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Digital sleep clinic: assessing efficacy of continuous positive airway pressure through sleep staging via connected devices: a study protocol

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Abstract

Background Obstructive sleep apnea (OSA) is a multisystemic chronic disease with disabling symptoms, cardiometabolic comorbidities and reduction in physical activity. Continuous positive airway pressure (CPAP) is the standard treatment for OSA. Only a few studies have characterized trajectories of sleep parameters upon initiation of CPAP and these are limited to one or two nights of polysomnographic recording in a sleep laboratory. This is due to the cost of carrying out these studies and poor tolerance by patients of multiple nights of polysomnographic recordings. No study has characterized sleep over multiple nights before and after CPAP initiation, assessing the multidimensional efficacy of CPAP on patient reported outcomes, objective and subjective sleep quality, oximetry, glucose control and physical activity.

New digital technologies enable overnight sleep studies over several nights in the patient's home, with a reliability of sleep characterization equivalent to polysomnographic recording.

The primary aim of this study is to investigate objective slow wave sleep (SWS or N3) quality before CPAP and during the first month of the treatment.

Secondary objectives are to assess changes in the following parameters before CPAP and during the first month of the treatment: other objective sleep parameters and sleep stages evolution (W, N1, N2 and REM), nocturnal oxygen desaturations, 24-h blood glucose profile, daily physical activity (the daily steps count), and patient reported outcomes.

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Methods Seventy patients prescribed CPAP for OSA will be recruited at Grenoble Alpes University Hospital (France) and monitored for 5 weeks using validated innovative wearable connected devices (the Dreem 3 headband, a pedometer, an oximeter, and a continuous glucose sensor) enabling them to track their own sleep and physiological parameters at home before and after CPAP initiation.

Discussion By pooling data from the CPAP telemonitoring and other connected devices we should be able to follow the multidimensional trajectories of patients after the initiation of CPAP. This will enable us to determine whether objective changes in sleep parameters in the first few weeks of CPAP treatment are associated with improvements in daytime sleepiness, quality of life, treatment adherence, glucose control and physical activity. The data will provide integrated markers of treatment efficacy and will allow adapted personalized management of OSA in the short and long-term.

Trial registration Clinicaltrials (NCT05197855).

Keywords Obstructive sleep apnea, CPAP initiation, Connected devices, Digital health

Background

Obstructive sleep apnea (OSA) affects nearly a billion people worldwide [1]. It is characterized by repeated complete (apnea) or partial (hypopnea) collapse of the pharynx during sleep, resulting in chronic intermittent hypoxia responsible for daytime fatigue and sleepiness as well as numerous comorbidities such as the onset or worsening of hypertension, diabetes, and other cardiometabolic pathologies. Symptoms associated with OSA include snoring, daytime sleepiness, fatigue, morning headaches [2] and deterioration in quality of life [3]. OSA alters objective sleep parameters including sleep macro- and microstructure [4], and is frequently associated with poor glycemic control [5, 6] and a reduction in physical activity [7, 8].

Continuous positive airway pressure (CPAP) is the most effective treatment for patients with OSA; with over 1.6 million patients on CPAP in France [9, 10]. Randomized controlled trials have confirmed that CPAP treatment reduces OSA symptoms and improves patients' quality of life [11]. CPAP has also been shown to improve sleep quality and architecture [12–14]. These studies suggest that sleep restoration, particularly slow wave sleep (SWS or N3) and REM sleep, may be linked to improvements in memory [12], thus prompting patients to maintain long-term adherence to the treatment. The main limitation of these studies is that pre-and post-treatment sleep patterns were assessed during isolated single nights of polysomnography (PSG). Little is known about the precise trajectories of this improvement, in part due to the cost and complexity of carrying out repeated recordings, and to the low acceptability by patients of multiple nights spent in a sleep laboratory. Also, other dimensions reflecting sleep apnea burden including glycemic control, physical activity and patient reported outcomes (PROMs) [15] have been poorly evaluated over several nights and days around CPAP initiation. One can hypothesize that an improvement in sleep architecture following CPAP initiation might in turn improve PROMs, CPAP adherence, glycemic control and physical activity.

The commercially available innovative connected device the Dreem 3 headband (Beacon, Boston, Unites States), derives EEG signals allowing automatic sleep staging that has been demonstrated as being in good agreement with that measured by in-laboratory PSG [16–18]. In the present protocol we use the Dreem 3 headband in the real-life at-home sleeping conditions of sleep apnea patients during several nights before and after starting CPAP. The device enables us to characterize sleep before and after initiation of CPAP treatment, and thus the trajectories and stability of changes in sleep parameters (depending on the patient being adherent to the treatment).

As sleep apnea is often associated with the development of adverse metabolic conditions such as insulin resistance and/or type II diabetes, eliminating nocturnal desaturations and improving sleep quality should contribute to improved glycemic control [19–21]. Thus monitoring is completed by the addition of a non-invasive sensor enabling the collection of 24-h blood glucose readings [22–24]. The effect of CPAP initiation is assessed for a few nights every week during the first month of the treatment.

Over recent years, CPAP remote monitoring has transformed the management of OSA and produced a large amount of data. Accumulated CPAP data provide objective information regarding night-to-night treatment efficiency and patient adherence. CPAP efficacy is estimated through the residual apnea-hypopnoea index (rAHI) and the raw data flow curves provided by CPAP devices (allowing to validate or not the accuracy of reported rAHI) [25].

The pooled data from the CPAP device itself, the Dreem 3 headband, and other connected devices will provide original data on the multidimensional trajectories of OSA patients after the initiation of CPAP.

The primary objective of our study is to investigate the evolution of slow wave sleep (SWS or N3) before and after the initiation of CPAP treatment.

Secondary objectives will be to characterize the link between changes in sleep architecture (the other sleep stages: W, N1, N2 and REM) and the following parameters: nocturnal desaturations, 24-h blood-glucose profile, daily physical activity, the patient's perception of sleep improvement, subjective sleep quality, insomnia severity, subjective daytime sleepiness, the patient's chronotype [26], anxiety and depression, quality of life and CPAP adherence, objectively collected on a daily basis during the study.

Methods/design

Design and study setting

This is a single-center, prospective study of adults diagnosed with OSA at the Grenoble-Alpes University Hospital, France between October 2022 and November 2024. The consensual patient's care pathway is not modified, although the amount of data collected via connected devices is greater than usual and patients are required to wear and activate the devices, and to fill-in several questionnaires. The study was approved by the French bio-clinical research ethics committee (Comité de Protection des Personnes Ouest V (CPP)) on November 25, 2021. All participants are required to give written informed consent to participate in the study and for the collection and biobanking of blood samples.

Main experimental stages

Patient participation in the study requires 3 visits to the hospital.

Screening visit (V0): within 3 months before inclusion

Once a diagnosis of OSA has been made by PSG and CPAP treatment prescribed, the sleep physician informs the patient about the study and answers any questions about the objectives, constraints, foreseeable risks, expected benefits of participation in this research, and explains the patient's rights during a face-to-face consultation at the hospital. The physician checks eligibility criteria (Table 1). The patient is given a maximum of seven days before deciding whether to participate or not.

Inclusion visit (V 1): fasted and at the hospital

The patient's informed consent to participate is obtained during a follow-up consultation with the sleep physician. For the purposes of the study, the patient completes questionnaires about their quality of sleep (Pittsburg) [27], insomnia severity (ISI) [28], daytime sleepiness (Epworth) [29], morning/nightlife questionnaire (rMEQ) and quality of life (SF36) questionnaires [30] online in the secured MARS database (https://epatient.mars-database.science/). The patient is supplied with a Dreem 3 headband, a pulse oximeter, a glucose sensor, and a pedometer, shown how to use them, and given instruction and follow-up booklets. The applications for the connected devices (Dreem 3 and the pedometer) are installed on the patient's smartphone, and a de-identified account is created.

Table 1 Inclusion and non-inclusion criteria

Inclusion Criteria
- Age ≥ 18 years old
- Newly diagnosed with OSA and prescribed CPAP treatment
- Able to use connected devices, and at ease with using smartphone applications
- Wifi and internet connection at home
- Consent to telemonitoring of CPAP adherence by the homecare provider (PSAD)
- Signed consent to participate in the study
Non-inclusion criteria
- Previously treated with CPAP or another treatment for OSA (e.g., mandibular device)
- Use of stimulant drugs
- Severe chronic obstructive or restrictive pulmonary disease, with or without oxygen supplementation
- Unstable cardiovascular disease or severe heart failure requiring hospitalization within the last three months
- New York Heart Association criteria, class III or IV disease
- Pregnant or breastfeeding woman
- Individual deprived of liberty by judicial or administrative decision
- Individual under legal protection
- In an exclusion period of another study or currently participating in a drug study
- Judged not eligible for the study by the investigator, for example patient with a poor understanding of French

Fasted blood samples are collected. Glycemia, insulinemia, lipids (total cholesterol, HDL cholesterol, triglycerides, etc.) and glycated hemoglobin are measured immediately. Blood samples are bio-banked for future analyses.

Pre-CPAP period: 7 nights before CPAP initiation: at home

During the week preceding the initiation of CPAP, the patient wears the Dreem 3 headband, pulse oximeter for 7 consecutive nights, the glucose sensor continuously, and the pedometer during the day; and fills-in the follow-up logbook.

Initiation of CPAP treatment by health care provider: First month of CPAP, at home

The patient wears the Dreem 3 headband and pulse oximeter together with the CPAP device for at least:

- the first 3 nights of treatment.
- 2 nights during the second week.
- 2 nights during the third week,
- and the 2 last nights of the fourth week.

The glucose sensor is worn continuously and the pedometer is used on a daily basis throughout the study period.

End-of-study visit (V2): at the hospital

After at least one month of CPAP treatment, the headband, pulse oximeter, glucose sensor, pedometer, and logbook are returned to the investigating center. During this consultation, the patient will receive a detailed report on the evolution of their sleep and related parameters, based on data from the CPAP and connected devices. The patient will again complete the same questionnaires as at inclusion (V1) and fasted blood samples are collected for the same tests as before.

Table 2 shows the participant timeline.

Outcomes

Main outcome

Evolution of slow wave sleep (SWS or N3) recorded by the Dreem 3 headband, collected over 7 nights before and 9 nights after CPAP treatment initiation.

Secondary outcomes

Changes in the different sleep parameters and sleep stages evolution (W, N1, N2 and REM), the level of physical activity (daily steps count), glucose and other metabolic parameters (between before CPAP initiation and during the first month of the treatment).

Table 3 details the different outcomes of the study.

Description of connected devices

Figure 1 illustrates the medical devices used, when they are used and the data they collect.

- CPAP device (AirSense, Resmed, Lyon, France): This is the first-line therapy device for OSA. Daily adherence data, daily leaks, and residual AHI will be collected through CPAP telemonitoring.
- The Dreem 3 headband (Beacon, Biosignals Boston, United States) is a CE-marked health and wellness wireless device, commercially available in France.The headband is worn at home during sleep. It records, stores, and automatically analyzes EEG data in real time to characterize sleep architecture. The headband is connected to a smartphone application via low energy Bluetooth with analysis supported by artificial intelligence (AI). Every morning, data are directly and remotely accessible to healthcare pro-

Table 2 Participant timeline

Timepoint	Screening (V0)	Inclusion (V1)	Pre-CPAP (7 nights)	Under-CPAP (9 nights)	End of study (V2) (1 month follow-up)
Enrollment					
Information	X				
Informed consent		X			
Intervention					
Medical device use			X	X	
CPAP				X	
Assessments					
Questionnaire		X			X
Standardized discharge report					X
Blood sampling		X			X

Table 3 Outcomes, measurements and device used

Outcome	Parameter	Scaling	Scoring	Device or source
Primary outcome				
Change in slow wave sleep (SWS or N3) between before and after one month of CPAP treatment	slow wave sleep (SWS or N3)	Continuous (min)		Dreem 3 Headband
Secondary outcomes				
Changes in the sleep stages (W, N1, N2 and REM)	Sleep stages (W, N1, N2 and REM) Total time spent in each sleep stage	Continuous (min)		Dreem 3 Headband
Sleep parameters	Sleep times Sleep efficiency Microarousals/ arousals	Continuous (min, %, index)		Dreem 3 Headband
Nocturnal oximetry	Mean nocturnal SaO_2, Minimal nocturnal SaO_2 ODI 3%	Continuous (%)		Oxymeter, Nonin1350
Blood glucose levels	Continuous subcutaneous glucose level	Continuous (mg/dl)		FreeStyle Libre 2 (Abbott)
Daily physical activity	Steps Distance	Continuous (Steps count, km)		Garmin Vivofit 4 pedometer
Patient reported outcomes (PROMs)				
Sleep Quality	Pittsburg sleep quality questionnaire	Continuous	0 to 21	MARS database
Insomnia severity	ISI questionnaire	Continuous	0 to 28	
Daytime Sleepiness	Epworth sleepiness scale (ESS)	Continuous	0 to 24	
Quality of life	SF-36 questionnaire	Continuous	0 to 100	
Morning/nightlife questionnaire	Patient chronotype score (tendency to sleep late or rise early) measured in the morning/early evening	Continuous	16 to 86	
Treatment compliance and efficacy	Mean CPAP use (rAHI)	Continuous (h/night, events/h)		
Blood glucose	Blood glucose	Continuous (mmol/l)		Blood samples
Insulin	Insulin	Continuous (µUI/ml)		
HbA1c	HbA1c	Continuous (%)		
Lipid profile: Triglycerides, Cholesterol, LDL, HDL	lipid profile: Triglyceride, Cholesterol, LDL, HDL	Continuous (mmol/l)		

fessionals via a secured, password-protected medical platform. The main signals recorded from brain cortical activity by the six EEG dry electrodes yield seven derivations (FpZ-O1, FpZ-O2, FpZ-F7, F8-F7, F7-O1, F8-O2, FpZ-F8; 250 Hz with a 0.4–35 Hz bandpass filter) [31, 32]. The main signals recorded for brain cortical activity are six EEG dry electrodes yielding seven EEG derivations (FpZ-O1, FpZ-O2, FpZ-F7, F8-F7, F7-O1, F8-O2, FpZ-F8; 250 Hz with a 0.4–35 Hz bandpass filter) [31, 32]. The Dreem headband automatically derives sleep stages (Wake, N1, N2, N3 and REM), total sleep time and wake-after-sleep onset (WASO) (Fig. 2).

The patient will also use:

- A pulse oximeter (Nonin1350, Sleepinnov, France) to measure arterial hemoglobin oxygen saturation (SpO_2) and pulse rate. This non-invasive and portable device is commonly used in healthcare settings and by individuals at home. The measurement process involves inserting the fingertip into the device, and within seconds the readings are displayed on the screen. Data are continuously recorded throughout the night every five seconds and downloaded by using specific software (blunight reader, sleepinnov, France) at the end of the patient's study participation. The Nonin sampling time (5 s) can not be fully adjusted to the oximeter sampling recommendation of 3 s. This represents a potential limitation in the full interpretation of oximetry raw data. Oximetry data will be synchronized with the data of the headband.
- A continuous Freestyle glucose sensor (Abbott, France) to monitor glycemia by measuring real-time subcutaneous glucose levels over 24 h. The patient scans the sensor at least once every 8 h using a dedicated reader.

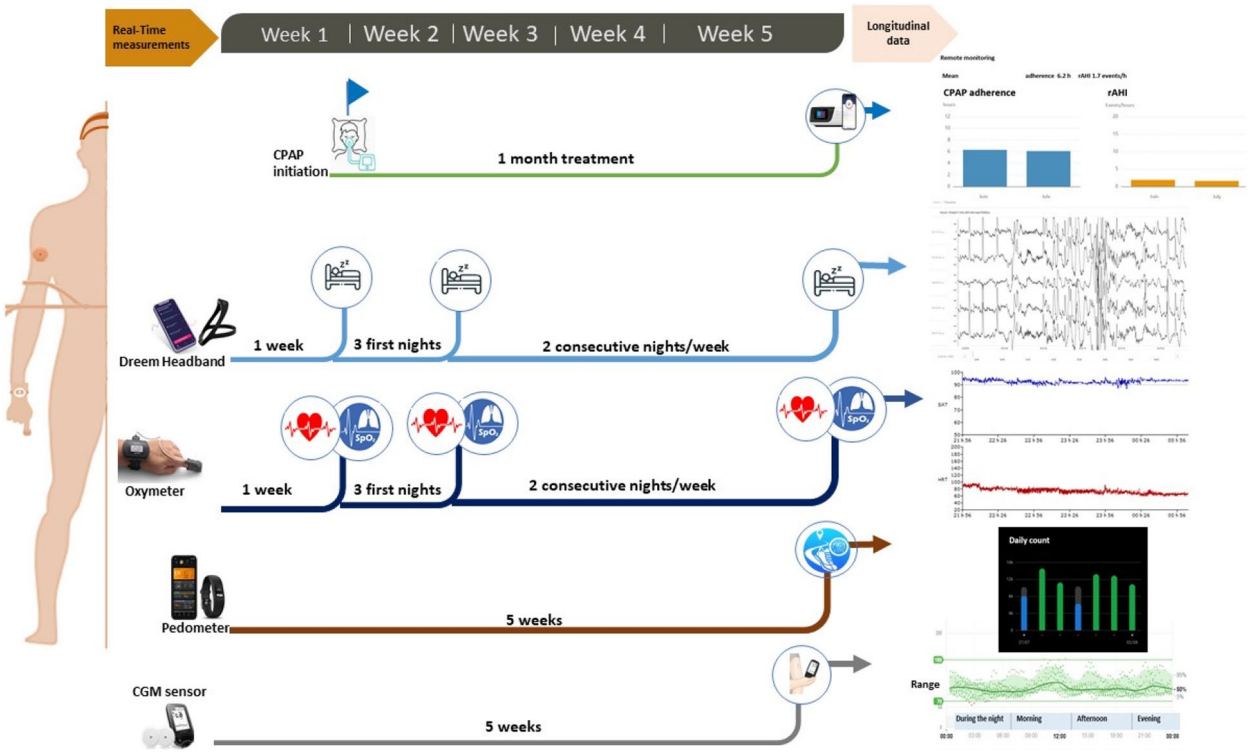

Fig. 1 Medical devices use during the study before and after CPAP initiation

Final reports are downloaded at the end of the patient's participation in the study using the reader which is connected to a secured medical platform, with a cloud-based data management solution for users of the FreeStyle Libre system (Libreview).

- A pedometer (Vivofit, Garmin, France) connected to the Garmin Connect™ phone application via Bluetooth to record daily physical activity data (number of steps and distance). Physical activity reports are readily accessible in the application.

Blood samples and biobanking

Blood samples will be collected for research purposes up to 15 mL for each visit with a maximum total over 30 consecutive days of 15 mL. The volume of blood collected respects the limitations recommended by French law for this type of study.

Authorization to collect blood samples and biobanking

The purpose of this blood sampling is to explore of the effect of CPAP treatment on cardiometabolic, inflammatory, and metabolic parameters. Collection and temporary storage (until the declaration of the end of the study) are made within the framework of this study provided the patient has given prior signed informed consent.

Where applicable, and if the patient has given prior consent for biobanking, samples collected will be stored in an authorized biobank (CRB02b AC-2021–4580) under responsibility the sponsor (in accordance with the regulations in force) at the end of the study.

Statistical analysis

Data analysis will take place at the EFCR Department of Grenoble Alpes University Hospital; and will be performed using SAS V9.4 and RStudio software under the responsibility of one of the senior co-authors (S. Bailly) an experienced biostatistician.

Statistical tests will be interpreted with the first-species risk α set at 5% in two-tailed situations.

Descriptive statistics for each parameter will be as follows:

- For quantitative variables, means, standard deviations, minimum and maximum values, medians, numbers, and numbers of missing values will be presented in tabular form.
- For qualitative variables, counts, numbers of missing values, and percentages will be presented in contingency tables.

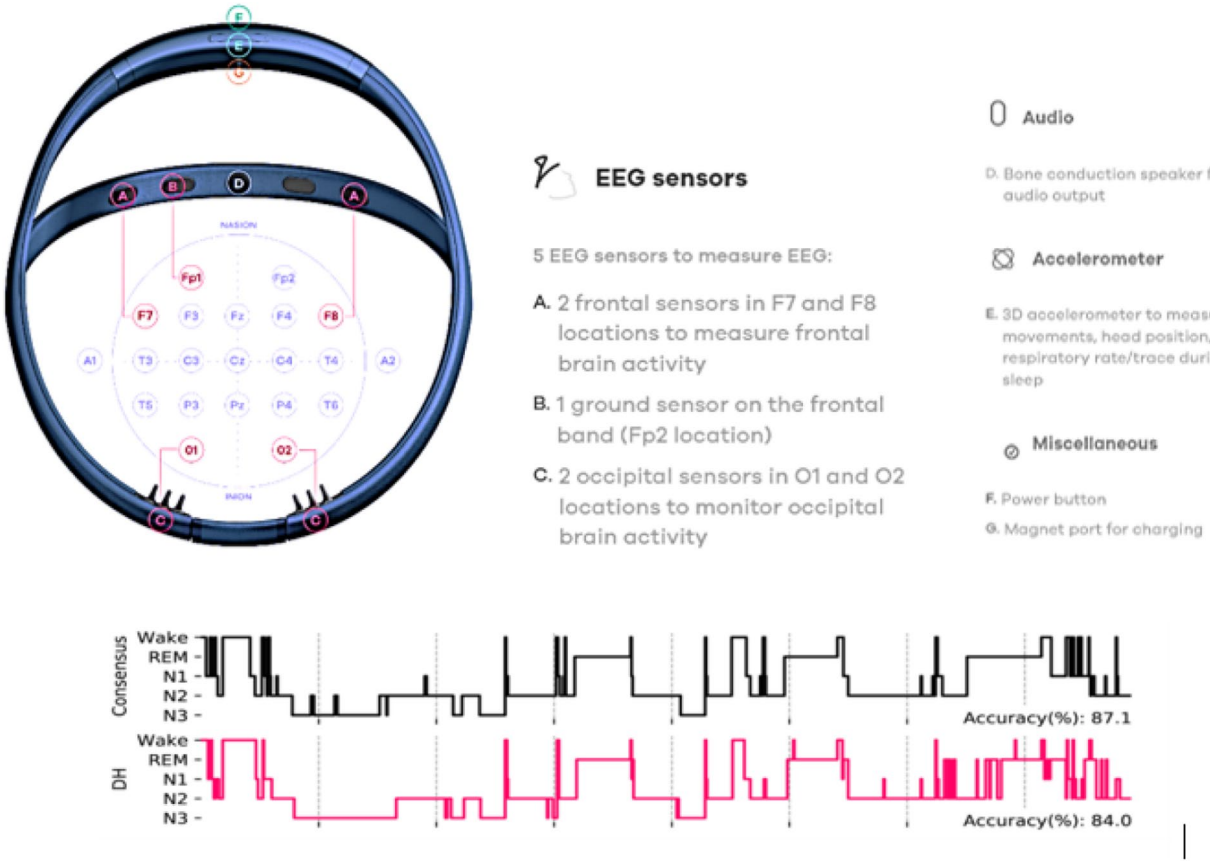

Fig. 2 The Dreem headband device

Missing data will be the subject of a specific analysis to determine the reason for any missing data and identify an appropriate imputation method.

For all objectives, quantitative (t-test) and qualitative (McNemar Chi^2) paired-data mean comparison tests will be used to compare parameter measurements before and after one month of CPAP treatment.

Analysis of primary outcomes

The comparison of slow wave sleep (SWS or N3) before and after CPAP will be carried out using a generalized linear regression model on the change in the percentage of slow wave sleep (SWS or N3) out of total sleep time (mean difference in measurements before and after 1 month of CPAP). Adjustments will be made for the main confounding factors identified by univariate analysis.

Analysis of secondary outcomes

The same approach will be applied to secondary outcomes. Analysis trajectories will be made for all outcomes, applying more advanced methodological approaches to explore the data in the form of trajectories [33].

Sample size calculation

This sample size calculation was based on the limited data available [34]. In this acute CPAP study, the improvement in N3 was closed to 10%. However, we expect to see an average increase of + 5% in slow wave sleep (SWS or N3) as a proportion of total sleep time. Assuming high measurement variability (SD = 12) and low intra-individual correlation between the two measurements (0.4), a sample size of 57 patients would enable us to demonstrate this minimal 5% difference in sleep time after 1 month on CPAP. To take into account missing data and study withdrawals (20%), a total of 70 patients will be included.

Data management

The participants' data transmitted to the sponsor by the investigators (or any other specialist) is anonymized. Under no circumstance should the names or addresses of the persons concerned appear in clear text. Individuals included in the MARS database are coded using a database number (PAXXXX), the first two letters of their

family name and date of birth (**/MM/YYYY), together with a code specific to the research project, indicating the order of inclusion.

The persons responsible for entering data in the MARS database are clearly identified in the MARS task delegation document.

The data collected may be used and transmitted for scientific purposes in the context of sleep apnea research, as well as for exploitation for regulatory submission purposes (by the study partners; in the event of withdrawal of consent, and unless otherwise specified by the patient, the data collected up to that date may be used.

Data access by study team members

All authors and medical staff implicated in this study will have access to the final and fully anonymized data set. Further access will be authorized under the supervision of the principal investigator.

Discussion and perspectives: The place of digital health in OSA management

Digital medicine currently offers new tools for the management of OSA from diagnosis to long-term follow up. The new ambulatory management pathways will provide a reliable alternative to in-laboratory sleep clinics in a near future [35, 36]. This is required to improve access to diagnosis and care, reduce waiting times, and to allow multidisciplinary integrated care supported by appropriate in-home monitoring [37].

Our study will generate a wide range of original data using in-home multidimensional multi-night monitoring. This proof-of-concept study aims to assess the interest and clinical relevance of combining several digital devices

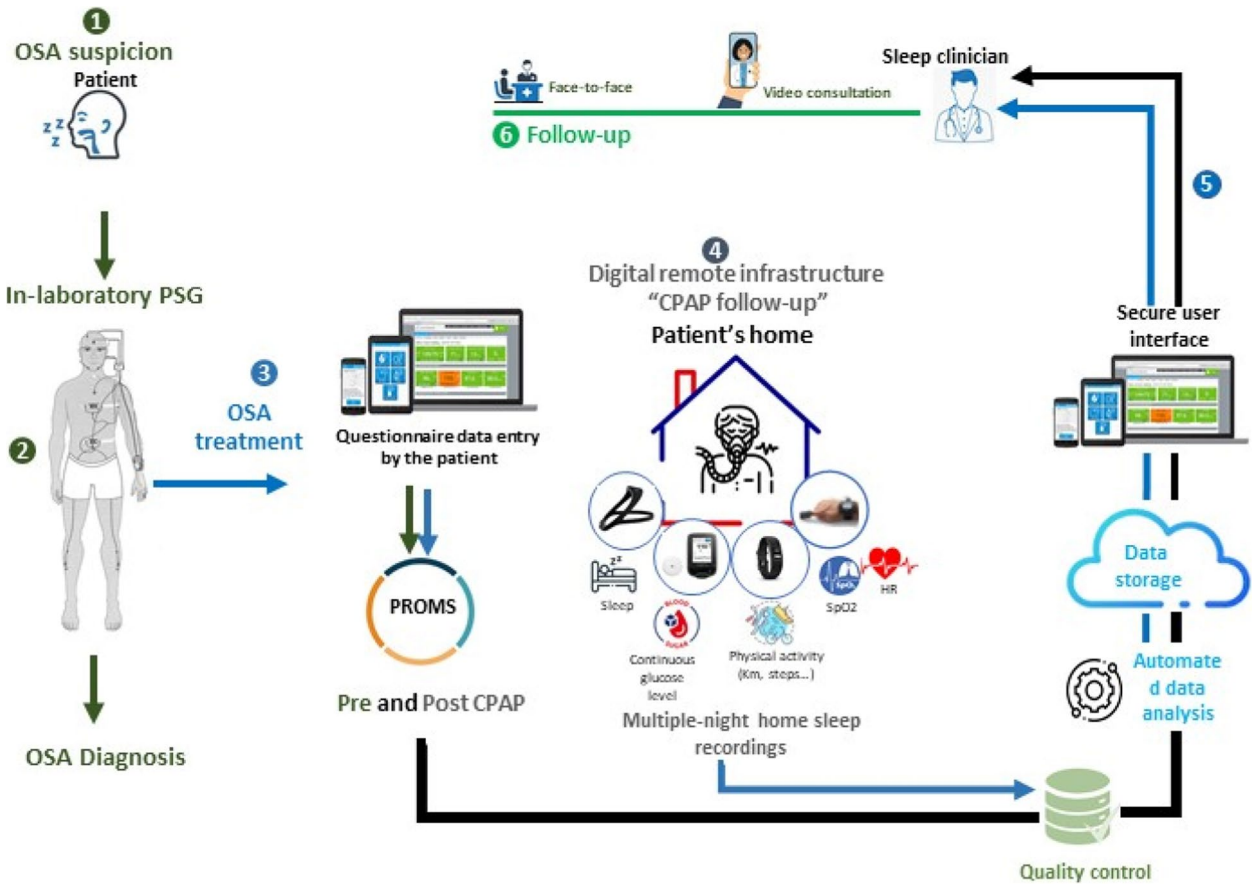

Fig. 3 The reinvented patient's pathway for OSA treatment with in-home follow-up. The virtual sleep laboratory would collect measurements made by the patient themselves such as patient reported outcome measures (PROMS), heart rate (HR), oxygen saturation (SPO_2), and physical activity over several days using innovative sensors. Data will be analyzed using automated ML algorithms with recourse to the sleep physician when in doubt. The treatment follow-up could be made at a face-to-face or video consultation with the sleep physician in the light of all available data.

Modified from JL Pépin et al. [38]

for collecting physiological parameters along with CPAP telemonitoring, and subjective measures based on patient reported outcomes.

In general, this project assesses the effectiveness and reliability of digital medicine, and whether the use of connected digital devices can be successfully integrated into the patient's routine care pathway and improve the follow-up and care of patients. As patients will have access to their own data, we hope this will increase the level of patient engagement in their long-term treatment.

Figure 3 depicts a proposal for a reinvented patient pathway for OSA diagnosis and treatment with a simplified home follow-up with expected good patient acceptance (Fig. 3).

The study findings should ultimately incite healthcare systems and policymakers to support future digital innovations and will assist researchers and clinicians in identifying and reinventing well defined pathways for personalized sleep apnea management.

Abbreviations

CPAP	Continuous Positive Airway Pressure
HR	Heart rate
LDL	Low-density lipoprotein
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
PROMs	Patient reported outcome measures
SPO_2	Oxygen saturation

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Authors' contributions
JLP is the principal investigator of the study. JLP, MJF, and RBM contributed to the conception and design of the study. JLP, SB, and RT are responsible for the inclusion of patients. RBM, RTe organized the study procedure and will carry out the clinical research. RBM and MJF wrote the first draft of the manuscript. S Bailly wrote the statistical analysis section of the manuscript. JLP, MJF, SB, and RT critically revised the manuscript for important intellectual content. RBM and SB designed the figures 1-2. All authors had full access to the study documents. All authors contributed to the manuscript revision, read and approved the submitted version.

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Availability of data and materials
The datasets generated by this study will be made available to the sleep research community.

Declarations

Ethics approval and consent to participate
The study is performed in accordance with all relevant guidelines and regulations (Declarations of Helsinki and French regulations).
The study was approved by the French bio-clinical research ethics committee (Comité de Protection des Personnes Ouest V in France (CPP)) on November 25, 2021. All participants are required to give written informed consent to participate and for the collection and biobanking of blood samples.

Consent for publication
Not applicable.

Competing interests
None of the authors declare competing interests.

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