Project "Sleep Revolution"

Clinical investigation plan for the study:

The effect of orofacial myofunctional therapy with autofeedback and the effect of anatomical and behavioral variables on adherence to orofacial myofunctional therapy in patients with mild or moderate obstructive sleep apnea (OMTAOSA)

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1 Background

1.1 Obstructive Sleep Apnea (OSA) in a clinical context

Sleep apnoea is a common disorder in the Norwegian, adult population. A Norwegian study has estimated the prevalence of OSA defined by an Apnoea Hypopnea Index (AHI) of ≥ 15 to be 8 % among adults aged 30-65 years [1]. If untreated, OSA is associated with increased risk of cognitive impairment, cardiovascular morbidity, mortality and daytime sleepiness [2].

Treatment with positive airway pressure (PAP) has been shown to reduce cardiovascular risk, to relieve symptoms and to be cost-effective in patients with moderate to severe OSA [3]. However, approximately 25% do not adhere to treatment and patients who adhere uses the machine less than prescribed [4]. Complementary, less efficient treatment modalities for OSA are: Lifestyle change [5], positional therapy [6], mandibular advancement devices (MAD) [7] and surgery [8].

Treatment with PAP is cumbersome. Accordingly, in mild to moderate OSA novel treatment options are warranted [9]. Orofacial myofunctional therapy (OMT) has in a recent Cochrane report been shown to be effective in mild to moderate OSA [10]. However, more randomized controlled trials (RCTs) with blinded assessment of end points and intention to treat design are needed. Auto-monitoring through participatory health technology is a promising method for the increase of treatment adherence[11].

Aims and hypotheses

2.1 Overall research aims

The overall aim of this study is to estimate the effect of OMT plus auto-monitoring (OMTa) compared to auto-monitoring alone. Moreover, we aim to identify anatomical and behavioural predictors of OMTa adherence.

3.0 Material and methods

The study is a single blinded RCT with blinded outcome evaluation and intention to treat analysis. The participants will know by default if they are allocated to the OMTa or waiting list with auto-monitoring during the 90-day intervention period. Blinded baseline- and outcome assessments will be performed by one doctor (Dr Feng) in Norway and one doctor (Dr Vaher) in Estonia.

3.1 Material

Patients referred to the Otorhinolaryngology department at Akershus University Hospital (Ahus), Norway and the Fertilitas Private Hospital (FPH) in Tallinn, Estonia. Eligible patients with a suspected or confirmed diagnosis of OSA will be asked to participate in this RCT. An informed consent form will be given or sent to the participant together with information to log in to the mobile application (app). The mobile app contains an electronical sleep diary based on the consensus sleep diary (appendix 1).

<u>Inclusion criteria:</u>

- Patients referred to Ahus or the Fertilitas clinic
- A diagnosis of obstructive sleep apnea according to the current International Classsification of Sleep Disorders (ICSD) version 3 criteria {Berry, 2020, The AASM Manual for the Scoring of Sleep and Associated Events: Rules`, Terminology and Technical Specifications`, Version 2.6.;, 2014, International classification of sleep disorders`, 3rd ed.}, with a respiratory event index (REI) <30.
- Not previously or currently treated with PAP or MAD
- Signed informed, written consent.
- Owning a mobile phone with software compatible for the study application

- Age ≥18 year.
- Body mass index <30
- Ability to breathe through the nose
- Ability to read and willingness to follow the protocol as described in the written consent form
- Teeth 5-to 5 should be present or fixed by prosthesis or implants.
- No botulinium toxin in facial muscles last three months

Exclusion criteria:

- Failure to fill in at least 70% of days in the electronic sleep diary provided in the mobile app for two weeks.
- Medical or psychiatric conditions which may interfere with the study protocol in the opinion of the investigator. Examples are acute psychosis, drug abuse and dementia. This will be noted in the study inclusion-exclusion document for each approached candidate for the study. The information will then be discussed in an exlusion committee consisting of dr. Skirbekk, Jagomägi, Dammen and Hrubos-Strøm.
- Tongue-tie as described below. Participants with mouth opening of <50% with the tip of the tongue at the incisive papilla compared to total mouth opening will be excluded.

Inclusion criteria will be assessed by the otorhinolaryngologist establishing an OSA diagnosis or the project co-ordinators.

3.2 Methods

Prior to the baseline consultation

All participants will receive a standardized information sheet with login information to the electronic sleep diary. Support on using the application prior to the baseline evaluation will be available by the study co-ordinators by telephone. Evaluation of exclusion criteria will be assessed prior to- or at the baseline study visit. Excluded patients will be referred back to clinical care. Signed informed consent will be obtained and archived on paper.

Baseline evaluation

Eligible candidates completing auto-monitoring less than 70% of the days prior to baseline assessment will be excluded (see exclusion criteria above). Questions related to the "Sleep Well" application will be answered. Dr. Feng and Dr. Vaher respectively will also ensure that at least 40 of 100 participants are female. After final inclusion, Dr. Feng and Dr Vaher respectively will schedule the sleep registration and an outcome evaluation session 90 days later. All data collected during the baseline evaluation will be collected in the "Redcap" case report form (CRF).

Further, clinical evaluation will consist of height, weight, standardized blood pressure and a breath holding test [12]. Digital oral scanning will be obtained at both sites. Thereafter, the quantitative scores (OMES) for assessing the myofunctional therapy will be performed and video filmed with one front camera and one camera with a 45-degree angle on the face. The purpose of the video filming is inter rater reliability analyses. All participants will be placed in a chair without arm- or backrest. Body posture on the chair will not be corrected. The baseline assessment will last approximately 90 minutes.

<u>Baseline assessment includes:</u>

- ***OMES-protocol***Appearance/Posture: face (symmetry), cheeks, mandible, lips, tongue and hard palate. Mobility: Subjects will be asked to perform 4-6 movements with each component of lips, tongue, cheeks and mandible.
- Functions: breathing mode, deglutition and mastication.
- The maximum possible score for functions will be 29 (breathing=3, deglutition=16, mastication= 10).
- Tongue movement described in the OMES protocol.

- ***Additional tongue assessment***: Evaluation of tongue tie using the quick-tongue tie assessment tool for measurements of Maximal interincisal mouth opening (MIO, mm) and interincisal mouth opening with tongue tip to maxillary incisive papillae at a roof of the mouth (MOTTIP) .

- ***Oral scanning***: 3D dental scanning will be performed at both sites. Pseudonomized electronic files will be analyzed with the "Dolphin®" software (Dolphin Ceph Tracing | Dolphin Imaging Software) in Estonia.
- ***Height measurement:*** The participant will be asked to stand barefoot in an upright position with their heels, buttocks, and upper back up to the wall and their head facing directly ahead. Feet together and arms by the sides. The distance from the floor to the highest point of the head will be measured by the nearest 0.1cm. The total height (cm) will be recorded.
- ***Weight measurement:*** The participant will be asked to step barefoot on a stand-alone unit with a digital scale. The Body mass will be measured with an accuracy of 100g. Participants will be asked to remove shoes and socks as well as heavy jumpers/jackets/jeans. The total weight (kg) will be recorded.
- ***Body Mass Index (BMI): BMI will be calculated by*** the formula of body mass (kg) divided by height squared (m^2) (kg/m^2)
- ***Waist Hip Ratio:*** Waist and hip circumference will be assessed in manual measurements with flexible but non-stretchable tape with an accuracy of 1mm. The waist circumference will be measured at the midpoint between the last rib and the Iliac Crest. The hip circumference will be measured at the level of the largest lateral extension of the hip. Both measures will be assessed in the horizontal plane. The waist and hip circumference will be recorded and the Waist Hip ratio will be calculated using the formula of waist circumference divided by hip circumference.
- ***Neck Circumference:*** Neck circumference will be measured with a flexible but non-stretchable tape measure with an accuracy of 1mm. The neck circumference will be measured in the midway of the neck, between the mid-cervical spine and mid-anterior neck. The subject will be asked seat relaxed with the arms hanging by their side and to maintain the head in the Frankfort Horizontal plane. For men, the measure will be taken immediately superior to the Thyroid cartilage (Adam's apple). The total neck circumference will be recorded (cm).

Hand grip strength[13] assessed by hand dynamometry of the dominant hand will be evaluated with a Jamar hand dynamometer (Jamar Hydraulic Hand Dynamometer (5030J1) | JLW Instruments (jlwforce.com)). The grip strength

will be measured in a face-to-face assessment with the participant sitting on a chair with a back support and fixed arm rests, feet on the ground. Their wrist should be just over the end of the arm rest, with the thumb facing upwards. The examiner should encourage the participant to squeeze as long and as tightly as possible until the needle stops rising. The measurement from the dial should be recorded to the nearest 1kg. If the participants arm rises above the chair the measurement should be disregarded. Three measurements will be recorded for each hand, while alternating sides (Procedure for measuring gripstrength using the JAMAR dynamometer (uhs.nhs.uk)).

Chewing test

A standardized chewing efficiency test is performed with the CHEW Box Digital Reporting services (DRS CHEW box) from Orehab Minds (https://www.orehab-minds.com/). The patient is instructed to perform 9 chewing sequences with standardized gelatin test units of soft, medium and hard consistency. Each sequence consists of chewing for 30 seconds with 30 seconds intermission, first only on the right side, next only on the left side and last on both sides, alternating every 5 seconds. Participants will be instructed to "divide as many pieces as you can". The chewed-up pieces of the test unit are spitted out in a sieve, rinsed and distributed on a plate which is placed inside the DRS CHEW box. The box takes a picture with standardized lighting, angle and camera distance. The 9 pictures from each chewing test are uploaded to a central database where they are analyzed. No identifying patient data is stored in this system. This results in a report where number of particles, average size, and distribution ratio of particle size is calculated. A comparison of chewing efficiency differences between sides and consistencies is presented both graphically and numerical, and is compared to a normal distribution for healthy adults.

The Iowa oral performance instrument (IOPI), https://iopimedical.com/, is used to measure the pressure of anatomical structures in the oral cavity. The calibration of the device was tested against another device in January 2022. Tongue strength will be assessed at baseline and after 12 weeks of OMTa. The subject will be instructed to place and press a disposable, standard-sized bulb as hard as possible with the tongue against the roof of the mouth for 2–3 seconds. The maximum pressure is demonstrated as tongue strength in kilopascals (kPa). After obtaining the measured value, the measurement will be repeated two additional times and the highest value will be scored. In addition, the subject will be instructed to maintain 50% of the highest pressure as long as possible. The maintained duration of time will be recorded as tongue endurance.

Lateral cephalography is applied to assess the oral maxillofacial anatomy. Participants are asked to relax their face and mouth, keep the teeth in centric occlusion, swallow once and hold the tongue in the position. The cephalograms are taken at 73 kVp and 15 mA, in natural head position with the patinet' sagital plane parallel to the X-ray film and the Frankfort plane parallel to the floor. Dr. Feng will trace all the required landmarks on the cephalograms. This preliminary cephalometric study mainly focuses on anatomical variables related to OSA. Four variables related to tongue morphology will be registered. In addition, hyoid position will be represented by the distance between the hyoid bone and the mandibular plane.

Patient reported outcomes collected during baseline evaluation:

The BEAMER questionnaire is being developed in a current, large study funded by the innovative medicines initiative. The core version consists of one visual analogue scale assessing general health, three questions assessing control and three questions assessing acceptancy.

The Epworth sleepiness scale (ESS) is a 8-item measure of daytime sleepiness. The questionnaire has been validated in a Norwegian population[14].

The physical health questionnaire (PHQ) is a 9-item measure of depression[15]. The questionnaire has been validated in a Norwegian population [16].

The General anxiety Disorder (GAD) questionnaire is a 7-item measure of anxiety [17]. The questionnaire has been validated in a Norwegian population [18].

The DS-14 questionnaire is assessing type D personality. The questionnaire has been validated in the Akershus Sleep Apnea Project [19,20].

Wearable technology

All participants will be asked to wear a Withings Scanwatch, https://www.withings.com/be/en/scanwatch, programmed in research mode. The research mode setting implies that the watch operates as a sensor. The patients can monitor their own sleep quality data inside the Withing's mobile application. Participants will be instructed to open the Withings application daily.

Randomization

At the end of the baseline consultation participants will be randomized to either OMTa or only auto-monitoring. Block-randomization with 10 lots per block, per study site, and a 50/50 allocation ratio will be used for waiting list and intervention and separated by sex in order to monitor the 40/60 gender balance. The lots will be made as a code on paper and concealed in opaque envelopes at each study centre. Each participant will also receive a unique e-mail address and a password in the same envelope. The randomization envelopes will be made and mixed by dr. Feng. Envelopes will be sent to dr Vaher in Estonia. Both researchers will be blinded for the content in the envelopes.

After baseline evaluation:

Polysomnography (PSG)

All patients, both intervention and waiting list group, will administer three nights of self-applied PSG (hereinafter called SAS). This is an alternative to in-lab services and PSG setups, in a self-applied form. The EEG is located only on the forehead (F-channels), with no electrodes located on the top of the scalp (C-channels) and back of the head (O-channels) as in traditional PSG[21]. The self-applied setup facilitates

the use of multi-night studies to capture night-to-night variability and the participants apply the sensors themselves, using an instructional video provided by Nox. In this study, we will do three nights in a row twice. PSG will be performed before the baseline consultation and before the outcome evaluation. The equipment will be given out at baseline consultation. After use the patients will mail the equipment back to Ahus/FPH or bring the equipment back to the first treatment session.

Outcome variables derived from polysomnography

The desaturation severity parameter (Des Sev) was introduced by Kulkas et al in 2013 [22]. We have recently validated this variable with traditional variables such as the AHI, oxygen desaturation index, time below 90% saturation and nadir saturation, all assessing OSA severity [23].

Sleep efficiency (SE) will be calculated as the scored total sleep time divided by the total sleep period (TST). TST is defined as time from "lights out" to "lights on" divided by scored total sleep time. Sleep will be scored in accordance with the current version of the American Academy of Sleep Medicine (AASM) manual (version 2.6, 2020)[24]. The scoring will be done by expert sleep technologists at Reykjavik University Sleep Institute, using Noxturnal Research (version 6.1.0.30257). The following adjustments are needed for the SAS electroencephalography (EEG) signal:

-The low pass filter setting for the EEG will be changed from 0.3 Hz to 0.5 Hz.

-The peak to peak amplitude of the slow wave activity will be changed from 75 µV to 50 µV. Moreover, in the standard PSG, signals are measured over the frontal regions and referenced to the contralateral ear or mastoid (F4-M1, F3-M2). In the SAS it is referenced to the average of E4 and E3. The frontal filter available in the software will not be used.

-The frontal electromyography (EMG) does not show loss of tone in REM in the same manner as chin EMG. This means that REM rules that refer to chin tone are not useable for the most part. But it is however possible use the EMG frontalis to aid in scoring arousals (in rapid eye movement (REM) in particular). Arousals in REM will be scored if there is an abrupt change in the EEG to faster frequencies accompanied by an increase in EMG tone as in the AASM scoring rules.

Participatory health technology

The auto-monitoring application is named "Sleep Well". The application communicates with a data cluster located in Iceland. The Sleep Well application contains a sleep diary[25]. The diary is inspired by the consensus sleep diary developed by Carney and co-workers (appendix 1)[26]. Subjective, quantitative sleep data including sleep efficiency will be calculated based on the formulas proposed by Reed and co-workers [27]. Exercises will be reported in an exercise diary in the sleep well application. A simple question for each of the three daily exercises will be delivered. Adherence to exercises will be assessed by the number of entries to the three daily questions. Administrative co-ordinators will support participants with technical issues.

Patient reported outcomes (PROMs) delivered by the "Sleep Well" application

The European sleep questionnaire is being developed in the Sleep Revolution project. A prototype of the questionnaire has been uploaded as a separate attachment.

Neuropsychological tests delivered by the "Sleep Well" application

Within the SleepWell application there are four cognitive tests which combined cover the major cognitive domains which are affected by sleep disorders. The data from these, will be in the same manner as other data from the SleepWell app, be transferred to the Sleep Revolution data storage within Reykjavik University in Iceland. The four cognitive tests are: i) Inspection Time Test; ii) Psychomotor Vigilance Test; iii) Corsi Block Test, and; iv) Stroop Test. In the following, we will go through each to provide a short overview of its purpose.

Inspection Time Test

The Inspection Time Test is another neuropsychological test to measure processing speed, perceptual speed, and selective attention. As this test is independent of motor speed, it is therefore applicable for testing participants with motor impairment. In the Inspection Time Test, the participant is presented with a stimulus with a long and short arm. Stimulus presentation duration is varying across trials. After every stimulus presentation, the stimulus is covered by a mask,

and the participant has to decide whether the short arm was on the left or right sight by pressing the corresponding response keys. The participant is instructed that the reaction time does not matter. This test is successfully and widely used.

Psychomotor Vigilance Test

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

Corsi Block Test

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

Stroop test

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

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

The completion of the tests will be voluntary in this study. Participants will be asked to perform the tests three times during the 90 day study period.

Description of the intervention

Participants opening a code unlocking the OMTa treatment module of the application will be given a direct communication link to the PhD students, Diana Hansen (Norway) and Andres Koster (Estonia) and two research co-ordinators. Dr. Hansen and Andres Köster has obtained an Academy of Orofacial Myofunctional Therapy (AOMT) certification diploma. One physical start up session will be scheduled at Ahus and at North Estonia Medical Center. This 60 minute session will be used to instruct participants in OMT exercises and use of the app. All participants will receive a disposable toothbrush and standardized balloons. After that, biweekly video sessions (time 20-30 min) will be scheduled. The exact same amount of sessions and equipment will be offered to the waiting list group after the outcome evaluation. The following exercises are pre-recorded and presented in the treatment module:

Tongue

1. Tongue brushing: Brush the superior and lateral surfaces of the tongue while fixing the tongue in different positions of the mouth. Repeat each movement for five times, three times a day for 14 days.

2. Tongue sliding: Place the tip of the tongue against the hard palate behind your upper front teeth. Slide the tongue backwards along hard palate. Repeat 20 times, three times a day.

3. Tongue suction: Suck the entire tongue upwards against your hard palate and press upwards. Both short and long pressure intervals. Repeat 20 times short, 20 times long, three times a day.

4. Tongue down: Force the back of the tongue down against the floor of the mouth. Keep the tip of the tongue in contact with the lower front teeth. Repeat 20 times, three times a day.

Soft palate

1. Elevate soft palate and uvula whilst saying ”ah” both intermittently (”a -a -a”) and continuously (”aaa”). Repeat 20 times, three times a day.
2. Balloon blow: Inhale through your nose, blow into a balloon with force. Don´t take the balloon off your mouth and repeat blowing for five times, three times a day.If socially not acceptable to blow the balloon, blow air through pressed lips five times. Please blow the balloon in the morning and evenings.

Facial

1 Put your finger in the oral cavity against your cheek. Pull against your finger with the cheek muscles. Repeat 10 times on each side, three times a day. If socially not acceptable to put the finger in the mouth, blow air from cheek to cheek. Please use finger in the morning and evenings.
2 Air pump: Blow air against your cheek while alternating sides. Keep lips closed. Repeat 10 times on each side, three times a day.

The list of exercises is a revised version of the protocol published by Guimaraes et al in 2009 {Guimaraes, 2009, Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome@@shared-groups}. Time per set of exercise is 10-15 minutes. The intervention will be ongoing for three months (12 weeks). Progression in exercises, subjective sleep parameters and treatment adherence will be evaluated in video sessions with the PhD students at respective locations. Problems will be solved with joint video sessions with the participant, the PhD student and an experienced OMT therapist.

Description of waiting list, auto-management condition

Participants receiving a code not unlocking the treatment module will have full access to all other parts of the mobile app. After 90 days, during the outcome evaluation, all participants will receive a new code unlocking the treatment module in order to keep outcome evaluators blinded.

Outcome evaluation

At outcome evaluation (estimated time 60 minutes), Dr. Feng (Norway) and dr. Vaher (Estonia) will repeat the following assessment from the baseline evaluation: A clinical evaluation will consist of height, weight and standardized blood pressure. Thereafter, the quantitative scores (OMES) for assessing the myofunctional therapy and patient reported outcomes will be repeated (see above). Finally additional repeated diagnostics with the hand dynamometer, chewing test and IOPI will be repeated. All data will be collected in the "Redcap" CRF.

Finally, each participants will be given a maximum of five feedback questions. The exact phrasing of the questions will be finalized when answers to similar questions in a pilot study have been analysed. The brief interview will be audio taped and transcribed.

Outcomes

The primary end point of the RCT is change in the AHI

Secondary endpoints:

1. Change in the Epworth Sleepines scale and PROMs in the European Sleep Questionnaire.
2. OMTa adherence
3. Change in other conventional OSA severity indices (oxygen desaturation index, time below 90% saturation, nadir saturation) and change in novel OSA parameters in SAS identified in the development phase of the project.
4. Change in objective and subjective sleep quality (PSG and sleep diary, respectively).
5. Change in physiological parameters assessed by wearables.
6. Change in objective daytime functioning testing (PVT and Stroop test).
7. Change in self-reported self-efficacy as assessed by the PAM.
8. Changes in the Orofacial Myofunctional Evaluation with Scores (OMES).
9. Changes in the IOPI strength and endurance
10. Changes in hyoid position as assessed by a lateral cephalogram
11. Prediction of improvement in SDB severity by objective parameters from a 2D cephalogram obtained at baseline.

5 Procedures

5.1: Responsibility

Participants of the study will be transferred from regular clinical practice to the research project for 90 days. During this period, the national project leader is medically responsible. Breaches of the protocol will be systematically addressed and reported to a hospital appointed monitor at the division of surgery. After the 90 days outcome evaluation, all participants will allocated to an open label follow-up condition. The frequency of follow-up consultations is dependent on future funding. During follow-up, participants of the waiting list, auto-management condition will be offered up to 10 video recordings free of charge with the PhD student. All participants will have unlimited access to the auto-monitoring platform and the intervention module during follow-up.

Cumulative safety information

OMT consists of exercises of tongue / lip muscle. There is no physical injury recorded but the therapy involves the use of time for training. Patients who will not master or have the effect of treatment may experience this as a burden.

Cumulative efficacy information

The concept of orofacial myofunctional disorders (OMD) refers to the abnormal resting posture of the orofacial musculature, atypical chewing, and swallowing patterns, dental malocclusions, mouth breathing, blocked nasal airways, and speech problems This novel paradigm defines OSA as an OMD developing from early childhood. OMT aims to re-educate the movement of muscles, restore correct swallowing patterns, and establish adequate labial-lingual postures.

Recent systematic reviews of the effect of OMT on OSA conclude that OMT as a participatory health intervention is promising as mono therapy in mild to moderate disease, and as an adjunct to other therapies in moderate to severe disease. However, the need for further studies is also highlighted due to the small

number of studies available, heterogeneity of interventions and high risk of bias with low quality of evidence [9,28,29].

5.2 Time frame

Data will be collected from August 2023 until August 2024.

6 Statistical analysis plan and power calculation

OMTa adherence will be dichotomized by performance of ≥85% of exercises in three domains based on the electronic exercise diary. Patients non fulfilling these criteria will be classified as OMTa non-adherent[30]. Results will be analysed as intention to treat regardless of OMTa adherence.

6.1 Statistical analysis

The Kruskal-Wallis test will be used for intergroup comparisons at each time point (T1 and T2). Intragroup comparisons will be performed by the Friedman test.

Inter-examiner agreement of OMT measurements will be determined by intraclass correlation coefficients (ICCs) and weighted kappa coefficient (Kw'). Effect sizes for statistically significant differences between T1 and T2 will be calculated using the Cohen's d statistic.

6.2 Power calculation

The number in each group is calculated to N=50 based on the results of Guimaraes et al[30]. The AHI was used in the calculation.

Independent samples t-test, two-sided, anticipated effect size (Cohen's d) 0.8 (high), power ≥80%, probability level 5%. This gives a minimal sample size of 26 per group. The expected drop out of patients during the OMTa trial is 25% corresponding to a total of 20 patients. To accommodate for this potential dropout and to have adequate power for subpopulation analysis for gender, the sample size was increased to 100 (50 in each group).

7 Costs/finance

Horizon 2020, grant number 965417

8 Ethical aspects

Study management, study monitoring, data and sample management

The study site will have a designated study coordinator and ethical guardian who will be appropriately trained and informed about the nature of the study, ethical and data security aspects; including informed consent, good clinical practice (GCP) and applicable regulatory requirements.

All clinical patient source data will be stored at the hospital according to clinical routines. The project leader will be responsible for the "code key" with which it is possible to connect the data to the patient and this data will be kept offline.

Regulatory / ethics status

The following directives will be applied: Good Clinical Practice (GCP) rules according to the declaration of Helsinki.

The ASAP Clinical Cohort has appointed a user representative from the Association for Sleep Disorders in Norway. The same representative will be invited to provide end user feedback in this study.

9 Spread of results, international collaboration and end of project

Results will be published in international, peer reviewed medical journals in accordance with the international committee of medical journal editors (ICMJE) criteria, https://www.icmje.org/. The international collaborators, Hanna Mäkinen and Triin Jajomägi are involved in training and supervision of the PhD student respectively. They will be involved in data analysis inside the Tjenester for Sensitive Data (TSD) platform. The project will end on February 28th 2025, data will be stored for an additional 5 years.

10 Appendix

1 Paper version of sleep diary

SØVNDAGBOK

Navn: Spørsmål 1 til 4 fylles ut før sengetid, resten av skjemaet fylles ut om morgenen. Husk å notere dato.

Dato:	Eksempel 30.08.19	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
1. Hvordan har du fungert i løpet av dagen? 1 = veldig bra, 2 = bra, 3 = verken bra eller dårlig, 4 = dårlig, 5 = veldig dårlig	4							
2. Aktive mestringsstrategier for dårlig dagfunksjon: a. Antall minutter korte lurer/hvile med lukkede øyne b. Ca antall gjesp i løpet av våkentiden c. Minutter bevegelse for å aktivere våkenhetssystemet	 10 min 10 2							
3. Har du tatt sovemedisin og/eller alkohol som hjelp til å sove? Notér medikament, samt evt alkoholinntak	1 Imovane 1 glass rødvin							
4. Når gikk du til sengs? Når skrudde du av lyset?	22.30 23.00							
5. Hvor lang tid tror du det tok å sovne?	45 min							
6. Hvor mange ganger våknet du i løpet av natten?	3							
7. Hvor lang tid tror du at du totalt var våken i løpet av natten?	30 min							
8. Når våknet du opp om morgenen uten å få sove igjen? Notér tidspunktet for din endelige oppvåkning.	06.15							
9. Når stod du opp?	06.40							
10. Hvordan vurderer du nattens søvn? 1 = veldig lett, 2 = lett, 3 = middels, 4 = dyp, 5 = veldig dyp.	1							

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