1 CLINICAL STUDY PROTOCOL

Protocol Title:

A randomized cross over trial exploring the Sleep Revolution diagnostic and therapeutic pathway in patients with obstructive sleep apnea

Protocol Number: SR 001.3

Short Title: Sleep Revolution WP 8 – prospective analysis

IND Number:	SR 001
EudraCT Number:	TBD
Investigational Product:	Sleep Revolution diagnostic and therapeutic pathway
Indication:	Obstructive Sleep Apnea (OSA), CPAP treatment
Grant provider:	European Commission Horizon 2020 grant **965417**
Protocol Version:	1.3
Protocol Date:	May 2023

INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and GCP) guidelines.
- Once the protocol has been approved by the independent ethics committee (IEC), I will not modify this protocol without obtaining prior approval of the IEC. I will submit the protocol amendments and/or any informed consent form modifications to the coordinating centre at Reykjavik University and the IEC, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study about the patients' state of health will be regarded as confidential. No individual patient identities will be disclosed. Instead, all patients may be identified by assigned numbers on all case report forms, or source documents forwarded to the central data coordination centre at Reykjavik University. Agreement must be obtained from the patient before disclosure of patient information to a third party.

<Name>

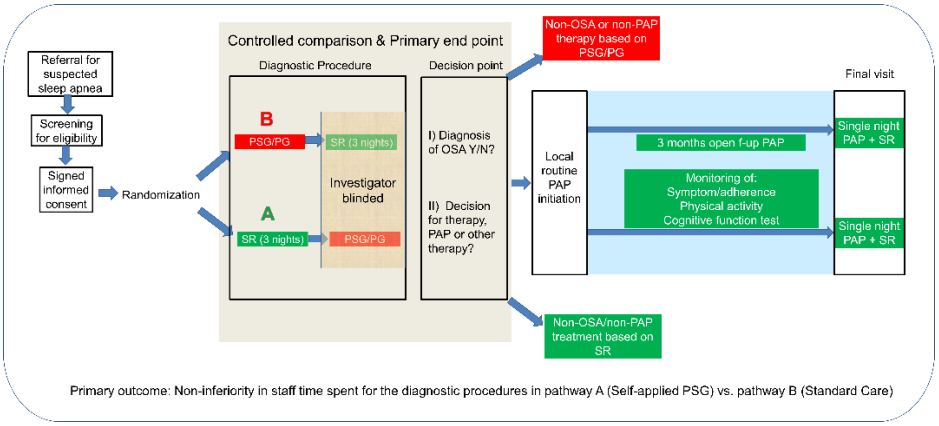
<Title> Investigator Signature

Date (DD-Mmm-YYYY)

Institution, ESADA study site

2 SYNOPSIS

Title of Study:	**A randomized cross over trial exploring the Sleep Revolution diagnostic and therapeutic pathway in patients with obstructive sleep apnea**
Protocol Number:	SR – 001
Investigators/Study Sites:	24 sites of the ESADA network in 15 European countries; estimated number of patients per center to be randomized: N=42
Objectives:	Primary objective: To compare staff time spent to complete the sleep apnea diagnostic pathways between standard care and the Sleep Revolution management model intended for patients with suspected obstructive sleep apnea (OSA). Secondary objectives: To evaluate novel Sleep Revolution diagnostic variables and their relation to symptom burden and OSA patient´s help request at baseline and treatment outcome. Exploratory Objective: Feasibility and safety of the self-applied sleep testing and the digital platform for both sleep and symptom assessment
Study Endpoints:	**Primary endpoint:** Staff time spent for the sleep apnea diagnostic pathway – comparison between Standard Care (SC) and the Sleep Revolution (SR) model in patients with obstructive sleep apnea (OSA) **Secondary endpoints – comparison SR versus SC:** - Patient satisfaction and preference with the diagnostic work-up - Patient satisfaction with the resolution of the initial help request through diagnosis and treatment (if applicable) - Number of OSA diagnosis, Positive Airway Pressure (PAP) treatment prescriptions, and non-PAP prescriptions by either pathway - Number of patients with PAP failure (no acceptance/low adherence) by either pathway - Prediction of PAP responders in terms of adherence and symptom improvement by novel diagnostic parameters (SR versus SC) - Association between sleep test output variables (PSG and HSAT) (respiration, hypoxia, cardiovascular function, sleep) and symptoms/comorbidities obtained in SC and SR **Exploratory endpoints - comparison SR versus SC:** - Technical failure rate of respective diagnostic pathway - Number and type of AE/SAE associated with diagnostics and CPAP treatment - Association between novel sleep parameters and biomarkers addressed in a subgroup of study centers (metabolic function, inflammation)
Study Design:	Study SR-001 is a multi-center, 2-arm, cross-over study comparing the diagnostic impact and accuracy of two different diagnostic pathways on the outcome of diagnosis and CPAP treatment in patients with suspected OSA. Patients referred to one of 24 sleep centers of the ESADA network participating in the Sleep Revolution project will be studied using both the clinical routine of OSA evaluation (standard care) and the novel Sleep Revolution based diagnostic pathway including self-applied polysomnography over three nights, digitally based symptom evaluation, and actigraphy based assessment of sleep wake rhythm and physical activity (experimental condition). Study participants will be randomized with respect to the order of two diagnostic pathways. The decision on diagnosis and treatment will be based on information from the first diagnostic procedure (SC or SR), the results from the second pathway will be blinded both to the investigator (sleep specialist) and the patient. Following diagnostic steps including sleep testing, symptom and physical status evaluation, patients will receive information regarding the sleep disorder diagnosis by the sleep specialist. In case of a diagnosis of clinically relevant OSA, treatment recommendations will be provided. Only patients initiating therapy with PAP will approached for participation in the subsequent part of the study- treatment start and follow up for 3 months.

	Information from sleep related examinations in the standard pathway will be manually scored by skilled technicians at each center using predefined criteria. Sleep tests in the SR pathway will be pre-scored by artificial intelligence-based algorithms for characterization of sleep and respiration, and the three PSG in the SR pathway will be manually edited only in epochs identified as unclear by the automated scoring process. For patients with indication for PAP, the titration, training and support will be organized applying local routines at each study center. At PAP-follow up, one night sleep evaluation using the SR self-applied polysomnography procedure will be performed in all patients. Evaluation of symptoms and cognitive function with standard care questionnaires and the new European Sleep Questionnaire will be performed together with physical activity assessment at both baseline, during treatment and at 3 months follow up. **Figure 1:** SR 001 Study Flow Chart  PSG=polysomnography, PG=polygraphy, SR=Sleep Revolution diagnostic pathway, PAP=Positive Airway Pressure treatment
Selection of Patients:	Main Inclusion Criteria: • Referral to the sleep center due to suspected obstructive sleep apnea as the main question for evaluation • Male or female aged 18 years and above • Willing and able to provide written informed consent • Willing and able to comply with the study design schedule and other requirements (e.g. no long-term travel conflicting with the planned visits throughout the study) Main Exclusion Criteria: • Any ongoing treatment for OSA or CSA • Known significant hypercapnic respiratory failure due to chronic obstructive pulmonary disease or other respiratory condition • Any other clinically determined contraindication for PAP treatment • Patients participating in any type of weight loss treatment program • Unstable congestive heart failure or angina pectoris • Any other condition - to the judgement of the investigator – which potentially may jeopardize the completion of the study according to protocol • History of alcohol or drug abuse during the last year, substance use disorder at screening
Planned Sample Size:	According to power analysis (non-inferiority design) based on time estimates in SC and SR care models, 1000 patients need to be randomized (500 patients in each of the 2 diagnostic pathways) corresponding to 42 patients per ESADA study centre. It is anticipated that approximately 2000 patients with incoming referrals will be evaluated for study participation.

<table>
<tr><td>Investigational diagnostic pathway (Sleep Revolution):</td><td>Sleep Test: Self applied somnography with NOX A1 and specific electrode set up (NOX SAS).

Symptom Evaluation: European Sleep Questionnaire, Sleep Revolution App: Assessment of subjective sleep timing, symptoms, and neurocognitive performance. Questionnaires of the reference investigational pathway (see below)

Continuous physiological monitoring: Heart rate and physical activity data for determination of sleep wake cycle and physical activity (Withings Scanwatch)

Sleep Analysis: Novel technology for automated analysis of sleep, respiration, hypoxia and cardiovascular parameters performed with newly developed and validated algorithms on the cluster

Analysis criteria: AASM scoring criteria version 2.6, post hoc sleep analysis using the novel European Sleep Scoring criteria (under development)</td></tr>
<tr><td>Reference Investigational diagnostic pathway (Standard Care):</td><td>Sleep Test: Standard diagnostic work-up using polysomnography (in-lab or at home) or home sleep test (in-lab or at home) according to clinical routine at the respective ESADA sleep centre

Analysis: Traditional manual sleep analysis with support of automated software algorithms

Analysis criteria: AASM scoring criteria version 2.6

Symptom Evaluation: Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Inventory (PSQI), Clinical Global Impression Scale – baseline and improvement by treatment (performed by physician and patient), Patient Global Impression Scale (severity and improvement by therapy, performed by patient), Insomnia Severity Index (ISI), Fatigue Severity Scale (FSS).

To evaluate new methods: ESQ, SR App and cognitive tests as described above but blinded results.</td></tr>
<tr><td>Diagnostic procedure performed for each patient independent of the study arm</td><td>Physical examination according to clinical standard including weight, height, and office blood pressure

Medical assessment: Standard medical history including medication and physical examination

Final patient meeting with dialogue around symptoms and findings, diagnosis, treatment recommendation and treatment plan

Data storage all study outcome data: At study site according to local routines. All study data will be reported through a Case Report Form managed by “RED CAP”, original sleep files will be transferred to the Sleep Revolution study cluster based at Reykjavik University.</td></tr>
<tr><td>PAP procedure performed for selected patients independent of the study arm</td><td>Treatment: In patients using PAP treatment, the established clinical pathway for start and follow up of PAP will be applied, clinical visits for follow up according to study schedule.

Treatment follow up after 3 months will be performed using both elements of standard care and the experimental study methodology with single night SAS. Patients are encouraged to the wear the activity watch and to provide data in the Sleep Revolution App throughout the entire study period.

End of study interview between patient and health care provider</td></tr>
<tr><td>Study Duration and Timetable:</td><td>Proposed start date (first subject, first visit): Q2 2023

Proposed end date (last subject, last visit): Q3 2024

<table>
<tr><td>First study subject approvals</td><td>30 May 2023</td></tr>
<tr><td>Midterm recruitment report</td><td>31 March 2024</td></tr>
<tr><td>Study recruitment finalized</td><td>30 September 2024</td></tr>
<tr><td>Clean study data file closed, and statistical analysis plan filed</td><td>1 December 2024</td></tr>
<tr><td>Top Line results to be discussed</td><td>15 January 2025</td></tr>
<tr><td>Final study report</td><td>28 February 2025</td></tr>
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Efficacy:	• Staff time for the diagnostic pathway: Sleep Revolution care versus Standard care • Patient reported preference for diagnostic method • Number of OSA diagnosis and PAP treatment prescriptions by either pathway • Patient-reported and investigator-reported outcomes at baseline and 3 months CPAP follow up (all randomized patients) - PGI-S/ PGI-I - CGI-S/ CGI-I - ESS, PSQI, ISI , DASS 21 - European Sleep Questionnaire – all domains including the follow-up module after 3 months of PAP therapy - Sleep Revolution App including sleep diary and neurocognitive function - Physical exercise activity data - End of study interview • Sleep test with polysomnography or polygraphy (including AHI, ODI, SaO_2, hypoxic burden for all study participants, N1-N3 sleep, REM sleep, arousal index, hours of sleep for those with a PSG recording,) • Sleep evaluation by AI algorithms: Various aspects of hypoxic burden, sleep quality classification, frequency of respiratory events and time in obstructive breathing, heart rate and sympathetic system response to sleep disordered breathing
Safety:	No specific safety concerns. The following safety assessments are planned according to the schedule of assessments: • Adverse events (AE), including treatment emergent- and serious AE • Physical examination including vital signs • Body weight and BMI
Other Assessments:	• Blood samples for metabolic function and markers of inflammation optionally defined in a sub-study
Statistical Methods and Planned Analyses:	Primary outcome variable Staff time spent for the sleep apnea diagnostic pathway (V1a to V1 c) – comparison between standard care and the Sleep Revolution model in patients with obstructive sleep apnea (OSA) Secondary outcome variable • Association between overnight hypoxic burden assessed in the SR care pathway (best hypoxic variable, mean of multiple sleep tests; if available) and the change in ESS score after 3 months of CPAP treatment in the sleep revolution study arm compared with the association between AHI (single night assessment) and the change in ESS after CPAP treatment in the conventional management arm (both models adjusted for confounders of ESS change) • Association between other Predictive capacity of novel sleep apnea severity markers (mean of 3 sleep tests) from the SR pathway compared with traditional OSA severity makers (single night assessment, AHI, ODI, mean SaO_2) and the for changes in ESS symptom score, and other secondary diagnostic markers (including the ESQ) variables, and the initial help request after 3 months of CPAP treatment in the sleep revolution study arm compared with the association between traditional OSA severity makers (single night assessment) and the change in ESS after CPAP treatment in the conventional management arm (both models adjusted for confounders of ESS change) • Strongest baseline variable – single or combined parameter - (anthropometrics, comorbidity, novel and traditional sleep apnea severity markers, baseline symptom burden assessed by traditional questionnaires or the European Sleep Questionnaire) as a predictor of improved symptoms improvement and quality of life change in the patient global impression scale (much and very much improved) after 3 months of CPAP therapy • Content validity of the European Sleep Questionnaire

	Tertiary outcome variable • Drop out analysis: Factors predicting loss of data in the SR care pathway (sleep test, SR App, ESQ) • Results from bio-sample analysis (baseline, treatment response) • Feasibility and rate of completeness using three nights SAS procedure • Patient reported tolerability of the SAS procedure

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AASM	American academy of sleep medicine
AE	Adverse event
AHI	Apnea Hypopnea Index
AI	Artificial intelligence
CGI S/I	Clinical Global Impression – Severity/Improvement with therapy
eCRF	Electronic case report form
DASS 21	Depression Anxiety Stress Scale
ECG	Electrocardiogram
ESADA	European sleep apnea database
ESQ	European Sleep Questionnaire
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
HSAT	Home sleep apnea testing
ICF	Informed consent form
IEC	Independent ethics committee
ITT	Intent-to-treat
ISI	Insomnia Severity Index
ISQ	Insomnia Severity Questionnaire
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PAP	Positive Airway Pressure
PG	Polygraphy
PGI S/I	Patient Global Impression – Severity/Improvement with therapy
PI	Principal investigator
PSG	Polysomnography
RS	Randomization system
SA	Sleep apnea
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Standard Care
SR	Sleep Revolution

4 INTRODUCTION

4.1 Background on Obstructive Sleep Apnea and treatment options

The prevalence of OSA in the adult population is approximately 10-12%. The prevalence of OSA in combination with pronounced daytime symptoms is 1-3%. OSA is known to worsen in both severity and prevalence with increasing degree of obesity [Garvey 2015].

The etiology of OSA is unknown. Although the majority of patients present with anatomically predisposing factors such as obesity, hypertrophied tissue in the upper airway (particularly in children) or short jaw, these are not consistent findings.

Mechanical therapies including continuous positive airway pressure (CPAP) are commonly used treatments for OSA [Garvey 2015]. Frequently, patients with OSA manage to use CPAP for only a few hours per night resulting in an insufficient therapeutic effect. It has been estimated that 15–30% of the patients reject CPAP treatment at first trial [Dzierzewski 2016]. Of those accepting CPAP treatment, 25–50% fail to adhere adequately [Collard 1997, Zozula 2001] and more that 50% of patients terminate the therapy within 2-3years of initiation [Grote 2000], [Pepin 2021]. However, patients with more severe apnea and debilitating daytime sleepiness are usually found to be more compliant because they are motivated by the prompt reversal of the OSA symptoms after CPAP initiation [Palm 2021]. Therefore, proper diagnostic procedures are necessary to identify patients with OSA who are likely to be treated successfully with CPAP treatment. Current diagnostic pathways have not been designed to focus on optimized CPAP treatment outcome. Frequently, patients will get a CPAP treatment trial without a prior assessment of likelihood for treatment success. This study aims to create better diagnostic variables for the prediction of clinically relevant OSA which is treatable with CPAP.

Other alternative treatment modalities outside the scope of this study include intraoral mandibular advancement devices (MADs) which can be used to move forward the lower jaw and thereby alleviate posterior airway obstruction during sleep. These devices are not as consistently successful as CPAP treatment, but they may be useful in selected patients with mild sleep apnea who cannot tolerate CPAP or do not want to undergo surgery [Bamagoos 2016]. Upper airway surgery (uvulopalatopharyngoplasty, tonsillectomy, nasal surgery, tongue reduction) may treat snoring and sleep apnea in a subgroup of highly selected patients. However, surgery carries risk such as bleeding, infection, pain, and complications related to anesthesia [Dicus Brookes 2017]. Finally, neurostimulation of tongue muscles is a recently introduced alternative treatment option with limited experience and high cost [Strollo 2014].

4.2 Diagnosis of obstructive sleep apnea

Diagnosis is made by a combination of A) Medical history and symptoms, B) physical examination combined with functional markers of respiratory and cardiometabolic function (e.g. blood gases, spirometry, blood pressure, fasting blood glucose/Hb1Ac) and C) the overnight sleep study [Grote 2021]. The final diagnosis of OSA is made by a trained sleep physician after considering all three components of the diagnostic process. The clinical relevance of the OSA diagnosis as well as the decision for the final treatment plan needs to be discussed in dialogue with the patient.

The AHI is often seen as the backbone of current OSA diagnosis, and a current review highlights the shortcomings of the AHI matrix in this context [Pevernagie 2020]: The AHI metric has low precision, high night to night variability, low association with symptoms, and weak predictive value for long-term outcomes in OSA patients. Nevertheless, the AHI frequency criteria still provide the main guide to assess severity assessment and treatment decisions for OSA patients.

4.3 Background on the Sleep Revolution (SR) project

The SR is a major, Pan-European research project financed by the European Union Horizon 2020 program [Arnardottir 2022]. The SR aims to tackle the above-mentioned major shortcomings by developing machine learning tools to individualize OSA care and to identify the wide range of OSA phenotypes better in the diagnostic process. This allows for more personalized treatment options, including increased patient participation. The new tools will be implemented to alleviate the costs and increase the availability of sleep studies by decreasing staff time associated with manual scoring. Finally, the project aims to design a digital platform that functions as a bridge between researchers, patients, and clinicians, with an electronic sleep diary, objective cognitive tests, and questionnaires in a mobile application. These ambitious goals will be achieved through extensive collaboration between 39 centers and by including expertise from sleep medicine, computer science, and industry and by utilizing tens of thousands of retrospectively and prospectively collected sleep recordings. The SR aims to create new pathways for improved clinical practice in sleep medicine, in particular for sleep apnea management.

In the current study is a major work package within the project, the new SR pathway for sleep apnea diagnosis and treatment follow up needs to be validated and tested with regard to the feasibility of following new technologies including patient related symptom assessment methodology, and data analysis approaches:

- Self-applied polysomnography
- Diagnostic assessment over long time periods including 3 consecutive nights of advanced sleep testing, at least one week of testing with actigraphy, physical activity, sleep symptom questionnaire, and sleep diary

- Artificial Intelligence based analysis of sleep tests for characterization of sleep, respiratory events and cardiovascular function with quality control by healthcare professionals (semi-automated process)
- Digital platform for data transfer from the patient to the health care professional
- Validation of new sleep parameters like hypoxic burden, sleep disturbance index and pulse wave derived cardiovascular indices against comorbidities, baseline symptoms, and response to treatment
- The novel European Sleep Questionnaire (ESQ)

4.4 Aims of the planned study

The aims of the current study can be summarized as follows:

A) Analyse differences in staff time associated with the SR pathway compared to Standard Care (SC)
B) Apply several novel diagnostic parameters and principles which influence the predictive value of the diagnostic method for CPAP treatment efficacy, tolerance and acceptance;
C) Assess the technical feasibility of the novel SR diagnostic pathway including self-applied polysomnography, and the cloud based digital platform for data transfer and data exchange between patients and caregivers;
D) Assess the content validity and the predictive capacity for CPAP success of the newly designed European Sleep Questionnaire (ESQ).

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective

Staff time comparison between the SR assessment and the standard care diagnostic pathways – non inferiority assumption

5.1.2 Secondary Objectives

A separate study analysis plan including a detailed description of all planned analyses will be compiled prior to the termination of data collection (last patient out).

- Capacity of the novel SR diagnostic pathway to detect clinically significant sleep apnea
- Clinically meaningful outcomes of CPAP treatment in patients with OSA
- Feasibility of the European Sleep Questionnaire (both technical failure and patients´ inability to perform the SAP)
- Feasibility of the SR digital platform for data transfer (percentage missing data, data transfer failure rate, patient experience, health care personnel experience)
- Safety and tolerability of self-applied polysomnography and patient centered reporting of clinical symptoms in a digital platform
- The predictive value of the sleep related variables detected from the SR diagnostic pathway (hypoxic burden, symptom burden) for three months treatment outcome after CPAP therapy (symptom improvement following therapy: daytime sleepiness and sleep quality) compared with sleep parameters obtained by standard care.

5.1.3 Exploratory Objectives

- Proportion of patients diagnosed with clinically relevant sleep apnea in each arm, proportion of patients with treatment recommendations for CPAP, mandibular advancement devices, or upper airway surgery in each arm of the study.
- Proportion of patients with PAP non-adherence (user time <4h/night) in each study arm
- Sleep apnea alleviation by PAP (calculation of overall efficacy of PAP adjusted for PAP adherence, mean habitual sleep time and residual AHI during PAP use)
- Evaluation of biomarker predictive for hypoxic burden and reduced quality of life (e. g hsCRP, TNF alpha, Hypoxia Inducible Factor)

5.2 Study Endpoints

5.2.1 Primary Endpoint

Staff time comparison between the SR assessment and the standard care diagnostic pathways – non inferiority assumption between the methods.

5.2.2 Secondary Endpoints

5.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints are as follows:

Important Secondary Endpoints	Other Secondary Endpoints
Parameters of the SR sleep test analysis: • Variables of novel hypoxic markers • Variables of respiratory event detection • Variables of novel sleep and arousal classification • Variables of novel cardiovascular classification (Pulse, ECG, and pulse wave analysis)	• Number of valid sleep tests in SR and SC diagnostic pathways • OSA classification based on three nights of self applied somnography versus classification by standard PG/PSG • Sleep apnea diagnosis criteria fulfilled in night 1, 2, or 3 in the SAS somnography
Parameters of the traditional sleep test analysis – both at baseline and change after 3 months of PAP treatment for • Sleep stages and arousal, total sleep time, sleep latencies, total sleep time, sleep efficacy • AHI, ODI, Mean and lowest saturation • Mean, highest and lowest heart rate	• Change in sleep quality parameters based on PSG (e.g. total arousal index) from baseline to Week 12 • Change in novel objective sleep quality measures (sleep continuum, sleep windows shorter than 30 seconds, other)
Results from the European Sleep Questionnaire • Change in daytime and nocturnal symptoms assessed by the ESQ at baseline and after 12 weeks of CPAP • Association ESQ parameters and PSG variables	• Clinical variables and daytime and nocturnal symptoms associated with response to CPAP treatment • Patient/Clinical Global Impression Scale Improvement (PGI-I/ CGI-I): Percentage of patients reported as improved (scores 1 to 3) from baseline to Week 12
• Patient/Clinical Global Impression Scale Severity (PGI-S/CGI-S): Change in mean score from baseline to Week 12	• Epworth Sleepiness Scale (ESS): Change in mean total score from baseline to Week 12 • Insomnia Severity Index (ISI): Change in mean total score from baseline to Week 12
• Pittsburgh Sleep Quality Index (PSQI): Change in mean global score and in mean scores of domains from baseline to Week 1 • Association between PSQI measures and sleep test results from SC and SR care • Physical activity and mean sleep duration pre and post CPAP	Association between overnight hypoxic burden (mean of 3 sleep tests) and the change in ESS score after 3 months of CPAP treatment in the SR study arm compared with the association between AHI (single night assessment) and the change in ESS after CPAP treatment in the conventional management arm (both models adjusted for confounders of ESS change

5.2.2.2 Safety Endpoints

The following secondary safety assessments are planned according to the schedule of assessments:

- Adverse events (AE), including treatment emergent- and serious AEs
- Physical examination
- Body weight and BMI
- Vital signs

5.2.3 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- Biomarkers including lipid status, Hb1Ac, HsCRP, NPro BNP, TNF alfa, Interleukin 6 are collected at baseline and 3 months treatment follow up: Association with the new PSG derived sleep variables (e.g. association hypoxic burden with inflammation) and change with treatment.
- OSA alleviation calculation-based AHI responder analysis: Proportion of patients achieving a ≥50% OSA alleviation during CPAP treatment calculated as the mean reduction from baseline in AHI at 3 months adjusting for CPAP adherence, mean sleep time and residual AHI during CPAP: Association between novel baseline diagnostic markers and the overall OSA alleviation by CPAP treatment; predictive value of AHI versus new diagnostic markers
- Drop out analysis: The frequency and clinical characteristics of patients dropping out from the study (no clinically relevant sleep apnea, no indication for CPAP, technical failure during sleep assessment) will be analysed separately as tertiary outcomes. Differences in clinical characteristics between the two study groups will be adjusted for.

6 INVESTIGATIONAL PLAN

6.1 Description of Overall Study Design and Plan

SR 001 is a multi-center, randomized, cross-over, open, parallel assignment study. It is designed to evaluate the efficacy, feasibility and tolerability of the novel SR OSA management algorithm when compared with traditional sleep apnea management in patients with moderate to severe OSA treated with PAP. The study consists of the baseline assessment in a cross over design: screening visit, randomized order of one sleep assessment by center specific usual care (SC) and the novel patient self-applied polysomnography on three consecutive nights in the SR diagnostic pathway at baseline. After the sleep assessment has been performed, an additional visit will take place at the end of the diagnostic work up summarizing the findings by providing a diagnosis of OSA and – if applicable – a treatment plan. The diagnostic information will be available from the SC or the SR procedure depending on the randomization outcome. The information from the second evaluation (SR or SC, respectively) is blinded to the patient and the sleep physician. In the subgroup of patients, where treatment with PAP is recommend, this treatment will be initiated in the second part of the study. PAP treatment will be initiated according to local clinical routines and followed up after 3 months with one night of self-applied polysomnography. During the diagnostic and the treatment periods, all study participants will monitor their sleep, physical activity and cognitive function by means of the SR App and an activity watch capable for monitoring (Withings). The maximum of the study duration for a patient from the screening visit to the follow-up visit is 20 weeks.

Patients will be randomized 1:1 to receive control or experimental clinical management as first diagnostic procedure. Randomization will be also stratified for sleep diagnostic methodology (PSG or polygraphy in the SC arm) at study entry.

The sleep related variables (i.e. including AHI, ODI, SaO2, N1-N3 sleep, REM sleep, arousal index, hours of sleep) for assessment of sleep apnea severity are obtained by PSG or by cardiorespiratory polygraphy according to the routines of the sleep center. All PSG exams will be performed in a facility specifically designed to meet standardized protocols (including calibration of signals, pre-defined lights-on and lights-off routines). The sleep study procedure will be identical on every occasion according to the routines at each center. The patients will be given 8 hours of time in bed. Scoring will be conducted according the AASM Version 2.6 released in January 2020 [AASM 2020] and all scorers in the study will receive standardized scoring instructions/training prior to study participation.

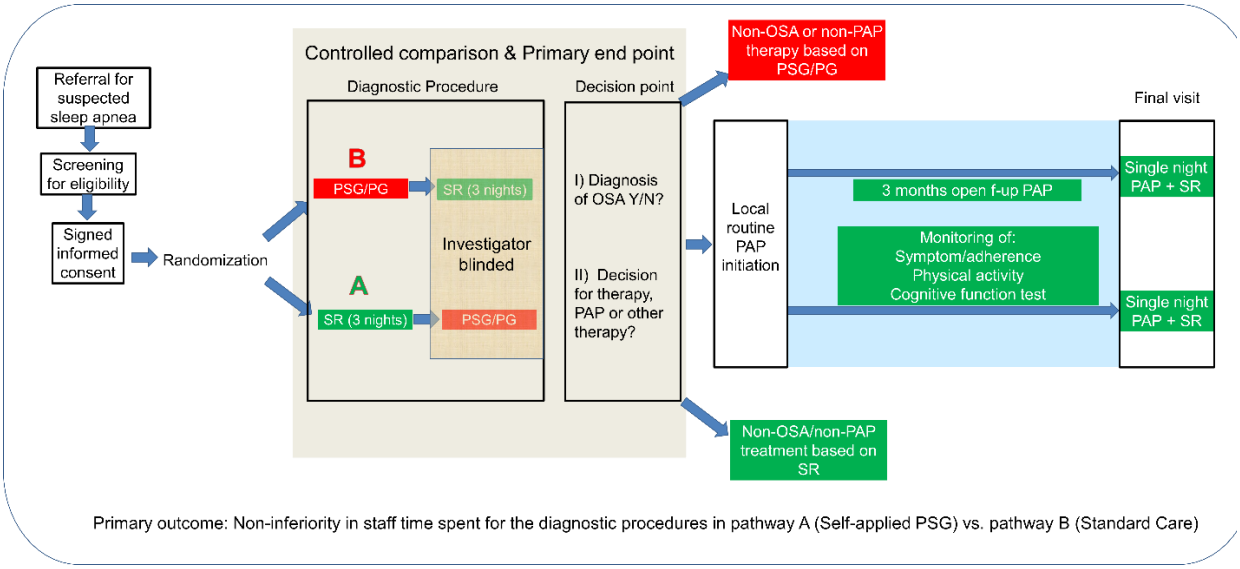
For efficacy evaluation patients or investigators will also be asked to complete a number of rating scales before, during and at the end of the study treatment period. These will include CGI-S/I and PGI-S/I, ESS, PSQI, ISI, and the ESQ (all described in detail below). An exit interview will ask for patient satisfaction with disease management and treatment outcome.

Start and initial follow-up of patients on PAP treatment will be performed according to the routines established at each study center without any systematic differences for each study group.

The patients will also be instructed to contact the clinic in between study visits in case of problems with PAP treatment. Start of PAP treatment need to be executed within 6 weeks after the date of diagnosis.

Assessments of safety will be done throughout the study and include vital signs, physical examination, body weight and BMI. Adverse events (AEs) will be collected from the timepoint of the informed consent signing and throughout the study period. An overview of the study design is presented in Figure 1.

Figure 1. Study Design



Abbreviations: PSG = polysomnography, PG=polygraphy, PAP=Positive Airway Pressure, SR=Sleep Revolution, OSA

6.2 Discussion of Study Design

This study will evaluate the novel SR management program in patients with suspected sleep apnea and the outcome of PAP treatment in the subgroup of patients with moderate to severe OSA patients. Several patients will not have clinically significant sleep apnea or do not cope with this treatment or will refuse to use CPAP. Any such patient subgroup will be analysed separately as tertiary outcomes (drop put analysis).

The planned treatment duration in this study is 12 weeks. This includes a 3-6 week CPAP adaptation period in each study arm where patients are encouraged to contact the sleep center in case of problems with CPAP therapy. Mask adaptation and resolution of adverse side effects from CPAP treatment will be targeted according to the established routines at each study center.

The final follow-up visit after 3 months of PAP therapy will be scheduled in advance. The work up with clinical interview, assessment of vital signs and blood samples, sleep recording during

CPAP treatment and assessment of relevant patient related outcomes (ESS, European Sleep Questionnaire, PGI etc.) will be performed in both treatment arms. Sleep evaluation with CPAP treatment on will be performed with the SR based algorithm including as single night of self-applied polysomnography. In case of terminated PAP use, the patients are encouraged to fulfill the follow up assessment without treatment (untreated controls).

6.3 End of Study

A patient will have fulfilled the requirements for study completion if/when the patient has completed all study periods, including the follow-up visit at Week 14, as indicated in the schedule of assessments (Table 2).

A patient has also reached the end of study participation by the following scenarios:

- Withdrawal of consent and/or preliminary termination of study participation
- No OSA diagnosis after the diagnostic process
- No indication for or non-willingness to test CPAP therapy
- Indication for Non-CPAP therapies instead of CPAP
- Technical failure of all sleep diagnostics tests performed (SR and SC)
- Patient's last visit for any protocol-related activity.

SELECTION OF STUDY POPULATION

6.4 Inclusion Criteria

General comment: The study aims to include the entire spectrum of patients seeking for the evaluation of suspected sleep apnea. To preselect patients with high or low probability of sleep apnea is obsolete. This goal should be kept in mind when asking referred patients to participate in this study.

Individuals must meet all the following criteria to be included in the study:

1. Referral to the sleep center due to suspected sleep apnea as the main question for evaluation
2. Male or female aged 18 years and above
3. Willing and able to provide written informed consent
4. Willing and able to comply with the study design schedule and other requirements (e.g. no long-term travel during the time of the study)

6.5 Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Any previous OSA or CSA diagnosis or treatment, in particular CPAP, within the last 10 years prior to screening
2. Known hypercapnic respiratory failure due to chronic obstructive pulmonary disease or other respiratory condition
3. Contra-indication for CPAP treatment
4. Patients who underwent an obesity surgery within the last 2 years prior to baseline or patients actively participating in any weight loss treatment program or use of any weight loss medication (prescription or over-the-counter) within 2 months prior to the first PSG night
5. Uncontrolled congestive heart failure
6. Myocardial infarction or coronary vessel intervention within the previous 6 months period or unstable angina pectoris
7. Known comorbidity which – according to the judgement of the investigator- could interfere with participation in the study and potentially jeopardize the completion of the study protocol including several nights of self-applied polysomnography or the start and continuation of CPAP therapy. Examples of such comorbidities are ongoing or past episodes of major depression, bipolar disorder, or any other significant psychiatric disorder, significant neurological or cognitive disorders including diagnosed dementia, Alzheimer's disease, Parkinson´s disease, stroke, ongoing epilepsy which, in the opinion of the investigator, might interfere with participation in the study, history of severe allergy/hypersensitivity or any ongoing allergy/hypersensitivity requiring continuous medical treatment against electrode material or adhesive material used in PSG recordings or during CPAP therapy (e.g. silicone), instable or terminal cancer, clinically significant gastrointestinal, metabolic, urinary, or hematological disorder.
8. Planned surgery during the study period which may interfere with the study protocol
9. History of alcohol or drug abuse during the last year, substance use disorder
10. Current regular use of sleeping aids, opioids, or central nervous system stimulants.
11. Participation in another clinical study during the last 30 days prior to screening which may affect the study procedures or outcomes
12. Current or active infection potentially affecting the sleep study results or the ability to tolerate CPAP treatment

6.6 Restrictions

No alcohol intake will be allowed 24 hours before and during the PSG nights. Study participants are recommended to refrain from alcohol consumption during the full study period. Patients are informed to avoid significant sleep deprivation up to three days prior to the scheduled sleep studies.

Please refer to Section 7.3 for information on prohibited prior and concomitant medications.

6.7 Study Withdrawal, Removal, and Replacement of Patients

If a patient discontinues the sleep evaluation at baseline, the recommended CPAP treatment (if applicable), and is withdrawn from the study for any reason, the date and the reason for study discontinuation must be recorded on the case report form (CRF). Patients who discontinue early from the study will be asked to return to the study site to complete the early termination (ET)/end of study assessments as indicated in the schedule of assessments (Table 2). It is of significant advantage for the study if patients quitting CPAP therapy can be re-evaluated with a single night SAS-PSG without any treatment in connection with the ET-visit.

Once a patient is withdrawn from the study, the patient should not reenter the study.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- unacceptable AE, e.g. from the diagnostic equipment or the CPAP therapy
- patient withdrawal of consent: at any time, a patient's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment. The reason for patient withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- patient fails to adhere to the protocol requirements (eg, failure to perform the diagnostic sleep test or to answer the questionnaires, failure to return for the defined number of visits)
- lost to follow-up: the patient stopped coming for visits, and study personnel were unable to contact the patient.
- alternative treatment for OSA outside the study protocol. Lifestyle changes like increases in exercise or weight reduction are excluded from this study withdrawal criterion. Those are captured elsewhere in the follow-up assessments (see details described below).

7 TREATMENT

7.1 Details of Study Treatment

7.1.1 Treatment Regimen

Positive airway pressure (PAP) applied via a nasal or oro-nasal mask is the most effective treatment in OSA. The positive airway pressure works as an airway splint which prevents the upper airway to collapse. The treatment was established in the beginning of the 80ies and is frequently used by millions of patients all over the world. PAP can be applied as a constant pressure, often referred to as CPAP. Auto-adaptive PAP (APAP) delivery was developed in the 90ies and shown to be equally effective and tolerated as CPAP treatment. In the current study, both CPAP and APAP can be used according to the clinical routines in each study centre of the ESADA network.

PAP treatment is highly effective and normalizes the respiration during sleep. However, adherence with PAP treatment can be compromised and remains the main challenge to achieve treatment success. Frequent side effects include dry mucosa and nasal discomfort, air leakage through nose or mouth, and skin irritations through the mask. Claustrophobia, involuntary mask removal during sleep, or non-acceptance by the bedpartner may also limit PAP use. A careful training and pressure adaptation at treatment initiation is required. National and international guidelines for these adaptation procedures are available and specific patient focus is provided during the first 4 to 6 weeks of treatment.

Overall long-term treatment success can be achieved in 50-80% of patients starting with PAP treatment. Degree of sleep apnea and symptom burden at baseline are the main prediction factors for good PAP adherence. Effective symptom improvement and reduction of cardio-metabolic dysfunction has been observed in patients using PAP treatment at least 4 hours/night. Reinforcement of treatment, successful management of side effects and intense coaching at treatment start are established tools to improve long-term adherence with PAP treatment.

In the current study, clinical PAP routines will be different between ESADA centres and PAP training will be performed according to the local, well-established routines at each centre and in lab or ambulatory treatment start procedures are appropriate. Telemedicine-based follow-up routines, if part of routine care, may also be used. However, to serve the study goal, three important principles have been applied:

- The routines for PAP management are similar for each randomization group (traditional versus SR diagnostic routine first) within each ESADA centre.
- All patients on PAP treatment have access to support and coaching by experienced health care personnel during the first weeks of PAP treatment.
- “One size does not fit all “. Different types of nasal or oro-nasal masks need to be available. In case of PAP adherence problems patients may be offered an alternative mask type.

Lifestyle changes including weight reduction are allowed during the study period. Lifestyle coaching as part of the patient-centered treatment strategy can be offered according to the clinical standard applied at each sleep center in the ESADA research network. Such lifestyle changes will be captured in the study by monitoring of weight changes, physical activity, and smoking habits. Final data analysis of CPAP treatment effects will be adjusted for simultaneous changes in lifestyle during the follow up period.

7.2 Measures to Minimize Bias: Study Treatment Assignment and Blinding

7.2.1 Method of Study Treatment Assignment

At screening, the order of diagnostic tests will be randomized. The "randomization system" (RS) will assign an unique identification number to the patient known as the patient number. This number will be associated with the patient throughout the study. Each patient signing an informed consent form (ICF) must be entered into the RS regardless of eligibility to obtain a patient number. This 8-digit number will consist of a 3-digit country specific code, followed by a 2-digit site identification and a 3 digit number assigned sequentially within each site to each patient, starting at 001.

At the randomization visit, all eligible patients will be randomly assigned in a 1:1 ratio to follow the routine clinical management or to be part of the SR clinical pathway. Centres using polysomnography as routine sleep evaluation procedure are asked to use this method in all of the study patients at this centre, and vice versa for those centers using cardiorespiratory polygraphy as the routine method. By this procedure, the study aims to recruit at least 40% of patients in the traditional clinical routine to be assessed by PSG. No formal stratification for anthropometric factors like age, BMI or gender or comorbidities will be performed.

Patients will be assigned a randomization number through the RS. Once a randomization number is allocated to one patient, it may not be assigned to another patient even if the former discontinued the study.

7.2.2 Blinding

This is an open label, randomized, cross over study. Blinding of the clinical pathway is impossible for the patients and the caregiver. However, results of the second diagnostic package (SR or SC) will be blinded at the timepoint for the final diagnosis and treatment recommendation at the end of the diagnostic process (see decision point in figure 1).

The PAP treatment phase and the follow-up are similar in the two groups.

7.3 Prior, concomitant and forbidden therapy

Medications taken by or administered to the patient at the time of screening will be recorded in the eCRF at the baseline visit. After baseline, any change in medication needs to be monitored and documented in the CRF.

Treatment with the following concomitant medications/therapies is prohibited prior to and during the study

Table 1. Prohibited Medication

Treatment	Timeframe	
	before the first PSG night	Visit 2 to Visit 8
Continuous use of hypnotics (excluding melatonin)	2 weeks	Prohibited, intermittent use allowed outside the nights with sleep assessments
Weight loss medication (prescription or over-the-counter)	1 month	Prohibited
Recreational drugs (e.g. tetrahydrocannabinol, marijuana, edibles)	14 days	Prohibited
Stimulants (e.g. methylxanthine and derivates, amfetamins, modafanil)	7 days	Prohibited
Frequent intake of opioids as pain medication (>3 days/week)	7 days	Prohibited
Frequent intake of diazepanes as anxiolytic (>3 days/week)	3 days	Prohibited

Anti-depressants or antihistamins or antiepileptic drugs are allowed when taken on stable dose for at least 2 months prior to the first PSG night. If the dose is changed during the study, this has to be noted in the study CRF.

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

8 STUDY POCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study.

Table 2. Schedule of Assessments

	Baseline Evaluation Period			PAP Treatment initiation and training	PAP Treatment Period		Follow-up Evaluation Period		Early termination visit [b]
	Baseline Visit[a]	Sleep Evaluation Baseline	End of diagnostic process				Sleep Evaluation Follow-up	End of study follow-up visit	
Visit	**V1a**	**V1b**	**V1c**	**V2**	**TC1**	**TC2**	**V3a**	**V3b**	**V4**
Week	**-1- -4**	**-1- -4**	**-1- -4**	**0-3**	**4**	**8**	**12**	**12±4**	**Within 2 w**
In- and exclusion criteria	X								
Subject information and informed consent	X								
Anthropometric and basic clinical data									
Demographic data	X								
General medical history & OSA history	X								
Physical examination	X							X	X
Height[c], body weight	X							X	X
Concomitant medication	X		X	X	X	X		X	X
Vital signs[d]	X								
Biomarker sample[f]			X					X	X
Randomization	X								
Objective evaluation of sleep and wake period									
Sleep evaluation: PSG or PG and SAS in random order		X (1 night clinical routine and 3 nights SAS)					X (1 night SAS)		
Sleep rhythm and physical activity (activity watch)	X (start)	X (continued	X	X	X	X	X	X (end of	

	Baseline Evaluation Period			PAP Treatment initiation and training	PAP Treatment Period		Follow-up Evaluation Period		Early termination visit [b]
	Baseline Visit[a]	Sleep Evaluation Baseline	End of diagnostic process				Sleep Evaluation Follow-up	End of study follow-up visit	
Visit	**V1a**	**V1b**	**V1c**	**V2**	**TC1**	**TC2**	**V3a**	**V3b**	**V4**
Week	**-1- -4**	**-1- -4**	**-1- -4**	**0-3**	**4**	**8**	**12**	**12±4**	**Within 2 w**
		throughout the study)						recording and data analysis)	
Diagnosis of OSA y/n			X						
PAP treatment start				X					
Follow-Up for PAP treatment					X	X	X	X	X
Patient related symptoms and outcome measures									
CGI-S/PGI-S			X					X	X
CGI-I/PGI-I								X	X
ESS, ISI, ISQ, PSQI, FSS	X							X	X
Sleep Revolution APP cognition, sleep diary	X		X		X	X	X	X	X
DASS21	X								
European Sleep Questionnaire	X							X	X
Cognitive test battery (voluntarily)	X							X	
Adverse events			X	X	X	X		X	X
End of study interview								X	X

Abbreviations: CGI-S = Clinical Global Impression Scale rating Severity, CGI-I = Clinical Global Impression Scale rating Improvement, ESS = Epworth Sleepiness Scale, OSA = obstructive sleep apnea, PGI-I= Patient Global Impression Scale rating Improvement, PGI-S=Patient Global Impression Scale

rating Severity, PSG = polysomnography, PSQI = Pittsburg Sleep Quality Index, SR APP=Sleep Revolution Phone Application with neurocognitive tests and a sleep diary, TC = telephone contact, V = visit

a Patients may be excluded based on data from the screening visit. They do not proceed to randomization or objective sleep evaluation.
b V4 procedures should be performed in all patients terminating CPAP treatment prematurely (if possible). V4 is very similar to V3b performed in those individuals who comply with the entire study procedures. In case of study termination at visit 1c (e.g. no sleep apnea, no CPAP therapy), no visit 4 is required.
c Height to be measured at screening only.
d Vital sign measurements should be at comparable and standardized conditions for each patient. f at selected sites only.

8.1 Informed Consent

Before performing any study-related procedures, the investigator (or designee) will obtain both oral and written informed consent from the patient after both oral and written information about the study.

8.2 Study Procedures

Assessments and their timing are to be performed as outlined in the schedule of assessments (Table 2).

Efficacy assessments are described in Section 9 and include PSG and patient- and investigator-reported patient outcomes (PGI-S/PGI-I, CGI-S/CGI-I, ESS, PSQI, European Sleep Questionnaire, PAP adherence and efficacy data, exit interview).

Safety assessments are described in Section 10 and include vital signs, blood pressure, safety laboratory, physical examination, body weight and BMI, and AEs.

Biomarker assessments are described in Section 11, respectively.

The investigator may, at his/her discretion, arrange for a patient to have an unscheduled assessment, especially in the case of AEs or a PAP related problem solving that requires follow-up. The unscheduled visit page in the eCRF must be completed in such a case.

Study discontinuation procedures are described in Section 6.7.

8.3 Diagnostic activities prior to decision point at the end of the diagnostic process

To compare the diagnostic process between the Sleep Revolution and the standard care process, all information gathered during the diagnostic work up will be restricted to the information available in the respective randomization arm. In detail, this information is specified as follows:

Sleep revolution pathway A according to figure 1: Scoring results from 3 nights (or parts thereof) of self-applied polysomnography, information from the digital platform including the ESQ questionnaire and the SR App data and the Withing watch (sleep diary, physical activity and cognitive function)

Sleep revolution pathway B according to figure 1: Scoring results from 1 night of standard care polysomnography or polygraphy (in house or at home), information from the questionnaires ESS, PSQI, ISI (or other data normally used in the standard care process).

The questionnaires, SR App and activity watches are handed out to the patient when starting the diagnostic procedure. See also a more detailed activity scheme at end of the protocol appendix.

9 DIAGNOSTIC AND TREATMENT OUTCOME ASSESSMENThe TS

The schedule of assessments (Table 2) outlines the different assessments to be performed throughout the study and their timing. During the diagnostic procedure, each patient will be investigated both with the traditional sleep testing (SC) and the three nights of SAS procedure included in the SR pathway. The order of SC and SR procedure is randomized.

9.1 Objective sleep assessment by polysomnography or cardiorespiratory polygraphy

Control arm using routine procedure at each ESADA site: Variables from the PSG recording will be derived during the study night. PSG procedures will be performed at the sleep laboratory or the sleep test at patients home according to international AASM guidelines. The patients will be given 8 hours of time in bed. Recommended minimum total sleep time is set to 4 hours. A repeat diagnostic sleep test may be performed if this criterion is not met.

PSG recordings will include a standard montage with electrode placements for electroencephalographic (EEG), electrooculographic (EOG), electromyographic (EMG), and electrocardiographic (ECG) recording. In addition, the montage will include channels for recording respiratory variables, e.g. respiratory effort, nasal/oral airflow) and oxygen saturation. When PSG is performed in the patient's home or unsupervised in the hospital, redundancy of EEG channels should be provided in order to ensure that sleep parameters will be evaluable despite the unsupervised recording setting.

PSG scoring will be performed by an experienced PSG technician at each study site, preferably by one scorer for all sleep studies in the current study. If this is not possible, the site has to ensure that interscorer agreement between scores reaches at least 85% and that all recordings from one patient will be scored by one technician. PSG scoring will be based on the current AASM manual version 2.6 [AASM 2020]. Hypopneas are scored with a 3% desaturation and/or arousal criteria. At least 4 hours of total sleep time is necessary for a valid AHI classification.

The PSG recording will provide at least the following diagnostic variables which will be included in the appropriate page of the eCRF:

- AHI_{PSG} [n/hr]
- ODI_{PSG}, 3 % and 4% [n/hr]
- Mean overnight SaO2 [%]
- Percentage sleep time spent below 90% SaO_2
- Percentage non-rapid eye movement stage 1 (N1) sleep [%]
- Percentage N2 sleep [%]
- Percentage N3 sleep [%]
- Percentage rapid eye movement (REM) sleep [%]
- Minimum overnight SaO2 [%]

- Total sleep time (TST) [min]
- Sleep efficiency (SE) percent [%]
- Total arousal index (TAI) [n/hr]

The entire PSG report including more than 100 parameters will be checked for validity of data and thereafter transferred to the central SR study-specific database for detailed analysis together with the raw data of the sleep test.

In case of sleep assessment by cardiorespiratory polygraphy (Home Sleep Apnea Test HSAT) at the study centre, all devices will be conform with the AASM level 3 classification. The montage will include at least channels for recording of respiratory variables, e.g. respiratory effort, nasal/oral airflow, oxygen saturation and a proxy for assessment of snoring. Arterial tonometry is a level 3 device, but the SR project aims to perform complex post hoc analysis of respiratory flow and effort which requires above cited respiratory flow and effort signals. Therefore, arterial tonometry may be used in parallel with a device providing the respiratory signals stated above. Polygraphic assessments will be performed according to established clinical routine at home or in the hospital/sleep center. Patients will be instructed on how to use the devices (home testing) or montage will be applied by sleep center personnel. Recording time is aimed be at least 8 hours and patients should sleep during their habitual hours. Total analysis time should be at least 4 hours for a valid AHI classification. Otherwise, a repetition of the sleep test is recommended. Scoring of respiratory events will use the AASM criteria version 2.6 for scoring HST including scoring hypopnea with at a least 3% desaturation criteria.

The PG recording will provide at least the following diagnostic variables which will be included in the appropriate page of the eCRF:

- AHI_{PG} [n/hr]
- ODI, 3 % and 4% [n/hr]
- Mean overnight SaO2 [%]
- Minimum overnight SaO2 [%]
- Total recording time (TRT) [min]
- Total analysis time (TAT) [min]

The entire PG report including more than 30 parameters will be checked for validity of data and thereafter transferred to the central SR study database for detailed analysis together with the raw data of the sleep test.

In order to provide a final diagnosis to the patient, the sleep test needs to be evaluated for clinical purposes within 3 working days.

Experimental study arm using self-applied polysomnography:

The NOX A1 is a CE marked polysomnography (PSG) device which allows for ambulatory assessment of sleep, respiratory and oxygenation function. The SAS system uses the NOX A1 together with a novel, CE marked electrode system for patient based self-application of all sensors to assemble the following data during sleep: Electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG); respiratory effort belts, oro-nasal air flow and pulse oximetry, body position, ECG, and snoring. A comprehensive user manual with written information, series of detailed figures, and a video explaining the hook up procedure, is provided and translated in all local languages of the ESADA network. The instructions are intuitive, short, and distinct, and explained in a step-by-step manner.
Data from validation studies of the system indicate very good practicability. The SAS should be used three nights in a row to assess the intra-individual variability of sleep and sleep disordered breathing.
All detailed information about the procedure will be provided both to the patients as well as to the caregivers in a separate user manual provided by the manufacturer. Patient information on how to use the device will be translated by the ESADA centers into the local language.

9.2 Objective assessment of activity and wake-sleep pattern and physical activity by continuous activity monitoring

The Withings Scanwatch records physical activity by an accelerometer and both pulse rate and oxygenation by photoplethysmography of the wrist circulation. The output of the watch includes time, date, and pulse rate statistics over certain time windows. In addition, estimated sleep length as well as a detailed sleep wake schedule separating light and deep sleep from REM sleep is provided. Finally, the watch provides information about the physical activity assessed by an built-in accelerometer.
The watch should be worn by the patient throughout the entire study period and needs to be charged and downloaded on a regular base. A detailed user manual will be provided to the patient and the study site.

9.3 Patient-Reported and Investigator-Reported Patient Outcomes

All scales and questionnaires are completed at the time points indicated in the schedule of assessments (Table 2).

All patients in both study arms will fill in validated scales and questionnaires. Patients in the both study arms will use the interactive digital platform for the novel questionnaires, sleep diary and neurocognitive function data. Patients will also use paper-based assessments or other routinely instruments applied at the individual ESADA sites as part of the standard procedure. A detailed description of the different assessment tools is provided below.

9.3.1 Patient Global Impression Scale (Severity / Improvement (PGI-S/ PGI-I)

The self-administered questionnaire PGI-S employs a 4-point scale (normal, mild, moderate, severe) [Busner, Targum 2007]. The patient is asked to select the statement that best describes his/her sleep apnea related complaints at the baseline visit. At the final follow-up visit of the CPAP treatment group, as indicated in the schedule of assessments (Table 2), patients' global assessment of improvement by treatment will be rated using the PGI-I. In the PGI-I, the patient is asked to indicate the change in his/her condition by treatment at a subsequent visit using a 7-point scale with 1 being "very much better" and 7 being "very much worse".

9.3.2 Clinical Global Impression Scale (Severity / Improvement (CGI-S/ CGI-I)

The questionnaires CGI-S and CGI-I are completed by the investigator [Busner, Targum 2007]. For the CGI-S, the investigator will, based on his/her clinical experience, rate on a 7-point scale how severely ill the patient is in terms of sleep apnea (global rating) at baseline. Global improvement will be rated by the investigator or designee using the CGI-I at subsequent visits according to the schedule of assessments. The CGI-I employs a 7-point scale with 1 representing a "very much improved" patient and 7 representing a patient who has become "very much worse'" due to treatment. The rating 4 represents a patient displaying no change from the treatment. For optimal data quality in the study, CGI-I and CGI-S may be performed by the same investigator.

9.3.3 Epworth Sleepiness Scale (ESS)

ESS is a self-administered questionnaire used to determine the level of daytime sleepiness [Johns 1991, Johs 1993]. The question: "How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing-off, not just feeling tired" is answered by the patient for 8 different every-day situations on a 4-graded (0-3) scale. The item scores are summed. Four different ranges for the total sum are presented at the end of the document enabling the patient to analyse the overall result.

9.3.4 Pittsburg Sleep Quality Index (PSQI)

The PSQI is a self-administered questionnaire which assesses sleep quality [Buysse 1989]. It generates 7 subscores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the scores for these 7 components yields one global score.

9.3.5 Patient satisfaction at end of study

Patient satisfaction with the treatment will be assessed at the end of the study. Patients will be asked for their satisfaction with A) the diagnostic procedure and B) with PAP treatment and how likely they will continue treatment (B only applicable in the subgroup of patients receiving PAP treatment). Answers can range from 1 "extremely satisfied/extremely likely" to 7 "extremely dissatisfied/extremely unlikely".

9.3.6 **European Sleep Questionnaire (ESQ)**

Via the digital platform the patients in the experimental study group will complete the ESQ – prototype (ESQ-p version 3.2 from March 13, 2023). The ESQ-p is a not yet-validated new instrument to comprehensively assess the individuals clinical background, symptom profile, expectations, complaints, and desires related to sleep health. The current prototype version has been designed through a multi-professional and international expert team and is based on both current evidence from clinical sleep science but also on the attempt to overcome the limitations of current questionnaires. The conceptual idea of the ESQ is to characterize several dimensions of sleep health instead of primarily seeking for one or several specific sleep diagnoses. Many symptoms in sleep medicine are nonspecific and may fit several diagnoses. Therefore, the ESQ makes no a priori assumptions as to diagnostic probabilities.

The questionnaire has the following headings: 1) General information (personal information, personal profile), 2) my help request, 3) my sleep profile, 4) factors affecting my sleep behavior, 5) my sleeping behavior affecting others, 6) symptoms of nocturnal sleep, and 7) symptoms of daytime functioning, 8) Final comments. The ESQ-p has an additional module, to be administered during or after treatment, to assess effects of therapy. The ESQ-p is attached to the Appendix.

9.3.7 **Insomnia Severity Index (ISI)**

The Insomnia Severity Scale (ISI) is a 7-item questionnaire on a 7-point Likert scale, surveying difficulties with initiating or maintaining sleep and associated adverse daytime consequences. Results range between 0 (no insomnia) and 28 (very severe insomnia). Scores between 8 and 14 are considered sub-threshold insomnia. The instrument has also been used and validated to assess changes by treatment. The ISI will be applied both at baseline and at CPAP follow-up after 3 months. The questionnaire will be used in the local language.

9.3.8 **Fatigue Severity Scale (FSS)**

The FSS was developed to assess fatigue and was first published when used in patients with multiple sclerosis and systemic lupus (Krupp L, 1989). The FSS is a nine-item instrument designed to assess fatigue as a symptom of a variety of different chronic conditions. The scale gauges the effect of fatigue on daily functioning, querying its relationship to motivation, physical activity, work, family, and social life. The questionnaire asks respondents to rate the ease with which they are fatigued and the degree to which the symptoms are problematic to them. This instrument is also capable to assess changes by treatment.

9.3.9 Depression Anxiety Stress Scale – short version with 21 questions (DASS21)

The DASS is a self-report instrument that measures depression, anxiety and stress during the past week. It distinguishes between anxiety and tension/stress. Each scale consists of 14 questions that are grouped into smaller subscales. The depression scale consists of 7 subscales; the anger scale consists of 5 subscales; The stress scale consists of 5 subscales. Respondents rate on a four-point Likert-like scale how much each statement applies to them during the past week. A short version of the scale with 21 questions is available as DASS21.

9.3.10 SR App (see also appendix for more detailed dewcription)

The SR App monitors on a daily basis morning and evening sleep diary questions (sleep latency, time to bed, time to wake up, sleep time, degree of wakefulness, daytime napping, daytime sleepiness or fatigue, amount of exercise). In addition, 4 cognitive function tests can be performed by the study participant. They are called “Flexibility Game”, “Reaction Game”, Memory Game” and “Perception Game”. The tests are designed to assess reaction time, flexibility, memory, and perception. The test should be performed during the diagnostic procedures and at least once a week during treatment follow up. Time estimates for the sleep diary are approximately 3 minutes and for the short neurocognitive tests 15 minutes per test battery (4 tests).

10 SAFETY ASSESSMENTS

Safety assessments (AEs, vital signs, body weight and BMI, physical examinations) are to be performed at protocol-specified visits, as specified in the schedule of assessments (Table 2).

10.1 Medical History

Medical history including OSA history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including all prior chronic and significant illnesses. Additional preexisting conditions present at the time when informed consent is given and up to the time of diagnosis (visit 1c) are to be regarded as concomitant.

Medical history will include alcohol consumption, smoking history and habits of substance use, if applicable. OSA history will be documented including date of onset of symptoms, previous OSA treatment or surgical interventions, regular bedtime, regular time for stand-up, sleeping for overall numbers of hours/night).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 10.5. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include age and sex.

10.2 Vital Signs

Vital signs include systolic and diastolic blood pressure, and heart rate. Vital signs will be evaluated at the visits indicated in the schedule of assessments (Table 2).

The patient must avoid smoking, drinking a caffeine beverage, and exercising for at least 30 minutes before the blood pressure is measured. The patient should void prior to blood pressure assessment. Neither the patient nor the staff should talk during the procedure. All clothing covering the location of cuff placement should be removed.

Blood pressure will be measured with the auscultatory method (sphygmomanometer and stethoscope) or an automated blood pressure measurement system with the patient in the seated position in a quiet room after 5 minutes of quiet rest. Potential stressors should be avoided to prevent any potential white coat effect on blood pressure levels. Three (3) repeated blood pressure measurements will be done.

The following variables will be recorded in the eCRF:

- Resting blood pressure (mmHg) (systolic, diastolic, and calculated mean arterial pressure [MAP]), mean of 3 recordings for each rounded up to the nearest integer
- Pulse (bpm), after 5 minutes sitting

Vital signs measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs. Irregular pulse in patients with no prior known arrythmia must be followed up with an ECG assessment.

10.3 Body Weight, BMI

Body weight (thin clothes and without shoes) will be recorded whenever vital signs are recorded. Height (without shoes) will be recorded at screening only. BMI will be calculated.

10.4 Physical Examination

A complete physical examination (head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; as well as neurological and musculoskeletal systems) will be performed at the visits indicated in the schedule of assessments (Table 2).

10.5 Adverse Events

10.5.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history section of the eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE pages of the eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

It is the responsibility of the investigator to document all AEs reported during the study. Patients will be instructed to report potential AEs at each study visit. AEs will be elicited by asking the patient nonleading questions, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?". All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency (continuous vs intermittent), intensity, relationship to study treatment, action taken with study treatment (CPAP), treatment of event, and outcome. Furthermore, each AE is to be classified as serious or nonserious. Changes in AEs and resolution dates are to be documented in the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the follow-up visit. Follow-up of the AE, even after discontinuation of therapy, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset date).

Specific guidelines for classifying AEs by intensity and relationship to study treatment are given in table 3.

Table 3. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

10.5.2 Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence, in the view of the investigator, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered serious AEs (SAEs) if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account the investigator's assessment. If the investigator believes that an event is serious, the event must be considered serious and reported as such.

11 BIOMARKER AND ADDITIONAL ASSESSMENTS

Biosampling and physiological measurements will be performed only at selected study sites:

Blood samples will be retained and analyzed for at the local lab for the following parameters (baseline and follow up; all or only a selection of samples), see listing below: Samples will be collected from patients who give specific consent to participate in this optional assessment.

Biosample

- Inflammation
  (hsCRP, TnFα, IL 6)
- Metabolic function
  (Hb1Ac, lipid profile with total cholesterol, LDL and HDL subfractions)
- Ventilation
  (Hypoxia Induced Factor, Carbonic Anhydrase activity)
- Cardiovascular function
  (proBNP, Troponin, eGlomerular Filtration Rate)
- Neurocognitive function
  (circulating markers of brain damage)

In selected sites the following assessments will be performed during routine diagnostic procedures:

- Arterial blood gas analysis
- Spirometry
- 24 hour blood pressure measurements using a prespecified protocol
- Transthorcacic cardiac ultrasound to determine cardiac function and pulmonary artery pressure

Data from these specific study-assessments will be stored in separate files and can be added to the final study analysis file at study termination. The data are not essential for the evaluation of the primary or secondary study outcomes but may be analysed in future tertiary, post-hoc outcome analyses. A pre-specified power analysis for such data is not performed.

12 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group.

12.1 Determination of Sample Size

Staff time is an important factor for the clinical feasibility of a diagnostic pathway. Todays clinical standard of sleep apnea diagnosis varies considerably between centers and countries in Europe (Fietze 2022). In house polysomnography as well as HSAT are frequently used to establish the final OSA diagnosis and resources in staff-time varies considerable between these two diagnostic methods.

The novel SR pathway aims to provide more diagnostic accuracy by means of three nights of gold standard sleep analysis at patients homes compared to the single-night measures used today. In addition, the SR pathway provides significant enhancement of clinical phenotyping of patients symptoms, complaints, primary request of help as well as detailed information about relevant aspects of lifestyle and personal habits (physical activity, alcohol consumption, sleep hygiene) and neurocognitive function. The gain of knowledge about the patients disease burden is obvious when using such a comprehensive approach. However, the actual costs in terms of staff time are not yet evaluated.

All innovation in medicine needs to be justified in terms of cost-benefit. We decided to use staff-time as the primary outcome of the current study. It is estimated that the time of the SR procedure is equal to the time presently used in the SC procedures. Use of the self-applied polysomnography together with machine-learning algorithms of sleep analysis and the digital platform of patient symptom self-reporting will safe staff time on one hand. On the other hand, instructions of patients for the different technologies as well as the medical evaluation of the new information may consume more time compared with the current procedure. We decided to use a non-inferiority study design with 30 minutes as a threshold for equality of staff time within the setting of 24 sleep centers in Europe.

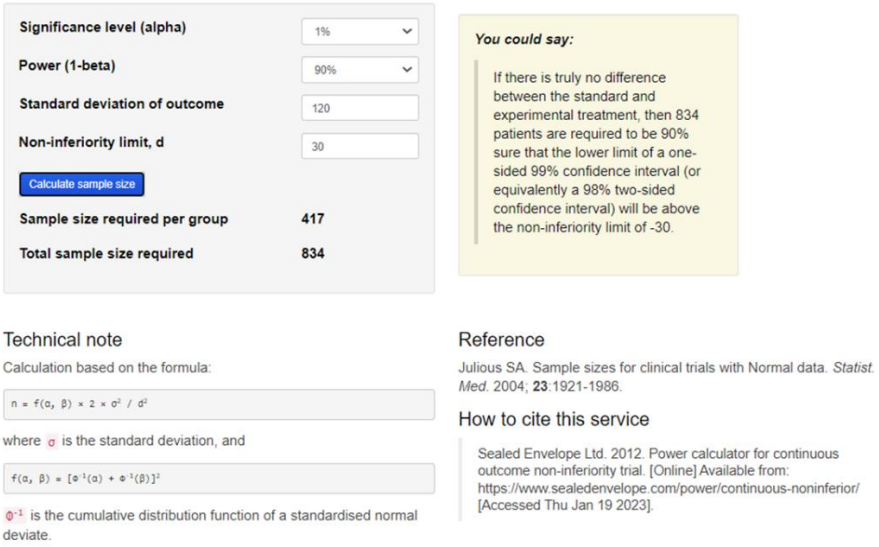
Calculation of the power sample is based on a previous publication (Fischer 2008) and the following assumptions determined from a Delphi round amongst the participating study centers. More detailed information on staff time for PSG and HSAT currently used at 24 different study sites are not available in the literature. One pilot study for the SR pathway has been performed

but no detailed measurements of staff time were performed. However, realistic estimates can be made (see table 3).

Table 3: Estimates of staff time (minutes) for the three different diagnostic principles used in the study: PSG=polysomnography, HSAT=Home Sleep Apnea Testing by means of cardiorespira-tory polygraphy, Sleep Revolution=Self Applied Somnography 3 nights, PC=Power Calculation)

Work modules	Standard PSG	Standard HSAT	Sleep Revolution	Value for PC
Preparation technical pre/post	15	10	35	
Instructions/Hook up	20-40	5-20	5-30	
Performance of the sleep test	120-480	0 (patient)	0 (patient)	
Evaluation of the sleep test	30-120	5-30	30-90	
Questionnaires	5	5	10	
Additional equipment	0	0	15	
Doctor: interpretation, communication	30-60	15-30	45-60	
Staff time: Estimated range of the mean	220-720	40-95	140-240	
Staff time: Estimated standard deviation of the mean	180	30	60	120

Power calculation:



The power calculation suggests 417 patients in each group, the expected drop-out rate of patients is 20% (results from the SR pilot study, unpublished data on file), resulting in 500 patients per group.

Per protocol interim analysis:

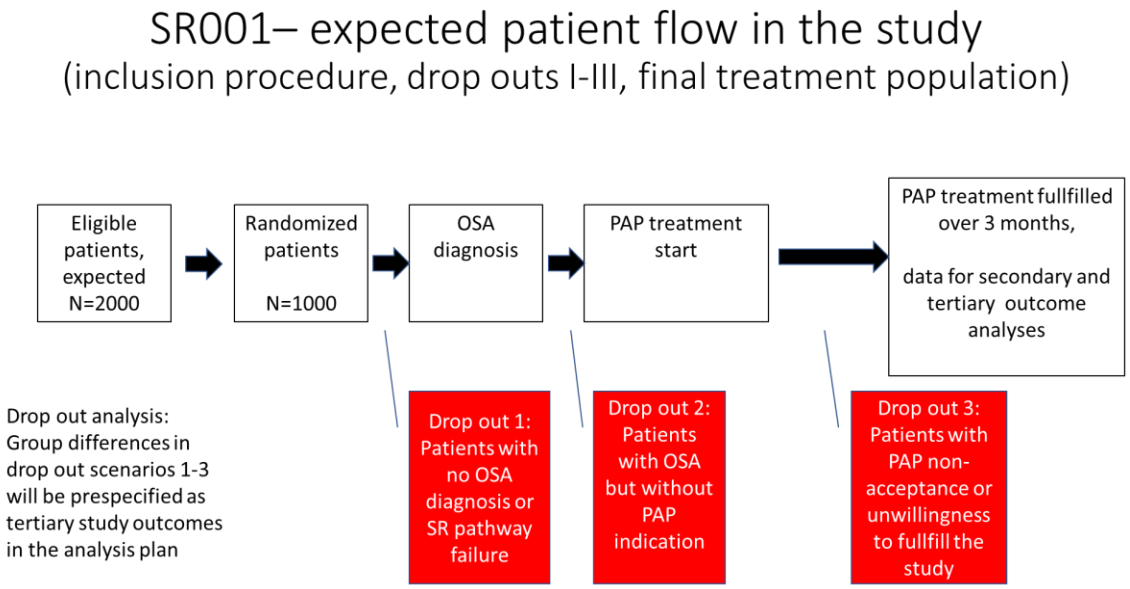
Due to the fact that the parameters for the primary power calculation are not based on data from well-sized previous studies, we were able to get the best estimates during a Delphi round of sleep experts from all involved study 24 centres. In order to avoid over-recruiting of patients we will perform a per-protocol interim analysis of the primary outcome variable after 500 randomized patients. Goal of the interim analysis is to find a better estimate for the final study size. The interim analysis will be performed by an independent statistician otherwise not involved in the study or the investigators of the SR project.

Drop out analysis:

The expected patients flow in the study is illustrated in figure 3.

It is expected that several patients will drop out of the study protocol including the patients not able to perform the self applied sleep test procedures, patients without a sleep apnea diagnosis, patients without CPAP indication and patients not able to accept or tolerate CPAP treatment. All drop out groups constitute tertiary outcome variables in the analysis. Therefore all patients will be included in the analysis of data.

Figure 3: Expected patient flow in the study



12.2 Analysis Populations

Enrolled Population

The enrolled population will include all individuals who sign the informed consent.

Intent-to-Treat Population (ITT)

The ITT population will include all patients who are randomized, irrespective of any deviation from the protocol or premature discontinuation. The group assignment will be designated according to initial randomization. The ITT population will serve to enable an analysis of the primary outcome variable (staff time).

Per protocol analysis population (PPAP) for the primary outcome

All patients finally fulfilling the complete diagnostic pathway (SR och traditional) will constitute the per protocol analysis population for secondary and tertiary outcome analyses.

12.3 Demographic and Other Baseline Characteristics

The demographic and clinical data of the two study populations (experimental and control group) will be compared with parametric or non-parametric statistical tests for continuous or categorical data. Distribution of data will be determined before the appropriate statistical test will be applied.

12.4 Efficacy Analysis

Primary endpoints:

Staff time for standard or SR based diagnostic procedures. Non-inferiority analysis. Threshold for non-inferiority will be a staff-time difference between methods of ≤30 minutes.

Secondary endpoints:

1. A comparison between AHI and novel SDB parameters: Association with baseline PROMs; PAP adherence; anthropometric data; comorbidities; medications; changes by treatment from baseline in subjective daytime symptoms as assessed in the ESS and the questionnaires; changes by treatment in electronic sleep diary testing.

2. Technical performance of the novel sleep test technology (self-applied PSG (SAS) over three nights) compared with the control condition (single night assessment): Failure rate; data loss for analysis, retest-variability; manual versus automated sleep stage and event analysis; internight variability in SDB severity and sleep quality in SAS; validation of wearables vs. gold standard SAS, feasibility for data collection and data analysis in a multi-centric and multi-linguistic setting.

3. A comparison between AHI and novel SDB parameters (hypoxic burden) for the prediction of the improvement in PROMs (change in patient-related outcomes from the ESQ and other established scales) by PAP intervention.

Tertiary endpoints.

Number of drop outs in the experimental and control clinical pathway (see figure 3: No OSA diagnosis, no PAP treatment, insufficient PAP adherence). Patient satisfaction with the diagnostic procedure.

For more detailed information on study endpoints see also table in 5.2.2.1.

12.5 Safety Analysis

All reported AEs will be listed and compared in the two study groups. The incidence of PAP treatment-emergent AEs will be included in incidence tables. Events with missing onset dates will be included as treatment emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study treatment will be used in the summary tables. SAEs and AEs causing discontinuation will be tabulated. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study treatment, action taken with study treatment, treatment of event, and outcome.

Vital signs like blood pressure and heart rate will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

12.6 Interim Analysis

An interim analysis is planned after the first 500 patients from the 24 study centers. It is anticipated that te number of patients is not equally distributed amongst all 24 center as the start of the study as well as the recruitment speed will differ between centers. The interim analysis will be performed for the primary outcome analysis parameter “staff time”. The group difference in staff time between patients diagnosed with the standard care pathway will be compared to staff time during the SR pathway. The results are used to perform a new power calculation.

In case less than 800 patients are necessary, power calculation for subgroup of patients, e.g. males/females or younger/elder patients will be explored. In case of the estimated number of patients to be randomized is between 800 and 1000, these numbers will be targeted. In case a larger number than 1000 patients is necessary to show inferiority between methods, the study protocol might be revised.

13 STUDY MANAGEMENT

13.1 Approval and Consent

13.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with International Council for Harmonisation (ICH) and good clinical practice (GCP) guidelines and according to the appropriate regulatory requirements in the countries where the study will be conducted.

13.1.2 Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted independent ethics committee (IEC) and competent authorities where applicable at each ESADA study site. Approval is required for the study protocol, protocol amendments (if applicable), Informed Consent Forms, recruitment material and patient information sheets and other subject-facing material.

13.1.3 Informed Consent

For each study patient, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Central study coordinator or its representative with a copy of the IEC-approved ICF before the start of the study.

13.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 13.3.

Clinical data will be entered by site personnel on eCRFs (Red Cap) for transmission to the central study cluster placed at Reykjavik University (RU). Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the RU must include only coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by RU. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Transfer of all study related data (sleep tests, questionnaires, data from the digital platform, clinical data in the Case Report Form, actigraphy data, telemedicine based follow up information of CPAP therapy) will be performed to the central study data server (cluster) at Reykjavik University. Data transfer agreements are already specified in the Joined Controller Agreement of the SR project signed with each study site.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs, the European Union Commissioners, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

13.4 Record Retention

Study records and source documents must be stored and saved for at least 10 years after the completion or discontinuation of/withdrawal from the study in accordance with the applicable local privacy laws, whichever is the longer time period.

13.5 Monitoring

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. The monitoring function will be organized by the study centres at Reykjavik University and Gothenburg University.

Monitoring visits, on-site or remote (telephone/video metings) and contacts will be made at appropriate times during the study. The Principal Investigator at each study site will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. If necessary, clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for patients included in the study.

The investigator at site will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

13.6 Quality Control and Quality Assurance

The central study coordinator or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to RU lies with the investigator generating the data.

RU, the EU grant provider or the central study coordinator, may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

13.7 Protocol Amendment and Protocol Deviation

13.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC for information only. The Central study coordinator will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

13.7.2 Protocol Deviations

Should a significant protocol deviation occur, the central study coordinators at Reykjavik University and Gothenburg University must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC and in accordance with applicable regulatory authority mandates is an investigator responsibility.

13.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

An independent ethics committee (IEC) at the respective study sites will review and approve this protocol and the Informed Consent Form prior to start of the study. All patients are required to give written informed consent before participation in the study.

14 REFERENCES

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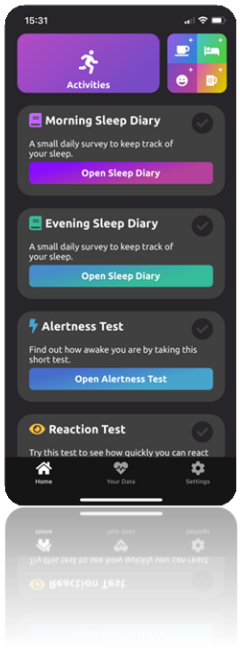
15 APPENDICES

Questionnaires used in the study

- Clinical Global Impression Scale (CGI-S and CGI-I)
- Depression Anxiety Stress Symptoms (DASS21)
- European Sleep Questionnaire (ESQ)
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- Insomnia Severity Inventory (ISI)
- Patient Global Impression Scale (PGI-S and PGI-I)
- Pittsburgh Sleep Quality Index (PSQI)
- Sleep Revolution phone App: Sleep diary and questionnaires

Detailed description of the Sleep Revolution technical applications used



THE SLEEP REVOLUTION APP AND DIGITAL MANAGEMENT PLATFORM

DESCRIPTION & SPECFICATION

Written by Anna Sigridur Islind, responsible for the digital infrastructure (WP7) in the Sleep Revolution project

The Sleep Revolution app

The Sleep Revolution is an EU-funded project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 965417. As a part of the Sleep Revolution project, we have designed and developed a mobile application (hereinafter called app) for the purpose of gathering data by research participants for six specific modules: i) Morning sleep diary, ii) Evening sleep diary, iii) Psychomotor vigilance test (flexibility game), iv) Stroop test (reaction game), v) Corsi block-tapping test (memory game) and; vi) Inspection time task (perception game). The last four modules are cognitive tests, presented to the participants as games. These six modules together, outline the basis of the app. Furthermore, the app allows the research participants to log activities (each activity has a time stamp, if used). These activities are: naps, caffeine intake, exercise, myofunctional exercises alongside questions related to that, sleep medication use, and alcohol intake as well the start of, and stop of activities related to the menstrual cycle. Moreover, the app allows the user to view the data inputted in the aforementioned modules through visualizations.

The app feeds data into a secure digital platform that has also been designed and developed as a part of the Sleep Revolution. The digital platform has two important components: a back-end and a front-end. The back-end is the data vault and that data vault, is physically located in Reykjavik University, running through a secure high-performance cluster which was bought specifically for the purpose of the Sleep Revolution project. The cluster and all data that is securely located and cared for at Reykjavik University in Iceland, is herein outlined as 'the infrastructure.' The data vault, or database, is as said earlier, located at Reykjavík University as a part of the infrastrucutre and the data from the app feeds into that particular infrastructure. Access control and security is of the high standards and is GDPR compliant. The front-end, which is accessible through a web-browser, displays data from the back-end (the data vault) after a research participant has securely logged into the digital platform. Once the research participants have logged in, they can see their own data and initiate a chat with the study coordinators, if they need assistance. That chat function is access through secure sockets. Moreover, there are additional eight cognitive games accessible through the digital platform, which the study participants have access to as well and can complete in a web-browser. An additional module with a more general sleep questionnaire to be answered by participants, will be added to the app when ready, but this module is currently under construction and is now accessible through the digital platform. This particular questionnaire is herein also referred to as the ESQ.

The data is visualized for each research participant where they can follow their own data, and only their own data. They can, as explained earlier, both see their own data in the app, but also in the digital platform as they share the back-end. The difference is that in the app, they can only see the data collected with the app whereas in the digital platform they can also see for instance

their smartwatch data collected with their Withings smartwatches, alongside the data collected through the ESQ, as well as results from their sleep study (SAS) in some cases. There are no advanced calculations, or machine learning algorithms analyzing the data from the research participants in real-time, instead the visualizations are based on simple data and presented in that way to the research participants. The data visualized, is merely a summary of the data collected through the app, coupled with the smartwatch data and other data and the visualizations do not provide any advice.

At this point we would like to forward that the Sleep Revolution app is not a medical device, nor is the digital platform connected to it; the Sleep Revolution app is a research device and so is the digital platform alongside the infrastructure as a whole. Furthermore, the app does not include any medical suggestions, nor does the digital platform. For the Sleep Revolution it is important that the research participant owns their data and is in control of their own data, and their view of the data is through visualizations. That notion follows GDPR, and the data will be stored and managed in accordance with GDPR. For those unfamiliar, GDPR is a new EU regulation (2016/679, in effect as of 25 May 2018 and forward), which takes a broader, updated view on storing personal data, in particular health data (EU GDPR Portal, 2018). GDPR is a unified regulation within the whole EU, and applies within EES as well (Albrecht, 2016; EU GDPR Portal, 2018). GDPR is the most important change in data protection and privacy since 1995, and aims to give control to citizens and as a part of that effort, control which will be implemented in this project as well and our view in the Sleep Revolution is that GDPR is one of our utmost important goals and guiding lights to follow throughout the project as a whole.

Architecture and framework

We used the React and React native frameworks to develop the Sleep Revolution app (React native for the app) and the digital platform (React within the front-end of the digital platform). These frameworks allow developers to create, test and deploy an app on multiple platforms, such as iOS and Android, with only one codebase. These frameworks are especially applicable for designing and developing apps for health purposes. The app is isolated within the operating system, either within iOS or Android and downloaded by the research participants to their phones, meaning that other apps or processes on the phone are unable to read or reach the app's data, and moreover, the app does not use cookies. The data does, however, feed into the abovementioned digital platform and is stored in the secure data vault, which feeds into the data store within the infrastructure, located physically at Reykjavík University. Currently, the app has been translated into fifteen languages. With that, we mean that all strings within the app were translated through a single file, and the language of the app can thereby be changed in settings, by the research participant.

Accessibility

Accessibility is an important factor when creating an app that is aimed at users that may have disabilities. There are many different abilities and disabilities to consider, and for each a set of design guidelines must be followed. Dyslexia and other cognitive disabilities require simple and clear language with a large, easily distinguishable and readable font; which we have ensured. Furthermore, large and reachable buttons are important for physical disabilities, such as difficulty with hand manuvering, which we also included. Red-green color blindness has a high prevalence, so to ensure inclusiveness, we have ensured that we are not too reliant on color significance. Instead, we have tried to communicate through patterns, or text with color (see Figure 1).

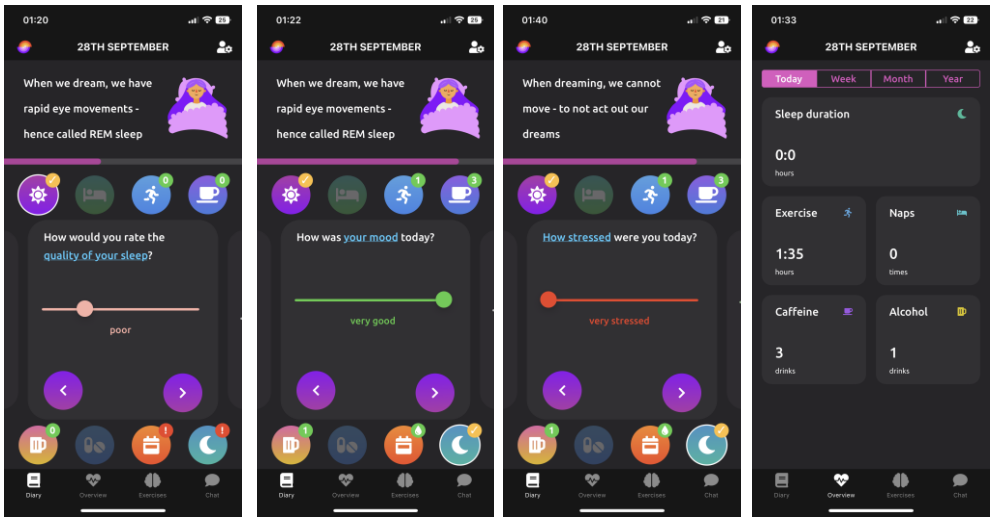


Figure 1: Selected views from the Sleep Revolution app. The app looks slightly different to the participants when they enter this particular study, due to specifics related to that particular study.

The sleep diaries

The Sleep Diaries include a set of questions, aimed to subjectively assess the participants everyday life.

Cognitive tests

The cognitive tests cover the major cognitive domains which are affected by sleep disorders. The tests are deployed through the Sleep Revolution app. The data will be transferred to the Sleep Revolution data storage within Reykjavik University. Within the Sleep Revolution app, there are

the aforementioned four cognitive tests: i) Inspection Time Test; ii) Psychomotor Vigilance Test; iii) Corsi Block-tapping Test, and; iv) Stroop Test. Each of these tests are delivered in a three-minute version and have been, in accordance to user testing, been reframed as games, as they outline gamified elements within the app while also serving as standardized cognitive tests. In the following, we will go through each to provide a short overview of its purpose.

Inspection Time Test (perception game)

The Inspection Time Test is another neuropsychological test to measure processing speed, perceptual speed, and selective attention. As this test is independent of motor speed, it is therefore applicable for testing participants with motor impairment. In the Inspection Time Test, the participant is presented with a stimulus with a long and short arm. Stimulus presentation duration is varying across trials. After every stimulus presentation, the stimulus is covered by a mask, and the participant has to decide whether the short arm was on the left or right sight by pressing the corresponding response keys. The participant is instructed that the reaction time does not matter. This test is successfully and widely used.

Psychomotor Vigilance Test (flexibility game)

This tests measures vigilance. Participants are instructed to press a key as soon as the target appears on the screen and get feedback about their reaction time or an error message if an in invalid response was given. Vigilance is one of the most affected domains by sleep disorders indicated by a large effect size. Further, impaired vigilance leads to impaired executive control. The Psychomotor Vigilance test is one of the most sensitive measurements for the impact of sleep deprivation on neurocognitive functioning. This test is presented within the app.

Corsi Block-tapping Test (memory game)

The Corsi Block-tapping tests are measurements of executive functions, more precisely working memory. The participant is presented with 9 boxes, which light up in specific sequence. Participants are asked to repeat the sequence. The test starts with 2 boxes and constantly increases the number of boxes. The participant has 2 chances for each sequence length. If one of the sequences was entered correctly, the next sequence is presented. If both of the sequences were entered incorrectly, the experiment ends. In the forward version, the sequence has to be repeated in the exact same order as presented. In the backwards version, the sequence is to be repeated in thereversed order. The Corsi Block tests are one of the most frequently used tests for evaluating the impact of sleep disorders on working memory and are therefore studied intensely in research on working memory. This test is presented in the app.

Stroop test (reaction game)

The stroop test is a frequently used test for measuring inhibitory control, selective attention, and cognitive flexibility. It requires the subject to inhibit an unwanted response and direct the attention to the task-specific goal. The test consists of three parts: In the first part, the subject is asked to read the words "green", "red", "blue", and "yellow" and the reading speed is measured.

In the second round, the colors are presented as blocks and the participant needs to name the correct color. In the last part, a color word is presented in another color, creating an incongruent condition. Here, the participant is instructed to name the color of the word and suppress naming the written word. Reliability and validity of this test are good. In the context of sleep disorders, the stroop test showed worse performance in patients with OSA. and insomnia and is therefore a good addition to this study. This test will be available in the app.

The digital platform

The General Data Protection Regulation (GDPR) allows for clarification of the rights of the participant, including helping them obtain visualizations of the information gathered about themselves in order to utilize the information to deal with their own health conditions in daily life and choose who they want to share it with. In the Sleep Revolution project, one of the aims is to investigate whether and how residents use a self-management tool including a sleep diaries (delivered through the app in the morning and evening) alongside the cognitive tasks can be delivered in a digital format, hereinafter referred to as 'the digital platform'. The app described here above, feeds data into our digital platform and that digital platform is accessible through a web application, locked with a login function.

The data that is collected through the digital platform, feeds into an infrastructure developed in the overall project (which outlines a high performance cluster, on which the aforementioned digital platform is running) and within that cluster, the data is kept safe. This infrastructure includes collection of self-applied sleep studies, (SAS), the sleep diaries delivered through the app, the cognitive tasks, the sensor data from an activity tracker (smartwatch from Withings) and the European Sleep Questionairre (ESQ). The core functionality developed is the digital platform can: a) obtain health information as the user provides, b) be available to all (universal design), c) support understanding of health information and d) handle the information in a safe and secure manner.

In addition to the app, patient reported outcome measures (PROMs) will be collected through REDCap (consent and questionnaires) on the one hand, and the digital platform (where we collect the data derived from the ESQ) on the other hand. These two complementary resources will yield data that lands in the infrastructure at Reykjavik University, in the secure data store resting at the cluster, held and maintained in Reykjavik as one of the cornerstones of the Sleep Revolution project.

Wearable devices

Within the project we will also collect physiological parameters using Withings Smartwatch, which is a wearable device placed on the wrist of the participants during the study period. The Withings smartwatch combines continuous measurements of heart rate, activity monitoring, and

includes fitness, and sleep quality algorithms. This smartwatch also contains a SpO2 sensor and three electrodes for ECG measurements. Data is collected via Withings anonymously and is automatically transferred to the Sleep Revolution digital platform that is designed and developed as a part of the Sleep Revolution project, the digital management platform is a secure, access-controlled data store resting on the aforementioned cluster, located at Reykjavik University (www.withings.com/uk/en/scanwatch).

SAS upload service to cluster

The data collected from sleep recordings will be securely transmitted to Reykjavik University in Iceland using a secure internet connection and a VPN. The data will be anonymized to protect participants' privacy. Once the data is received, it will be automatically processed using a computer program and stored in a restricted area accessible only to the authenticated SR infrastructure.

To upload the research data from the sleep recordings, researchers from approved institutions (such as Ahus) will use a secure website (within the infrastructure) that requires a password for access. This website is designed and developed to ensure that the data is protected and that only authorized researchers can access it. The data is delivered to the infrastructure and lands in the cluster after the transfer process.

To access any part of the Sleep Revolution infrastructure, including the website and virtual machines, researchers will need to log in to a VPN (Virtual Private Network). The VPN is designed to provide an additional layer of security and ensure that only authorized users can access the infrastructure.

Once the data is uploaded, researchers can work on their data using virtual machines that are only accessible to researchers from their own institution. This way, nobody outside their organization can view their data. The virtual machines are part of the SR network, which is designed to keep the data secure and prevent unauthorized access.

All of these measures have been put in place to ensure that the privacy and confidentiality of the participants are maintained, and that the data is handled in a responsible and ethical manner. The use of strong encryption, secure transmission channels, and authentication protocols will help to prevent unauthorized access or data breaches. By using this method, we can ensure that the participants' privacy is protected and the data is handled in a responsible and ethical way.

16 Timelines and practical tasks

1. Choose participants for the study
    a. Introduction letter sent
    b. Consent
    c. Research ids given to participants
    d. Hand out of logins for the platform (ESQ) and the sleep diary

2. Baseline
    a. ESQ on Platform (participant needs to login and fill out)
    b. Additional questionnaires (ESS; PSQI, ISI) + PGI-S + DASS 21 in RedCap (participant gets personalized link via e-mail to fill out)
    c. CGI-S in (could be in RedCap) (filled out by MD)
    d. Sleep studies (3-night SAS and one-night PSG or PG)
    e. Health mate app and Watch setup
    f. Sleep Revolution app and Sleep Diary setup

3. Decision about diagnosis and treatment plan
    a. Patient and sleep expert meet for explanation of the results from the diagnostic work up (only information from the first sleep test procedure – clinical routine of Sleep Revolution procedure)
    b. Diagnosis of OSA yes/no is made based on the available information
    c. Informed treatment decision of patient and sleep expert
    d. Study ends for all subjects without a sleep apnea diagnosis or those OSA patients who do not continue with CPAP treatment

4. Treatment/intervention period starts(12 weeks), only in patients with OSA diagnosis and PAP treatment indication

5. At home:
    a. Daily – fill in the sleep diary in the SR app
    b. Weekly – perform cognitive tasks in the SR app
    c. Wear the Withings watch

6. After 12 weeks treatment
    a. One-night sleep study SAS with cPAP
    b. ESQ follow up questionnaire (participant needs to login and fill out)
    c. Additional follow up questionnaires (ESS; PSQI, ISI)+ PGI-I + DASS 21 in RedCap (participant gets personalized link via e-mail to fill out)
    d. CGI-I in RedCap (could be in RedCap) (filled out by MD)
    e. Participant hands in the watch at the same time as sleep equipment and stops using the sleep diary.