Statistical Analysis Plan

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
- **SAP Version and Date:**
  2.0. dated 26th of June 2025
- **Principal Investigator WP8 study, Gothenburg University:**
  Ludger Grote, Professor in Respiratory Medicine
  Institute of Medicine, Sahlgrenska Academy
  Sahlgrenska University Hospital
  413 45 Gothenburg, Sweden
- **Principal Investigator Sleep Revolution Project, Reykjavik University**
  Erna Sif Arnarsdottir, Assoc Prof.
  Reykjavik University, Sleep research group
  Menntavegur 1 | 101 Reykjavík | Iceland
- **Chief Data and Cluster Manager, Sleep Revolution Project, Reykjavik University**
  Katrin Hera Gustafsdottir, Msc
  Reykjavik University, Sleep research group
  Menntavegur 1 | 101 Reykjavík | Iceland
- **Chief Biostatistician ESADA Consortium, Université Grenoble Alpes:**
  Sebastien Bailly, Professor
  Université Grenoble Alpes
  621 avenue Centrale
  38400 Saint-Martin-d'Hères, France

Responsible author of the statistical analysis plan: Ludger Grote

Administrative information

SAP version and date:	This SAP is version 2.0, dated June 25st 2025
Study protocol version	This SAP document has been written based on WP8 study protocol version 1.3 dated 29th of May 2023

SAP revision history:

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
[1.3]	[1.0]		First draft	28. May 2024
	1.1		Discussion Anna Sigga, Ludger Sebastien	26. September 2024
	1.2		Discussion Jan Hedner, Sebastien Bailly	January 30th 2025
	1.3		Discussed joint meeting	April 25th 2025
	1.4		Delphi round with modifications	April 25 to May 15th 2025
	1.5		Final discussion of open questions with Sebastien Bailly during the Sleep Revolution Grand Assembly meeting	June 4-5 2025
	1.6		Final discussion and amendments	June 26th 2025
	2.0		Final version approved	June 26th 2025

ABBREVIATIONS

AE	Adverse Event
ABOSA	Automatic Blood Oxygen Saturation Signal Analysis
AHI	Apnea Hypopnea Index
APP	Mobile phone application for patient reported data
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
BPM	Beats Per Minute
CI	Confidence Interval
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESADA	European Sleep Apnea Database
ESQ	European Sleep Questionnaire
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS-PSG	Self-Applied Somnography – Polysomnography
SC	Standard Care
SC-PSG	Standard Care Polysomnography
SD	Standard Deviation
SOC	System Organ Class
SR	Sleep Revolution
VIF	Variance Inflation Factor

2. Table of Contents

Content

2. Table of Contents....4
3. Study Overview....5
Background....5
Study Objective:....6
Study Design:....6
Trial Design....8
4. Study endpoints and analyses....8
Exploratory Objectives....11
5. Aims and Hypotheses....13
6. Sample Size Calculation....13
7. Randomization and Blinding....15
Blinding....16
8. Statistical Methods....16
9. Handling of Missing Data....21
10. Data Monitoring and Quality Assurance....21
11. Assumptions and Statistical Considerations....22
12. Software and Tools....23
13. Reporting and Interpretation of Results....24
14. Changes to the Analysis Plan....25
15. Appendices....25
16. Signature Page....32

3. Study Overview

Background

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.

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. 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 core metric of current OSA diagnosis, and a current review highlights the shortcomings of the AHI matrix in this context: The AHI metric has poor 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.

The “Sleep Revolution” is a major, Pan-European research project financed by the European Union Horizon 2020 program. 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 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. The SR aims to create new pathways for improved clinical practice in sleep medicine, in particular for sleep apnea management.

In this context, the current study is designed on a 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 new technologies including 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 recently developed European Sleep Questionnaire (ESQ)

The current statistical analysis plan is focussed on the predefined primary and main secondary objectives of the study (protocol version 1.3 from May 29 2023). Evaluation of all different

components of the study data will require several years of additional research and will not be captured in this document.

Study Objective:

- 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 objective: To evaluate novel Sleep Revolution diagnostic variables and their relation to symptom burden, patient´s help request during baseline assessment and outcome of sleep apnea treatment with CPAP after 3 months.
- Further secondary objectives: Feasibility and safety of the self-applied sleep testing and the digital platform for both sleep and symptom assessment

Study Design:

The study is performed at 24 sites of the European Sleep Apnea Database (ESADA) network in 15 European countries. Most relevant details of the study design are listed below:

- 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 assessment and evaluation of 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 be 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 baseline, during treatment and at 3 months follow up.
- Estimated number of patients per center to be randomized: N=42 is the targeted number per site

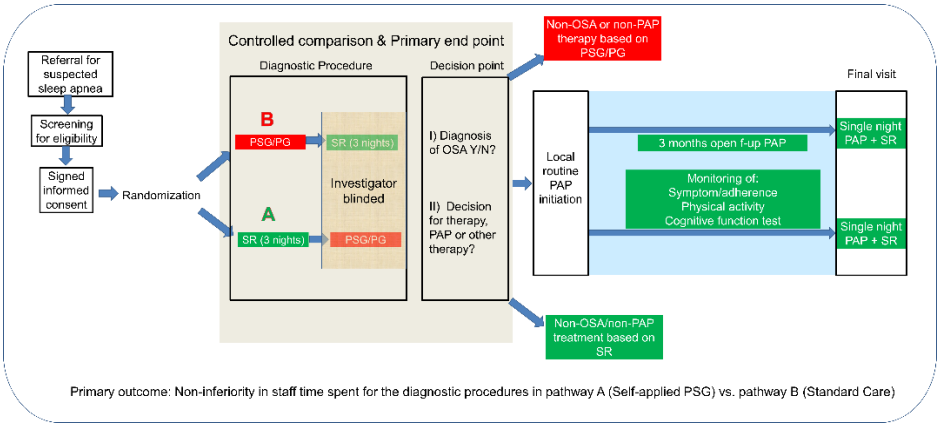
Study Population:

- 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 Central Sleep Apnea
  - 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

Study Duration:

The study started in December 2023 with the first patient inclusion and active patient assessments (last patient out) is expected in July 2025.

Figure 1: SR 001 Study Flow Chart



PSG=polysomnography, PG=polygraphy, SR=Sleep Revolution diagnostic pathway, PAP=Positive Airway Pressure treatment

Trial Design

The WP8 study is designed as a randomized, controlled, parallel-group, multi- center, multi-country, non-inferiority comparative study.

Randomisation

Eligible patients are allocated in a 1:1 ratio between Standard Care procedures and the Sleep Revolution procedure, using a randomization procedure. The randomization was performed in blocks of 4 patients. The randomization allocates the patients to the first diagnostic procedure which is also the basis of the clinical decision making. However, each patient will also be studied with the respective other diagnostic arm (SC or SR).

The randomization process is described in full within the clinical trial protocol. Details of the randomisation including the final random allocation list is held securely and unavailable to unauthorized trial personnel.

---

4. Study endpoints and analyses

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). The detailed staff time protocol is provided in Appendix A.

Secondary analyses:

General descriptive analysis of the patient population

- Description of baseline characteristics of all study participants and the two randomised patient groups (Sleep revolution group and standard care group) according to the following variables: anthropometrics, comorbidities, medications, results from questionnaire data like the degree of daytime sleepiness (ESS score) and additional questionnaire data listed below:

Description of completeness and quality of the technical data collected in the study

- Number of sleep recordings with acceptable quality for the Sleep Revolution study arm – at least 1, 2 or all three nights of Self applied Somnography (SAS-PSG),
- Number of sufficient nights in the standard care procedure (SC-PSG)

- Number and proportion of sufficient Withing Watch recordings including physical activity and photoplethysmographic data (pulse, sleep apnea assessment)
- Number of sufficiently answered data in the Sleep Revolution APP with regards to
    - Sleep diary
    - Symptom assessment
    - Cognitive test battery
    - Lifestyle information
- Number of sufficiently answered data in the European Sleep Questionnaire data,
- Number of sufficiently answered questionnaires in the Sleep Revolution platform
    - Epworth Sleepiness Scale, Insomnia Severity Index, Fatigue Severity Scale, Pittsburgh Sleep Quality Inventory, Depression Anxiety Stress Scale – short version with 21 questions (DASS21), Clinical Global Impression Scales

Capacity of the novel SR diagnostic pathway to detect clinically significant sleep apnea

Sleep apnea severity and sleep quality

SR procedure: 3 nights: Means, Minimum, and Maximum for: AHI, ODI, T90, Total Sleep Time, % sleep stage distribution, hypoxic burden assessed by ABOSA software

Standard care procedure: AHI, ODI, T90, Total Sleep Time, % sleep stages, hypoxic burden assessed by ABOSA software

"First night" and "between night" effects: Differences between nights 1, 2 and 3 in the sleep recording results, in particular night 1 versus 2 or 3. Analysis of variability: %supine position, REM-sleep%, and alcohol intake prior to sleep (dichotomic)

Frequency of OSA diagnosis in Standard Care versus SR care

Frequency of no sleep apnea, and "mild to severe" OSA according to the AHI criteria AHI<5, 5-<15, 15-<30 and ≥30 events/hour in both arms (SR and SC)

Frequency of treatment recommendations

Distribution of recommendation for PAP, OD, surgery, weight reduction, no treatment for the two randomised patient groups: Standard care versus Sleep Revolution based diagnosis

Frequency of other sleep diagnoses in Standard Care versus SR care

Frequency of insomnia, combined OSA and insomnia (COMISA), Periodic Limb Movement Disorders (PLMD), Restless Legs Syndrome (RLS)

Prespecified subgroup analyses:

- Sex, even pre-post menopause
- Technical feasibility analysis: Age stratification by tertiles
- Weight change group in the PAP follow-up study

Clinically meaningful outcomes of CPAP treatment in patients with OSA

- Adherence with and efficacy of PAP treatment

Mean values for the treatment period, variability of PAP use over time, residual AHI, leakage.

CPAP-non users: Identification of those patient characteristic: more complex analysis of predictors for PAP non -users by parameters from the diagnostic process (standard care and SR case)

- Effects of PAP treatment

Change in physiological data like AHI, blood pressure, weight, sleep test data (sleep stages, oxygenation), as well as APP derived cognitive function, and more subjective data like the ESS scores, questionnaires, and the ESQ follow up module; Sleep App parameters: overall wellbeing, treatment rating by the patient, sleep habits (diary), degree of physical activity (subjective ratings). All those data need to be adjusted for PAP adherence.

Comparison between objective changes by treatment (see point above) with patient reported perception of treatment (data from the questionnaires and APP) through descriptive analysis, correlation analysis and cluster analysis

Comparison of objective and subjective patient changes with the rating of the sleep doctors in the CGI-change by treatment scale.

Feasibility of the European Sleep Questionnaire (both technical failure and patients´ inability to perform the SAP)

- Time spent to fill in the questionnaire, even possible or subparts of the questionnaire
- Completeness of data in the ESQ
- Subgroup analysis separated by age and sex
- Patients feedback

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
- Patient centred reporting of clinical symptoms in a digital platform

The predictive value of the sleep related novel variables detected by the SR diagnostic pathway (hypoxic burden (ABOSA software), symptom burden (ESQ based data) for three months treatment outcome after CPAP therapy:

- symptom improvement following therapy: daytime sleepiness and sleep quality
- adherence with PAP treatment (hours used, number of patients with PAP adherence at least 3 or 4 hours, proportion of PAP non acceptance)
- comparison of outcomes with parameters from standard care

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) , these data are sampled only in few centers as it was not part of the mandatory protocol. Separate analysis in case of sufficient sample size of probes taken.
- Technical failure rate of respective diagnostic pathway
- Association between novel sleep parameters and biomarkers addressed in a subgroup of study centers (metabolic function, inflammation)
- Comparison of sleep test results from Standard Care and Sleep Revolution procedure for each patient where both sleep recording principles were applied (irrespective of randomisation code). Systematic comparison of OSA severity measures and sleep quality.

Safety Endpoints

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

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

Table with secondary efficacy endpoints:

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. Aims and Hypotheses

Aims

- Analyse differences in staff time associated with the SR pathway compared to Standard Care (SC)
- Apply several novel diagnostic parameters and principles which influence the predictive value of the diagnostic method for CPAP treatment efficacy, tolerance and acceptance.
- 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.
- Assess the content validity and the predictive capacity for CPAP success of the newly designed European Sleep Questionnaire (ESQ).

Primary Hypothesis:

- *The SR procedure provides more reliable and individualized health data during the diagnostic process compared with standard care without an excess of staff time.*

List of secondary Hypotheses:

- *The ESQ is able to detect treatable traits in sleep apnea patients not yet captured in standard care questionnaires.*
- *Novel biomarkers from sleep obtained by continuous and automated analysis provide information which better predicts patient outcome*
- *Self-applied polysomnography is technically feasible but successful application of the technique depends on active patient involvement/participation with acceptable technical failure rates below 10% of sleep tests.*
- *The first night effect in multiple sleep recordings on sleep apnea metrics is limited and does not systematically differ from the night to night variability between night 2 and 3.*
- *The outcome of PAP treatment is non-inferior in the SR pathway to SC pathway.*
- *Additional secondary analyses and hypotheses may be defined including separate protocols and SAP´s. Those will be reviewed and need to be approved by the SR executive committee. More details including an updated SAP will be made available.*

---

6. Sample Size Calculation

Staff time is an important factor for the clinical feasibility of a diagnostic pathway. Today's 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 patient's home compared to the single-night measures in the sleep laboratory used today. In addition, the SR pathway provides significant enhancement of clinical

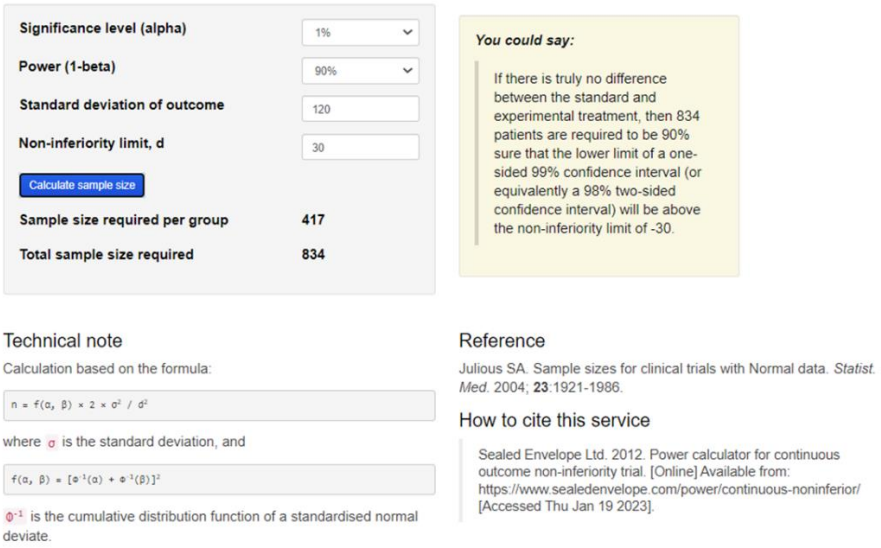
phenotyping of patient symptoms, complaints, primary request of help as well as detailed information about relevant aspects of lifestyle and personal habits (physical activity, alcohol consumption, sleep hygiene) and neurocognitive function. The gain of knowledge about the patient´s disease burden is obvious when using such a comprehensive approach. However, the actual cost in terms of staff time has not yet been 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 reduce staff time on one hand. On the other hand, user instructions to the patient for the different technologies as well as the evaluation of 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 (expert consensus) 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 measurement of staff time was performed. However, realistic estimates can be made (see table below).

Work modules	**Standard PSG**	**Standard HSAT**	**Sleep Revolution**	**Value**
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, Ferretti et al 2024), resulting in 500 patients per group.

---

7. Randomization and Blinding

Randomization Method

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, 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. The randomisation list is exemplified in appendix B.

Blinding

This is an open label, randomized, cross over study. Blinding of the clinical pathway is not possible for either the patient or 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.

---

8. Statistical Methods

8.1. General Considerations
The primary study outcome variable (staff time) will be analysed using an intent-to-treat (ITT) as well as a per-protocol analysis. Similarly, secondary and tertiary/exploratory outcome variables will be performed in the per protocol analysis cohort.

8.2. Descriptive Statistics
Describing baseline characteristics as outlined in chapter 4, such as mean (SD) for continuous variables and frequency (percent) for categorical variables, will be presented in tables and -if appropriate – in figures. These data include clinical and anthropometric data, staff time, sleep data, results from questionnaires, sleep diaries and cognitive function test results. In addition, descriptive data from the Withings Actvity-Watch will be presented in tables according to the similar principles. Descriptive statistics will be based on non-imputed data, thus the number of evaluable outcome measurements at the time of primary interest will also be presented. The rate of missing data will be also presented.

8.3 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.

8.4. Primary Analysis
Primary outcome: Staff time– comparison between standard care and the Sleep Revolution model in patients with suspected obstructive sleep apnea (OSA).

- **Primary Outcome**

The primary outcome is staff time, spent for the sleep apnea diagnostic pathway (V1a to V1 c) measured in minutes, required per patient, for the randomized study procedure (SC or SR care).

- **Study Design**

This is a parallel-group design comparing two patient groups (Group A and Group B). Patients are nested within centers, and the analysis will account for potential clustering by center. This is a non-inferiority comparison in staff time.

- **Analysis Population**

The primary analysis will be conducted on the intention-to-treat (ITT) population, including all randomized patients according to their assigned group.

- **Descriptive Statistics**

Descriptive statistics will be presented for staff time by group, including:

- Mean (standard deviation), Median (interquartile range), and Minimum/Maximum

- **Primary Analysis**

To compare staff time between the two groups while adjusting for center effects, a linear mixed-effects model (LMM) will be used:

- Fixed effect: Group (Group A vs. Group B)

- Random effect: Center (to account for clustering)

- Model specification:

$$StaffTime_{ij} = \beta_0 + \beta_1 * Group_{ij} + u_j + \varepsilon_{ij}$$

where:

- StaffTime_{ij} is the staff time for patient i in center j

- β_0 is the intercept

- β_1 is the fixed effect of group

- u_j ~ N(0, σ_u^2) is the random effect for center

- ε_{ij} ~ N(0, σ^2) is the residual error

Adjustment for potential confounders would be considered if groups are unbalanced for some covariate due to random.

- **Estimates and Inference**

The estimated mean difference in staff time between groups will be reported with 95% confidence intervals and p-values.

Model assumptions (normality of residuals, homoscedasticity) will be checked using diagnostic plots.

- **Sensitivity Analyses**

A per-protocol analysis will be conducted to assess robustness.

If the distribution of staff time is highly skewed, a log-transformation or non-parametric methods may be considered.

Two additional sensitivity analyses will be performed based on patient characteristics like A) sex and B) by the median of the age (total patient population).

Further sensitivity analysis will be performed regarding subgroups of centers and patient characteristics for sleep test methodology in the standard care arm:

- polygraphy versus polysomnography,
- home versus in lab sleep evaluation,
- manual versus automatic sleep evaluation,
- and subclassification of staff time (Technician/nurse time for patient meeting, sleep analysis, physicians time with the patient.)

8.5. Secondary Analysis

A number of secondary analyses are listed in chapter 4 and in appendix C, secondary, tertiary and exploratory endpoints. A detailed description of all these analyses to be performed in the upcoming years is not feasible for this SAP. Therefore, only a few most important analyses are described below exemplifying the advanced statistical models to be applied to the large amount of study data.

- **Example 1: Association between Overnight Hypoxic Burden and Change in ESS Score**

This section describes the analysis plan for evaluating the association between overnight hypoxic burden and the change in ESS score after 3 months of CPAP treatment in the Sleep Revolution study arm, compared to the association between AHI (single night assessment) and ESS change in the conventional management arm. Both models will be adjusted for confounders of ESS change like age, sex, BMI, AHI and ESS score at baseline.

Analysis Population: The primary analysis will be conducted on the intention-to-treat (ITT) population, including all randomized patients according to their assigned group.

Descriptive Statistics: Descriptive statistics will be presented for the primary outcome by group, including: Mean, standard deviation, Median, interquartile range and Minimum/Maximum

Primary Analysis: To evaluate the association between overnight hypoxic burden and change in ESS score, and compare it with the association between AHI and ESS change, two linear mixed-effects models (LMM) will be used:

1. Sleep Revolution Study Arm:
- Fixed effects: Overnight hypoxic burden, age, sex, BMI, baseline AHI and ESS. We will analyse the collinearity between AHI and hypoxic burden metrics. If the collinearity is very high we need to decide to use AHI or HB or we will perform an analysis by tertiles of AHI.
- Random effect: Center

2. Conventional Management Arm:
- Fixed effects: AHI, age, sex, BMI, baseline AHI and ESS

- Random effect: Center

Model specification for the Sleep Revolution and standard care study arm, respectively:
$ESS\_Change_{ij} = \beta0 + \beta1 * HypoxicBurden_{ij} + \beta2 * Age_{ij} + \beta3 * BMI_{ij} + \beta4 * SEX_{ij} + \beta5 * BaselineAHI_{ij} + \beta6 * BaselineESS_{ij} + u_j + \varepsilon_{ij}$
where:
- ESS_Change_{ij} is the change in ESS score for patient i in center j
- β0 is the intercept
- β1-β6 are the fixed effect coefficients
- $u_j \sim N(0, \sigma_u^2)$ is the random effect for center
- $\varepsilon_{ij} \sim N(0, \sigma^2)$ is the residual error

Estimates and Inference: The estimated associations between hypoxic burden and ESS change, and between AHI and ESS change, will be reported with 95% confidence intervals and p-values. Model assumptions (normality of residuals, homoscedasticity) will be checked using diagnostic plots.

Sensitivity Analyses: Sensitivity analyses will be conducted to assess the robustness of the primary analysis:
- A per-protocol analysis will be conducted.
- If the distribution of ESS change is highly skewed, a log-transformation or non-parametric methods may be considered.

- **Example 2: The above-mentioned analysis principle will apply even to the following association analyses:**

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 SaO2) 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
  - Statistical models or tests
  - Correction for multiple comparisons (e.g., Bonferroni, Holm)

- **Example 3: 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.

8.6. Exploratory Analysis

- 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

8.7. Subgroup Analysis

The following subgroup analyses will be performed for secondary and exploratory analyses:

- Males and Females in each group
- Age group 18-<45 y, 45-<65 y, 65 years and more
- Subgroups of patients studied in the standard care pathway using different settings:
  - Polysomnogrpahy (AASM level 1 and 2) versus cardiorespiratory polygraphy (level 3)
  - Home sleep testing versus in sleep laboratory assessment
  - Manual sleep test scoring versus automated scoring

8.8. Sensitivity Analysis

Sensitivity analyses for secondary, tertiary, and exploratory endpoints will be performed according to the outlines above in case of imputation of larger amounts of data (>10%), log transformation of data, or in subgroup analyses specified above.

8.9. Interim Analysis

In the original protocol, an interim analysis was planned after the first 500 patients from the 24 study centers. However, the Sleep revolution Executive Committee decided not to perform an interim analysis due to the following reasons:

- No safety objective with the new technology
- Not feasible to stop the trial over several months (already delayed due to COVID 19)
- Good recruitment over the entire spectrum of centers
- To maintain highest statistical power for the primary and secondary outcome analyses
- Risk for unbalanced recruitment in individual ESADA centers due to time delay

8.10. Imputation of missing data

In the event of missing data, standard imputation procedures will be employed to ensure the robustness of the statistical analysis. The following steps will be taken to handle missing data:
1. Identification of Missing Data: The dataset will be examined to identify any missing values in the variables of interest.
2. Assessment of Missing Data Mechanism: The mechanism of missing data (Missing Completely at Random, Missing at Random, or Missing Not at Random) will be assessed to determine the appropriate imputation method.
3. Imputation Methods:
- Mean/Median Imputation: For continuous variables, missing values may be imputed using the mean or median of the available data.
- Regression Imputation: Missing values may be imputed using regression models that predict the missing values based on other available variables.
- Multiple Imputation: Multiple imputation techniques may be employed to create several imputed datasets, which will be analyzed separately and combined to produce overall estimates. In case of Multiple imputation, the method of chained equations (MICE package in R) may be performed if needed.
4. Sensitivity Analysis: Sensitivity analyses will be conducted to assess the impact of the imputation on the results. Different imputation methods will be compared to ensure the robustness of the findings.
5. Documentation: All imputation procedures and decisions will be thoroughly documented to ensure transparency and reproducibility of the analysis.

---

9. Handling of Missing Data

- **Method of Handling Missing Data:**
  See chapter 8.10 above.
- **Sensitivity to Missing Data:**
  See chapter 8.10 above.

---

10. Data Monitoring and Quality Assurance

- **Data 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 meetings) 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.
- **Quality Assurance Procedures:**
    - 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 local 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.

---

11. Assumptions and Statistical Considerations

- **Normality Assumptions:**
  To ensure the validity of the statistical tests, the following assumptions will be tested:
  1. Normality: The normality of residuals will be assessed using the Shapiro-Wilk test, Q-Q plots, and histograms of residuals. If the residuals deviate significantly from normality, transformations (e.g., log transformation) or non-parametric methods may be considered.
  2. Independence: The independence of observations will be checked by examining the study design and ensuring that there is no clustering or repeated measures within the same group. For mixed-effects models, the random effects will account for potential clustering.
  3. Homoscedasticity: Homoscedasticity (constant variance of residuals) will be assessed using residual plots (residuals vs. fitted values). If heteroscedasticity is detected, robust standard errors or weighted least squares may be used.
  4. Linearity: The linearity of relationships between predictors and the outcome will be checked using scatter plots and residual plots. Non-linear relationships may be

addressed using polynomial terms or splines in the model.
5. Multicollinearity: Multicollinearity among predictors will be assessed using Variance Inflation Factors (VIF). Predictors with high VIF values may be removed or combined to reduce multicollinearity

- **Transformation of Data:**
  To meet the assumptions of statistical tests, data transformations may be applied as necessary. For example, if the data is highly skewed, a log transformation or other appropriate transformation will be considered to normalize the distribution. The choice of transformation will be based on the nature of the data and the specific assumptions of the statistical tests being used.

- **Outlier Handling:**
  Outliers can significantly impact the results of statistical analyses. The following steps will be taken to identify and manage outliers in the dataset:
  1. Identification of Outliers:
  Visual Inspection: Box plots and scatter plots will be used to visually inspect the data for potential outliers. Statistical Methods: Z-scores and the IQR (Interquartile Range) method will be used to identify outliers. Data points with Z-scores greater than 3 or less than -3 will be considered outliers. Additionally, data points falling below Q1 - 1.5*IQR or above Q3 + 1.5*IQR will be flagged as outliers.

  2. Management of Outliers:
  Verification: Outliers will be verified to ensure they are not data entry errors. If an outlier is determined to be an error, it will be corrected or removed. Sensitivity Analysis: Analyses will be conducted with and without outliers to assess their impact on the results. Transformation: If outliers are not errors and cannot be removed, data transformation techniques (e.g., log transformation) may be applied to reduce their impact. Robust Methods: Robust statistical methods that are less sensitive to outliers (e.g., median-based measures) may be used.
  The decision to retain or exclude outliers will be documented, and the rationale for the decision will be provided.

---

12. Software and Tools

- **Statistical Software:**
  The statistical programs SPSS and the R software package R version 4.3.1, located in a data cluster at Reykjavik University, Iceland, are available. All analysis will be performed by authorized personnel on this cluster.

- **Data Management Software:**
  REDCap and Excel are used for data management.

---

13. Reporting and Interpretation of Results

- **Presentation of Results:**
  Results will be clearly presented using tables, figures, and confidence intervals:
  Tables will summarize descriptive statistics, model estimates, and p-values.
  Figures (e.g., bar charts, box plots, scatter plots) will illustrate data distributions, group comparisons, and model diagnostics.
  Confidence Intervals (95%) will accompany key estimates to indicate precision.
  Text will highlight main findings, including any deviations or unexpected results.
  These methods will ensure clarity and support interpretation of the study's outcomes.

- **Interpretation of Results:**
  Significant findings ($p < 0.05$) will be interpreted as evidence of an association or effect, while non-significant findings will not be taken as proof of no effect but rather as inconclusive. Effect sizes and confidence intervals will be emphasized to assess clinical relevance, regardless of statistical significance.

- **Potential limitations of the Analysis:**
  This is a pan European study including patients from 24 sleep centers in 15 countries. New technology will be applied to all patients and health care professionals. The following limitations of the analysis may occur:

  - **Heterogeneity Across Centers**: Differences in referral patterns, clinical routines, experience with remote technology, and treatment traditions across the 24 centers in 15 countries may introduce variability that is not fully accounted for, potentially affecting the comparability of patient populations and treatment effects.
  - **Health System Variability**: Diverse healthcare infrastructures and access to care may influence treatment delivery, follow-up, and adherence, impacting outcome measures.
  - **Cultural and Societal Influences**: Variations in cultural attitudes toward symptoms, treatment expectations, and doctor-patient interactions may affect both patient-reported outcomes and clinician assessments.
  - **Baseline Differences**: Systematic differences in symptom burden and patient expectations at baseline between countries or centers may confound treatment effects, even after statistical adjustment.
  - **Physician Perceptions**: Differences in physician experience and perception of treatment benefits may influence clinical decision-making and subjective outcome reporting.
  - **Generalizability**: The findings may not be generalizable to settings outside of Europe or to centers with significantly different healthcare models or patient populations not studied in the current setting.

14. Changes to the Analysis Plan

- **Amendment Procedure:**
  Any changes to this Statistical Analysis Plan will be documented and reported as follows:
  1. Documentation: All changes will be recorded in a version-controlled document, specifying the nature of the change, the rationale, and the date of the change. Each change will be approved by the principal investigator and the study statistician.
  2. Reporting: A summary of all changes will be included in the final study report. Major changes will be described in detail, including their potential impact on the study results and conclusions. Any deviations from the original SAP will be transparently reported in publications and presentations of the study findings.
  3. Version Control: The SAP document will include a version history table, listing all amendments with corresponding dates and descriptions. This table will be updated with each new version of the SAP.

---

15. Appendices

- **Appendix A: Staff time protocol**

WP8 – study

Standard Operation Procedure (SOP) for Staff Time Assessment (Primary Study Variable)

This SOP for the staff time assessment includes the description on how staff time should be assessed in the Sleep Revolution WP8 clinical trial. Importantly, staff time assessment is linked to the diagnostic procedure from start to end of a particular diagnostic activity and the procedure for providing information to the patient at the end of the diagnostic process (diagnosis and treatment recommendation). Notably, time associated with information around the use or follow up of CPAP therapy as the second part of the WP8 study should not be considered in this context.

Primary study endpoint in the WP8 protocol:
"Staff time consumption for the diagnostic procedure comparing the SR assessment and the standard care diagnostic pathways – non inferiority assumption".

Estimates for the power calculation by study protocol:

The different components of the staff time to be captured are summarized in the table below (copied from the study protocol). The table was used for the power calculation of the study.

Table 3: Estimates of staff time (minutes) for the three different diagnostic principles used in the study: PSG=polysomnography, HSAT=Home Sleep Apnea Testing (Cardiorespiratory polygraphy, Sleep Revolution=Self Applied Somnography 3 nights)

Work modules	Standard PSG (minutes)	Standard HSAT (minutes)	Sleep Revolution (minutes)
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

1. **Activities <u>not</u> monitored in the staff time sheet:**

Procedures strictly linked to the clincal study protocol procedure itself but not to the clincal management of the patient

- Patient recruitment: Systematic review of the clinic referrals for potential candidates for study participation
- Patient recruitment: Introduction of the patient to the study objectives, methodologies, patient´s time to respond to questions relation to the general overview of the study procedures, time used to provide information to the patient about details about participation in the study
- Time related to the signed informed consent procedure per se
- The randomisation procedure in general

2. Sleep Revolution diagnostic arm of the study

The following working steps need to be monitored in the WP8 Study Time Sheet

a. BEFORE ARRIVAL OF THE PARTICIPANT

- Assure that information needed to complete the phone call used to recruit the participant has been recorded (some extra but useful pieces of informstion include: mail, type and brand of the smartwatch in order to determine if the device uses Android or IOS).
- Prepare the box with everything needed for the participant (including instructions, identification number, email and password for the participant's login to the app and site) on the day prior to the study.
- You can set the device (A1S) for auto start

- You may prepare the batteries but it is not recommended to put them in the device or in the pulse oximeter in order to prevent them from loosing power. Förstår inte denna mening. Är det korrekt så som nu justerat.
- CHECK AND CHARGE the Withings Scanwatch. Prepare it according to the guidelines and perform a factory reset before starting it.ember to include the charger in the bag caried by the participant.

b. DAY OF THE STUDY

- Welcome the participant
- Create and start the participant's eCRF on RedCap so you have a checklist and a possibility to note necessary information (unless you want to do the collection manually) (https://wiki.sleep.ru.is/doku.php?id=esada_instructions:timeline_esada_ecrf , https://wiki.sleep.ru.is/doku.php?id=esada_instructions:redcap_instructions#add_edit_a_record_-_for_ecrf_project)
- Configure the device (A1S)
- Complete the clinical measurements (height, weight, blood pressure).
- Briefly demonstrate the device to the participant and show where instructions may be found (both the laminated sheet and the QR code for the video instructions)
- Show the login credentials (as previously pointed out it is suggested that the username and password for the participant is printed before handing the device over)
- Assist with the set-up of the Scanwatch
- Assist with downloading and configuring the App
- If needed, show how to access the website
- Send questionnaires via RedCap (The maximum number of reminders to be send to the participant needs to be determined)
- Assure that the participant understands that there are two separate questionnaires, one on RedCap and one on the SleepRevolution web platform
- Inform the patient and arrange for the return of the device

c. AFTER THE DAY OF THE STUDY

- Monitor responses on the RedCap platform
- Monitor responses on the platform (ESQ)
- Download and upload the sleep studies

3. Clinical routine diagnostic arm at the study site

- Please follow the routines of the diagnostic procedures practiced at your clinic (e.g. in-lab PSG or polygraphy)
- . Please use the sleep diagnostic test usually applied for your local diagnostic pathway.
- Prepare the diagnostic test
- Perform diagnostic test
- Analysis of the diagnostic test

4. Meeting between sleep doctor and patient

- Review of questionnaires and sleep diagnostic report by the doctor
- Physical examination.
- Meeting of doctor and patient, clinical interview, information related to diagnosis and treatment
- Medical files: Hospital IT system as a medical note

STUDY TIME PROTOCOL (PRIMARY STUDY OUTCOME VARIABLE)

Study Site:

Patient Study ID:

Patient Initials:

Randomized to (mark correct field)
Sleep Revolution first: Standard care first:

Date of study start:

Procedure	**Time (5 minutes intervals only like 5, 10, 15 .. etc)**	**Initials**
SLEEP REVOLUTION PROCEDURE Date of start:		
Preparation of the sleep study and digital methodology, initiation of the App and the platform		
Patient instruction and handing over of A1S to the patient		
Trouble shooting and monitoring of the patient during home sleep studies		
Patient contact at return of equipment		
Upload of data and transfer to data to the medical records		
Final scoring of the sleep recordings		
Bring all data together for the patient-doctor consultation		
Additional activities not listed above		
Sum of activities in the SR pathway		
STANDARD CARE PROCEDURE Date of start:		
Preparation of the sleep study		
Ambulatory sleep study (if applicable): All procedures from welcome at the first day prior the sleep test and to the discharge after successful sleep test procedure (see also explanation text)		
In-house sleep study (if applicable): All procedures from welcome in the evening and discharge in the morning		
Upload of data and transfer to data to the medical records (see also explanation text)		
Scoring of the sleep recordings		
Assemble all data for the patient consultation with sleep doctor		
Additional activities not listed above		
Sum of activities in the routine pathway		
Communication between sleep doctor and patient		

Patient consultation with the sleep-doctor including final diagnosis and treatment decision if applicable, documentation in the medical record		
Any activity not listed above		
Sum of all activities in the study		

- **Appendix B: Block Randomisation Scheme**

  Exemplification of the randomisation scheme using a block randomisation of 4. One scheme generate by the randomisation system (RS) is visualised below.

Individual number	Type of first diagnostic procedure	Patient name	Patient date of birth
1	Standard Care		
2	Sleep Revolution		
3	Standard Care		
4	Sleep Revolution		
5	Standard Care		
6	Sleep Revolution		
7	Sleep Revolution		
8	Standard Care		
9	Sleep Revolution		
10	Standard Care		
11	Standard Care		
12	Sleep Revolution		
13	Standard Care		
14	Standard Care		
15	Sleep Revolution		
16	Sleep Revolution		
17	Sleep Revolution		
18	Sleep Revolution		
19	Standard Care		
20	Standard Care		
21	Standard Care		

- **Appendix C: List of secondary analysis projects planned for the WP8 study**

Below we listed a number of scientific projects which are planned for the analysis of the study data (non-exclusive list, further research questions under development).

Night to night variability

- Clinical phenotypes
- Sleep apnea indices including hypoxic burden measures
- Sleep quality
- Relation between N2N variability with symptom burden
- Association between N2N variability and cognitive function
- Treatable traits in patients with high and low N2N variability
- Pulse wave (PW) parameters including PW amplitude, -reflection, pulse rate

Gender and age aspects of the Sleep revolution based diagnostic and treatment pathway

Hypoxic burden – variability and association with symptom burden and treatable traits

Hypoxic burden as a predictor of treatment adherence

Cognitive function over time assessed by the SR App and relation to sleep quality, sleep apnea severity and hypoxic burden

Improvement of **cognitive function** by PAP therapy - relation to symptoms and sleep quality at baseline as well as comorbidities

Sleep quality and clinical features in **REM-OSA**

Treatment emergent central sleep apnea **(TECSA)**– polysomnographic

COMISA – diagnostic features in the WP8 study and their impact on prediction of therapeutic outcomes

Self-applied polysomnography over several nights versus long term monitoring of sleep and breathing using an **activity watch (Withings data)**

Association between symptom characteristics in the **European Sleep Questionnaire** and traditional, validated sleep questionnaires

Recognition of **cardiovascular function** during sleep in cardiovascular and metabolic disease and its modification by sleep apnea and sleep apnea therapy

Sleep health dimensions and its association with symptom burden assessed by traditional and novel symptom assessment tools (ESQ and SR App)

Sleep heath dimensions in individuals with suspected sleep apnea: detection by pulse wave analysis

Sleep irregularity/restriction in European sleep apnea patients – evaluation of the SAS nights, activity watch data and the sleep diary

Advanced sleep signal analysis (e.g. unsupervised and supervised analysis, deep learning)

- EEG multiple versus single night
- ECG analysis
- Automated versus manual evaluation
- Improved scoring of "uncertain areas" in the EEG
- Different hypoxic burden measures using different oximeters
- Pulse wave analysis for sleep staging and cardiovascular risk assessments – different analysis algorithms and their outcome
- Recognition of respiration by traditional and novel signals/parameters – accuracy, feasibility and reproducibility
- Feasibility of self-applied polysomnography – analysis of artifacts and technical failure rates in relation to clinical data and patient clusters
- Arousal burden in sleep apnea assessed by novel technology
- Assessment of ventilatory burden using different technologies and analysis algorithms
- Cardio-respiratory coupling during sleep using standard and simplified sleep parameters
- Interaction between sleep and ventilation using advanced automated algorithms
- Automated cyclic alternating pattern analysis in OSA patients – symtom associations

Comprehensive validation of the **European Sleep Questionnaire** in a population of patients with suspected sleep apnea

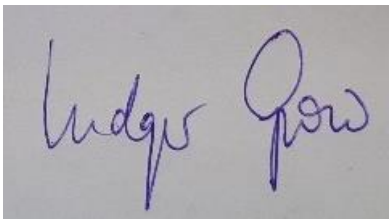
- Comparison with validated sleep questionnaires
- Regional aspects
- Gender aspects
- Age aspects

Economic evaluation of the Sleep revolution diagnostic and treatment pathway

Predicting the **change in daytime sleepiness** by OSA treatment by novel means

The relationship between **objective and subjective sleep quality** with unsupervised learning

16. Signature Page



Ludger Grote, Principal Investigator for the WP 8 (ESADA) study at Gothenburg University

Dated June 5 2025

Anna Sigridur Islind acting Principal Investigator Sleep Revolution Project at Reykjavik University, dated 26.05.2025

Katrin Hera Gustafsdottir, Chief Data Manager and Sleep Revolution Cluster Coordinator at Reykjavik University, dated 26.05.2025

Sebastien Bailly, Chief Statistical Advisor of the ESADA consortium, at Grenoble University dated