001 certified and was specifically designed for users to meet legal data retention requirements

An audit trail of all changes made to data files can be reconstructed since each file addition and deletion is permanently logged. All data will be stored for at least 2 years after the completion of the study. All data belonging to the same subject will receive a unique patient code. This number will be composed of the center nr (1 to 4) followed by the enrolment nr of that subject (e.g. the third patient enrolled in center 1 will receive the nr 1-3).
For each center, a coding table will be maintained in paper format which maps the patient code to the patient's name. This coding table is securely stored and locked away when not in use and is temporarily maintained to allow for association between the NightOwl Sensor data (which is always coded such that the patient's name is never transferred to Ectosense NV) and PSG (which is coded upon upload to the cloud storage system). As soon as all PSG and data of all subjects has been exported, coded, and uploaded, the coding table will be permanently destroyed by means of secure shredding in order to render the dataset stored on the cloud storage system anonymous.

Only the anonymized data stored in the cloud storage system will be used for the analysis described above. Hence, none of the researchers performing the statistical analysis will have access to uncoded data.

<u>Questionnaires and data collection sheets</u>

1. Ethnicity and race self-reporting questionnaire.
    a. This questionnaire will be coded, scanned and uploaded to the cloud storage system for each subject. After uploading the physical copy will be securely shredded.
    b. This questionnaire is proposed by the FDA guidance document for the *Collection of Race and Ethnicity Data in Clinical Trials*.

Table 1: Ethnical and racial self-reporting questionnaire

Ethnicity Data Standard

Are you Hispanic, Latino/a, or of Spanish origin? (One or more categories may be selected)

a. ____No, not of Hispanic, Latino/a, or Spanish origin
b. ____Yes, Mexican, Mexican American, Chicano/a
c. ____Yes, Puerto Rican
d. ____Yes, Cuban
e. ____Yes, Another Hispanic, Latino/a or Spanish origin

These categories roll up to the Hispanic or Latino category of the OMB standard

Race Data Standard

What is your race? (One or more categories may be selected)

a. ____White
b. ____Black or African American
c. ____American Indian or Alaska Native

These categories are part of the current OMB standard

d. ____Asian Indian
e. ____Chinese
f. ____ Filipino
g. ____Japanese
h. ____Korean
i. ____ Vietnamese
j. ____ Other Asian

These categories roll up to the Asian category of the OMB standard

k. ____Native Hawaiian
l. ____ Guamanian or Chamorro
m. ___ Samoan
n. ____Other Pacific Islander

These categories roll-up to the Native Hawaiian or Other Pacific Islander category of the OMB standard

2. Subject additional information sheet
    a. This information sheet will be coded, scanned and uploaded to the cloud storage system for each subject. After uploading the physical copy will be securely shredded.

Table 2: Subject additional information sheet

Subject code:

Age:

Gender:

Weight:

Length:

References

1. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;1313(3):479-504. doi:10.5664/jcsm.6506.
2. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep

Medicine. J Clin Sleep Med. 2007;3(7):737–747.

3. Malhotra A, Younes M, Kuna ST, et al. Performance of an automated polysomnography scoring system versus computer-assisted manual scoring. *Sleep*. 2013;36(April 2013):573-82. doi:10.5665/sleep.2548.