-Adherence and preference of Continuous Positive Airway Pressure versus Mandibular Advancement Splints in Obstructive Sleep Apnea patients: a randomized trial

This is a proposal for a multi-centre trial (three centres) to compare the adherence of the two main therapies used for the management of obstructive sleep apnea (positive airway pressure therapy – PAP, and mandibular advancement splints – MAS). This study consists of a randomized cross-over trial followed by an observational trial. It will assess in 60 participants the adherence to PAP and MAS treatment. More specifically, in the cross-over trial, over a 1-month period on PAP and 1 month on MAS (after treatment adjustment/titration), we will objectively assess adherence and also assess the efficacy of each treatment in the reduction of apnea, hypopneas, and symptoms. To understand long-term treatment outcomes, an observational trial will follow the participants over 6 months, during which time the participants will have access to both treatments and will use the treatments as they prefer (one treatment exclusively or interchangeably as they wish) (see Appendix 2 and 3 protocol schema and timeline). To assess this phase, we will evaluate adherence as an average hours/night and days/month of treatment usage and investigate its association with symptomatic improvement (quality of life, daytime sleepiness, and fatigue). We will also compare the participant's initial treatment preference to treatment adherence and determine if treatment adherence can be predicted by participant preference and disease characteristics.

1. The Need for a Trial

1.1 What is the problem to be addressed?

The Disease—Obstructive Sleep Apnea: Respiratory sleep disorders are a major health problem affecting over 1,000,000 Canadians and are the cause of significant increases in healthcare costs,[1] morbidity, and mortality. Obstructive Sleep Apnea (OSA) leads to poor-quality sleep, excessive daytime sleepiness, reduced vigilance, neuro-cognitive dysfunction, activation of the sympathetic nervous system, and elevations in blood pressure. There is a three- to seven-fold increase in automobile crashes related to OSA with an estimated cost of $159 billion in the United States[2] and 1.7 times more healthcare utilization in the 24 months prior to OSA diagnosis compared to matched non-OSA controls.[3] OSA is commonly described as being as prevalent as asthma and type II diabetes. Disease severity is classified according to the apnea-hypopnea index, AHI (the number of times the airway closes or narrows per hour of sleep). Recently the overall prevalence of moderate to severe disease (AHI$\geq$15) was found to be 10% in 30–49-year-old men; 17% among 50–70-year-old men; 3% in 30–49-year-old women, and 9% among 50–70-year-old women[4].

Treatment Options for Obstructive Sleep Apnea: OSA is a chronic disease and the treatments available are not curative and depend on high patient adherence for proper long-term effectiveness (efficacy + adherence). Efficacy is commonly described as the normalization of the pauses of breathing during sleep (AHI), improvement of symptoms, and improved health outcomes. The two most common and effective therapies used to treat OSA are: (1) Continuous or Auto-adjusting Positive Airway Pressure (CPAP/APAP here described as PAP), a device which consists of a face mask attached to a plastic tube and a machine that blows compressed air through the patient's airway during sleep to keep the airway open; and (2) Mandibular Advancement Splints (MAS), which are dental splints used to keep the mandible in an advanced position, opening the upper airway during sleep. While both therapies reduce upper airway collapse during sleep, they differ in efficacy, cost, and side-effects. PAP is more effective in reducing apneas while MAS is easier to use with higher self-reported adherence. Despite these differences, they have shown similar results in improving symptoms such as quality of life, sleepiness, and health outcomes and biomarkers of cardiovascular disease such as blood pressure,[5,6] endothelial function,[7] and microvascular reactivity.

Treatment Reimbursement: Adding to the uncertainty that physicians have with MAS effectiveness, this type of treatment is not covered even by extended health benefits in many provinces. Currently, public funding of PAP equipment is available in Ontario, Manitoba, and Saskatchewan while there is no public or private funding for MAS in these provinces. In the provinces where there is no public funding for PAP, extended health agencies (e.g. BlueCross, SunLife) tend to cover both treatments. Still, patients who purchase but discontinue PAP use (46–83%) are not eligible for MAS therapy reimbursement. In cases where PAP is partially covered by some ministries, the non-adherence translates into a waste of healthcare dollars on under-utilized PAP machines. Recently Medicare in the United States started to cover both treatments (PAP and MAS), which is similar to countries where medicine is more socialized such as France, Belgium, and Sweden. As a result, in Canada, there are a high number of patients left untreated. Starting PAP or MAS treatment without knowing that a patient will be highly compliant is a costly endeavour.

Health Service Expenses: Diagnosis, treatment, and long-term follow-up are the important keys in the analysis of the cost of OSA treatment. Additionally, treatment failure, reassessment, and poor patient adherence contribute to further treatment costs. MAS and PAP are both cost-effective treatments for OSA when compared to no treatment.[10] Sadatsafavi and colleagues[10] proposed that when adherence is the same, PAP was cost-effective versus MAS in most scenarios tested. Interestingly, when adherence was taken as a variable, MAS became the best treatment strategy if PAP adherence was 70% and MAS was at least 80%. Across Canada provincial and private insurance guidelines vary widely. In British Columbia, 67% of the population is covered by extended medical insurance (data from Ministry of Health). While the provincial health system covers diagnosis, it does not pay for treatment. The private health providers have been covering PAP treatment, but the coverage of MAS is still not uniform between providers, nor is the time interval when the patient can try a second treatment option.

Treatment Adherence: There are many factors that affect treatment adherence including social and economic factors, the healthcare system/team, and characteristics of the disease, disease therapies, and patient-related factors. Adherence has been defined by the World Health Organization as "the extent to which a person's behaviour—taking medications, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider".[11,12] PAP is a cumbersome treatment and many patients take the mask out in the middle of the night. A patient is considered adherent to PAP if it is used for 4 hours per night during 70% of the nights, and following this criteria PAP adherence ranges from 40–60% of the patients. However, Antic and colleagues[13] found that only 4 hours per night was not sufficient for patients to achieve normal daytime function and the longer the patient used the PAP, the greater the improvement in symptoms. This may be explained by the occurrence of apneas once the PAP is removed at night. Therefore, out of the 60% of patients so-called adherent to PAP, many are not fully recovered due to the limited hours of use. Auto-adjusting PAP appears to have a higher adherence rate than continuous PAP[14] and therefore auto-adjusting PAP will be used in this trial. Based on a recent systematic review,[15] comparisons of treatment usage between PAP and MAS predominantly rely on self-reported adherence data. However, previous studies have shown that self-reported PAP adherence gave significantly higher estimations of nightly and weekly use than objectively monitored PAP data[16,17] and therefore the actual adherence to MAS is unknown. Based on the definition of 4 hours/night as an effective treatment, 43% of patients on PAP and 76% of patients on MAS showed good self-reported adherence.[18] [18] Previous studies, which found similar health outcomes between PAP and MAS despite the presence of residual apnea while patients used MAS, hypothesize that the sub-optimal efficacy of MAS therapy is counterbalanced by the superior adherence relative to PAP. To explain such a hypothesis, long-term effectiveness (efficacy + adherence) has been described as the mean disease alleviation, where the OSA alleviation is calculated by a combination of adherence and efficacy over a certain period of time as described below from two studies. Grote and collaborators[19] described the mean OSA alleviation of PAP as 52%, while

Vanderveken and collaborators[20] described the mean OSA alleviation of MAS as 51%. There are no studies comparing the mean disease alleviation with objectively measured MAS adherence.

Therefore "long-term comparative effectiveness studies between PAP and MAS that include objective measures of treatment adherence are needed to better understand possible and effective treatment regimens for patients with OSA."[21] PAP adherence timers have been used since 1994[22] and are currently a standard part of PAP machines. Despite being previously developed at UBC,[23] only recently has there been a development of adherence monitors (commercially available) which can withstand the oral environment and record adherence between 3 to 6 months.[24] A Canadian company, Braebon Medical Corporation, has developed an adherence chip with a 6-month memory capacity. We have recently finished collecting pilot data *in vitro* and as well in 10 healthy volunteers showing high accuracy and ease of use of such a monitor (see Appendix 4 and 5). Still, to date there has been no study comparing PAP and MAS using this type of technology, where the difference of mean disease alleviation between PAP and MAS has been calculated. T<u>herefore, the comparison between the effectiveness of these treatments taking into account objectively measured adherence is unknown</u>. Also, this will be the first study to assess treatment usage when both are made available to participants.
Patient Preference in Chronic Disease Management: Research has shown that medical treatment plans involving and valuing patient participation usually produce the most positive patient outcomes. <u>In fact, studies have shown that patient participation in chronic disease management leads to improved treatment adherence and a higher quality of life</u>.[25] OSA patients' perspectives are necessary in the development of a management model that is sensitive to patient preferences for treatment and would be a substantial contribution to contemporary self-management discourse in OSA. Based on a recent systematic review,[15] four out of six cross-over trials asking for patient treatment preference at the end of the trial found a higher preference for MAS treatment.[16,17,26,27] In one study, preference was in favour of PAP (44% vs. 30% preferring MAS)[18] and in another preference was equally distributed between PAP and MAS.[28] Using a discrete choice experiment, Pelletier-Fleury and collaborators[29,30] found that before the onset of treatment, 60.2% and 36.2% preferred PAP and MAS, respectively. Still, <u>no studies have assessed patient preference prior to the treatment</u>. We plan to assess participant preference prior to treatment initiation with the use of a recently developed decision aid,[31] and determine the impact on and possible prediction of treatment adherence.
Combination Therapy: Usually patients are offered one treatment or the other, but the combination of PAP and MAS therapies warrants further investigation. Our pilot data[32] showed the feasibility of using MAS as an alternative treatment in patients previously established on PAP who wanted an optional treatment for circumstances such as short trips or camping (paper in Appendix 6). This was the first study to investigate the applicability of alternating treatment on a regular basis. At the end of the trial, 85% of the patients reported using MAS, and 75% of them said they would purchase the MAS at a cost similar to that of the PAP. <u>When compared to sleepiness on PAP, patients showed a significant further improvement in sleepiness when using PAP and MAS interchangeably. One could hypothesize that patients were less likely to occasionally drop treatment, and therefore the long-term effects on sleepiness were further consolidated</u>. The pilot study did not have objectively measured adherence. A combination of treatments would permit greater flexibility and improved treatment outcomes. There is a need to objectively assess adherence and assess if the combination therapy should be used as a clinical protocol in patients with residual symptoms/sleepiness after PAP or MAS therapy.

1.2 What is/are the principal research question(s) to be addressed?

Primary Questions: Is there a difference in objectively measured treatment adherence? Is there a similar mean disease alleviation between PAP and MAS treatment for participants with mild to severe OSA?
Secondary Question: Is there a further improvement in treatment adherence and mean disease alleviation if treatment preference is taken into account?

Main Hypothesis: *Cross-over trial*—Adherence to treatment is higher for MAS therapy when compared to PAP and this difference will offset the higher efficacy of PAP and result in similar symptom improvements and mean disease alleviation between the two treatments. *Observational trial*—having both treatments available to use interchangeably will further improve treatment adherence. The secondary aim is to assess participant preference prior to treatment initiation with the use of a recently developed decision aid,[31] a questionnaire developed to explain both treatments to treatment-naive participants and evaluate if their initial preference does correlate to their final treatment adherence.

1.3 Why is a trial needed now? Evidence from the literature.

As stated above, good **long-term adherence** to treatment is required for ideal improved health benefits. A recent non-concurrent cohort study followed 208 control subjects and compared them to 249 patients with severe OSA, where 177 were treated with PAP and 72 with MAS, over a mean period of 5 years. They found MAS to be an equally effective therapy in reducing the risk of fatal cardiovascular events in patients with severe OSA when compared to PAP.[33] As previously described, there are various trials showing that despite the presence of residual apneas on MAS (inferior efficacy) compared to PAP, MAS presents similar health outcomes. Recently, Phillips and collaborators[21] compared 24-hour blood pressure measurements following PAP and MAS treatment in a large randomized cross-over trial of moderate to severe OSA patients over a 1-month trial period. They found no effect of either MAS or PAP in the reduction of blood pressure, but few of the patients were hypertensive. The treatments were found to be similar in terms of sleepiness and driving simulator performance. Both treatments improved quality of life (QOL) on a disease-specific questionnaire, although MAS was superior to PAP in improving four general QOL domains. Phillips and collaborators could only rely on self-reported adherence to speculate that the higher MAS adherence was responsible for the similar effects of the two treatments. In a recent systematic review, Sutherland et al.[15] states that there is no way to objectively verify the inference that greater MAS treatment usage may equilibrate therapeutic effectiveness with PAP. Furthermore, the authors describe objective adherence monitoring as representing a significant advance in MAS therapy that will help clarify the treatment role of MAS in OSA. Although there is a lack of preference studies in the OSA literature, the recent cross-over study by Phillips et al[21] gives some insight into the impact of such an approach in OSA. As per personal communication, they found that at the end of the study, nearly half of the patients preferred MAS and importantly, adherence to both PAP and MAS was higher in patients who preferred that option, showing the need to understand patient preference and how it can impact treatment adherence. The implications of an effective patient-centered approach is a future with significantly more patients adherent to OSA therapy, be it PAP or MAS, and consequently better health outcomes.

Our pilot study demonstrated that an enhancement of the reduction in symptoms could be achieved with the availability of both treatments for a patient. However, to date the lack of difference between PAP and MAS effectiveness or a further improvement in sleepiness when the combined therapy is offered can only be understood based on speculation that MAS is often used for longer hours or when patients would be withdrawing therapy; no study has compared objectively measured adherence.

In summary, the current literature increasingly supports MAS as an effective alternative to PAP even though the mechanism of the similarities in treatment outcomes between these therapies is poorly understood and relies on self-reported adherence data. Our pilot data suggest that a combination of these therapies may be necessary to achieve optimum adherence to treatment and to enhance control of symptoms in a subset of patients. Therefore this current application focuses on comparative effectiveness outcomes that include objective measures of sleep and adherence as well as a consideration of informed participant preference for treatment to better evaluate PAP and MAS treatment[34] (see Appendix 7). The evidence generated will help patients and physicians choose the therapy that will be mostly used by the patient and therefore will improve the patient's health and quality of life on a long-term basis. We believe this is the right time for this project; we have the expertise and technology to better understand treatment differences and the role of each proposed treatment to help patients with OSA.

1.4 Give references to any relevant systematic review(s) and discuss the need for your trial in light of the(se) review(s).

According to the latest Cochrane review (2009)[35] "There is increasing evidence suggesting that MAS improves subjective sleepiness and sleep disordered breathing compared with a control. PAP appears to be more effective in improving sleep disordered breathing than MAS. The difference in symptomatic response between these two treatments is not significant, although it is not possible to exclude an effect in favour of either therapy. Until there is more definitive evidence on the effectiveness of MAS in relation to PAP, with regard to symptoms and long-term complications, it would appear to be appropriate to recommend MAS therapy to participants with mild symptomatic OSA, and those participants who are unwilling or unable to tolerate PAP therapy. Future research should <u>recruit participants with more severe symptoms</u> of sleepiness, to establish whether the <u>response to therapy differs between subgroups</u> in terms of quality of life, symptoms, and persistence with usage." In line with this review, we have developed this trial to involve all levels of OSA severity to better understand persistent usage (adherence), symptoms, and quality of life.

1.5 How will the results of this trial be used?

Embedded in the trial procedures is the training of various health professionals at three centres across Canada (e.g. dentists, nurses, graduate students). The results will be used for research purposes as well as generating evidence-based data to understand adherence to MAS and improve practices focused on a patient-oriented intervention. The knowledge acquired will accelerate changes to translate into: (a) developing clinical applications and protocols by refining a patient-centered decision; (b) establishing practice guidelines for the treatment of obstructive sleep apnea; and (c) starting negotiations with third party health providers (extended health insurances) in creating new healthcare policies and improving access to care across Canada.

Network Collaboration: In January, June and October 2013, under the leadership of Julie Carrier, the Canadian Sleep & Circadian Network (CSCN), including many members of this trial (Fernanda Almeida, John Fleetham, Najib Ayas, Frédéric Series, and Gilles Lavigne), met in Montreal, Baltimore and Halifax, respectively. The results of the current proposed trial will be shared with the network and the database will be used in future common trials and help standardize treatment policies in most provinces. The three Canadian centres participating in this proposed trial are members of the ORANGE Cohort (ORal Appliance Network for Global Effectiveness). Under the leadership of Fernanda Almeida, ORANGE was formed by 14 academic centres spanning 4 continents. The key component of the network is the development of a **clinical cohort** database to build capacity for future evidence-based treatment decisions. The participants who agree and desire to continue on MAS treatment from the current proposed trial will be entered in the ORANGE - REDCap cohort study.

Guidelines: The Canadian Thoracic Society, Canadian Sleep Society, American Thoracic Society, American Academy of Dental Sleep Medicine, and American Academy of Sleep Medicine are the ideal bridges between a large-scale research study and transferring the knowledge to new national and international clinical guidelines. These guidelines will aim to improve clinician knowledge, patient health outcomes, and access to care. The Canadian Thoracic Society, through the Canadian Respiratory Journal, has recently published papers on the use of portable monitors[36] to facilitate the diagnosis of OSA and also on guidelines for oral appliance therapy[37] (Appendix 8). As an example of this, Fernanda Almeida has adapted it for the College of Dental Surgeons of BC,[37] which has turned it into guidelines for the role of dentists in the treatment of sleep apnea, facilitating training for dentists to provide treatment to sleep apnea patients. A future guideline would address different treatment options with an understanding of the impact of treatment adherence on long-term effectiveness. Also, it will highlight the impact of participant preference and the importance of participants' perspectives on treatment decisions.

Our groups have been involved in the development of Canadian guidelines for the use of PAP and MAS and will further use the data from the proposed study in discussions with provincial health ministries and private insurance advisory boards to enhance access to treatment for patients with OSA.

1.6 Describe any risks to the safety of participants involved in the trial.

The proposed trial will use treatments that have been the standard of care for OSA since the 1990s. The risks and benefits of these treatments are well understood. Both therapies present some side-effects, which are minor and reversible when treatment is discontinued within the first year. Participants with major cardiovascular morbidity, highly elevated overnight oxygen desaturations, or with an AHI greater than 50 events per hour (AHI>50) will not be included in the trial. Further exclusion criteria can be found in section 2.5. At the end of the trial, all participants will meet with a sleep medicine specialist to discuss their best treatment regimen. Therefore there are no concerns with participant safety in this trial.

2. The Proposed Trial

2.1 What is the proposed trial design? E.g. Open-label, double- or single-blinded, etc.

The proposed study is a randomized open-label, two-treatment, two-period cross-over trial followed by an observational trial. The two treatments will be used separately for 1 month each (after treatment adaptation/titration of 2 months for each device). Treatment efficacy will be monitored at baseline and after each treatment arm with a portable sleep monitor (type III). Daily treatment use data will be downloaded at each visit that has been preceded by appliance use. Participants' symptoms (quality of life, sleepiness, and fatigue) will be assessed at baselines and after 1 month for both treatments. Participant's initial preference will be determined by using a patient decision aid developed for sleep apnea treatment.[29] Throughout the trial, participants will be asked about their preference using a treatment preference questionnaire. During the observational trial phase, all participants will have access to both interventions at home and be allowed to choose on a daily basis the intervention to use. After each 1-month treatment period and at 1 month and 6 months after the initiation of the observational portion, we will assess treatment adherence, participant symptoms (quality of life, sleepiness, fatigue and side effects) and treatment preference.

2.2 What are the planned trial interventions? Both experimental and control.

The control intervention is PAP therapy with an adherence monitoring chip, which is the first line of treatment for obstructive sleep apnea. The "experimental" intervention is the use of MAS with an embedded adherence smart chip.

2.3 What are the proposed practical arrangements for allocating participants to trial groups?

Included participants will be randomized twice, first to the order of treatment adaptation/titration and second to the order of treatment during the cross-over trial. Central randomization will be employed. Permuted blocks of varying size will be employed. Randomization will be stratified by centre for the first randomization and will be stratified by centre and treatment adaptation/titration order for the second.

2.4 What are the proposed methods for protecting against sources of bias?

Randomized allocation will protect against possible treatment allocation bias. Blinding of participants and healthcare providers is not possible due to the obvious differences in interventions, MAS or PAP. Adherence will be measured objectively for both therapies. At the end of the randomized controlled trial, efficacy and adherence will be disclosed to the participants. To decrease possible bias where the most effective therapy could be described as the only possible alternative, participants will receive the results of the efficacy of and adherence to each treatment via a written report, written mainly to inform them of the results. All letters will be written by one physician (Dr. Fleetham) together with one dentist (Dr. Almeida). The measurement of AHI improvement will be standardized and will be calculated always as a comparison between portable sleep monitors recordings, not to the diagnostic PSG. All participants will have a baseline assessment with a level III portable sleep study, and the same level III sleep studies at the end of each treatment period (i.e. under PAP and MAS treatment). Sleep scoring of the portable sleep studies (type III) will be done centrally by one sleep technologist blinded to treatment group. By re-randomizing participants after adaptation/titration to the cross-over study treatment sequences, we will minimize bias due to withdrawals (i.e. versus a single randomization at time of recruitment). Additionally, CPAP technicians and dentists involved in the study are given instructions not to share information at any time during the trial with the participants in favor of one treatment or the other.

2.5 What are the planned inclusion/exclusion criteria?
This trial will recruit patients with an objective diagnosis of obstructive sleep apnea in the general population from three participating centres.

Study Population

Eligibility Criteria

Inclusion Criteria

For consideration as a subject for this study, the patient must meet all the following criteria:

1) Treatment naïve (never used CPAP or oral appliance, nor had surgery for sleep apnea);
2) Age 19-75 years old who are able to freely provide informed consent;
3) Body Mass Index (BMI) $\leq$ 35;
4) $\geq$ 8 teeth per arch to support treatment with MAS;
5) An objective diagnosis of OSA based on the protocol's criteria outlined below:
   a) an Apnea-Hypopnea Index (AHI) within the range 10 $\leq$ AHI $\leq$ 50 documented with polysomnography in the last 2 years; ***OR***
   b) a Respiratory Disturbance Index (RDI) within the range 20 $\leq$ RDI $\leq$ 50 documented with level III portable sleep test; ***OR***
   c) an Oxygen Desaturation Index (ODI) $\geq$ 10; and
6) Sleep investigations confirming the objective diagnosis of OSA performed within the past 2 years.

Exclusion Criteria

The patient is excluded if the patient meets any of the following criteria:

1) Extensive periodontal disease with significant tooth mobility;
2) Inability to protrude jaw;
3) Insufficient vertical opening to accommodate treatment with MAS;
4) Uncontrolled congestive heart failure (defined as a prior clinical diagnosis, an ejection cut-off of 40% or clinical sign in the opinion of a primary care physician or cardiologist) that makes it unsafe in the opinion of the investigators for the subject to participate in the trial;
5) Coronary artery disease unless stable for at least 6 months and considered by the investigators to have a stable disease;

6) Any history of angina, myocardial infarction or stroke;
7) Any history of major depressive disorder along with current moderate-severe disease;
8) Active cancer management (unless in remission for more than 1 year);
9) Known renal failure (with need for dialysis);
10) Pregnancy (if a subject becomes pregnant during the trial, the subject will be withdrawn from the trial);
11) History of a near miss or prior automobile accident due to sleepiness within the past 12 months; and/or
12) At nighttime, 30% of the night is at ≤ 90% oxygen saturation levels.

2.6 What is the proposed duration of the treatment period?

Both therapies require adaptation and titration of about 2 months; these procedures will occur after the first randomization and prior to start of the cross-over phase. Once participants have been adjusted for both therapies, there will be a 1-week wash-out period and then participants will be randomized to the order of treatment (PAP/MAS or MAS/PAP). Each treatment period is 1 month to allow for a sustained response on AHI, adherence rates, and to observe changes in symptoms (sleepiness, quality of life, fatigue and side effects). There will be a 1-week wash-out period between treatments. In a previous randomized cross-over trial comparing PAP and MAS treatments for cardiovascular outcomes, the intervention duration was 1 month.[21] After the cross-over design, participants will begin a 6-month observational phase where the usage of both interventions and symptoms will be assessed. Consequently, a total of 10 to 12 months will be required for each participant.

2.7 What is the proposed frequency and duration of follow-up?

In total, 15 visits will be required to complete this study and data will be collected mainly at 5 time points: at baseline prior to the first randomization (**T0**), during the cross-over phase following 1 month of first (**T1**) and second interventions (**T2**), and during the observational phase after 1 and 6 months (**O1 and O2**) for each participant. One post-intervention follow-up visit (cross-over phase) is sufficient to observe a response to the intervention as reported in the published literature (see section 2.6). During the other visits, adherence data will be downloaded and information on side effects will be collected.

2.8 What are the proposed primary and secondary outcome measures?

The primary outcomes are objectively measured adherence (hours/night and nights/week of intervention use), indicated by the smart chips and symptoms; apnea-hypopnea index (events/hour of sleep from Stardust–Phillips Respironics[38]) to measure intervention efficacy (e.g. AHI); Functional Outcomes of Sleep Questionnaire (FOSQ)[39] to evaluate disease specific quality of life; Epworth Sleepiness Scale (ESS)[40] to compare daytime sleepiness; and Chalder fatigue scale to assess fatigue in the present state.[41] Secondary outcomes are adherence to both treatments used interchangeably and general quality of life/health status with short form 36 (SF-36)[42] to assess general health status, side-effects questionnaires, to assess the side effects of both treatments; the treatment decision aid tool and treatment preference questionnaire to assess treatment preference.

2.9 How will the outcome measures be measured at follow-up?

Participants included in this trial (see section 2.12 for recruitment procedures) who consent to participate will be invited to the clinical research laboratory of their respective centre for the baseline assessment. Please reference to Appendix 2 and 3, the schematic of study design and the data collection timeline.

Baseline: baseline visit and set-up for at-home overnight sleep recording (T0). During this visit, a calibrated investigator and/or graduate research trainees will collect baseline data which includes medical history, socio-demographic, and anthropometric (weight, height) variables, and participant will fill out the following questionnaires: quality of life (OSA-specific) using FOSQ, treatment preference (PAP, MAS, either, or neither), daytime sleepiness using ESS, Chalder Fatigue Scale, general health using SF-36 and the specific OSA treatment decision aid tool. In addition, the calibrated investigator and/or graduate research trainee will train the participant to set up the type III ambulatory sleep recording (one night) and provide a sleep diary to fill out.

Treatments adjustment/titration: Prior to the cross-over study, each treatment will be customized to the participant. The order of treatment titration will be randomized. The procedures described below will be standardized and monitored according to current best practices for PAP and MAS titration.

Titration Protocol PAP: Participants will be given their PAP (REMSTAR Auto PAP) by a trained and standardized technician and have their mask adjusted. After 1 week of PAP use, the sleep technician will assess the pressure data and set-up the upper pressure bound to the 90th percentile via internet. In addition, the sleep technician will call the participant to trouble-shoot any problems. Participants will be followed-up in the clinic 1 month and 2 month after the PAP is dispensed to them. Shortly before the end of the 2 month titration period, participants will receive an oximeter to use overnight with their PAP to ensure that adequate titration has been achieved. Objective improvement is defined as an ODI < 5. If oximetry shows that adequate titration has not been achieved yet, 1 or 2 month of additional PAP titration will be required.

Titration Protocol MAS: Participants will have a molding of their teeth done and a custom-titratable appliance (Somnodent Flex G2) will be fabricated and inserted by a trained and standardized dentist. Participants will have the position of their mandible adjusted over a period of 2 months. After an initial 1 week adaptation period, mandibular advancements of 0.1 mm per day will start until the maximum of 55 advancement turns has been reached or the maximum comfortable mandibular advancement is achieved. Participants will be followed up in the clinic 1 week, 1 month and 2 months after the appliance is dispensed to them. Similar to PAP titration, MAS titration will be objectively assessed and participants will receive an oximeter to use overnight with their appliance shortly before the end of the titration period to ensure that adequate titration has been achieved. Objective improvement is defined as an ODI < 5. If oximetry shows that adequate titration has not been achieved yet, 1 or 2 month of additional MAS titration will be required.

Cross-over trial—assessment of objectively measured adherence and efficacy in OSA reduction. After this 2 months adaptation/titration phase, participants will be re-randomized at the beginning of the RCT phase where they will use each treatment in a randomized order for 1 month. If necessary, the MAS will be set back 1 mm at the start of the trial period to achieve comfort. The participants will have a 1-month sleep diary report to fill out to calculate estimated sleep duration.

Period 1 (T1): After using the first treatment for a month and performing a home sleep study using a portable monitor while under treatment; participants will come to the clinic and we will download the adherence data. Data will be gathered on body weight, changes to medical or medication history, sleep diary, FOSQ, ESS, fatigue, SF-36, side effects and treatment preference. **Wash-out period:** participants will be instructed not to use any treatment for 1 week. **Period 2 (T2):** Participants will then cross-over to the other treatment arm and use it for a period of 1 month. The follow-up for this phase will be identical to period 1.

Sleep studies: The ambulatory sleep recording device (type III) will be sent to the participants via scheduled drop-off by courier service a few days before the end of each of the 1 month trial periods. This method allows us to maximize participation and study adherence, in addition to having a successful track record with previous sleep apnea cohorts.[43] The at-home sleep study includes a flow signal through RIP effort and nasal cannula, SpO_2, pulse, snoring, and body position. Following overnight recording, the ambulatory sleep recording device (type III) will be returned to the clinical research laboratories by the participant when he/she come in for his/her visit scheduled to take place on the day following the overnight at home sleep study. Participants will keep a sleep diary to estimate hours of sleep per night during T1 and T2.

All overnight sleep data (T0, T1, T2) will be downloaded and sent to a centralized server to be scored by a sleep technologist (Peter Hamilton) according to American Academy of Sleep Medicine criteria.[44] This sleep technologist will be blinded to treatment group. No identifying information will be provided so that "data pairs" cannot be identified. Atypical sleep and respiratory signals will be sent to the treating sleep specialist for further assessments and participants will be informed of these results.

Treatment Disclosure: After all results of the cross-over study have been interpreted, participants will meet with the responsible research team member who will provide a written letter summarizing in lay language the sleep study results and adherence for both treatments. All letters will be written in conjunction by Drs. Fleetham and Almeida. Participants will fill out a treatment preference questionnaire after understanding the efficacy and adherence of each treatment. After this appointment, participants will go home with both treatments and will be allowed to use either treatment exclusively, alternating, or even in combination if they so choose.

Observational trial—long-term treatment effectiveness. **O1 and O2:** Participants will continue to use the treatment of their choice for 6 months. After 1 and 6 months, treatment adherence data will be downloaded from both devices and sleep diary will be collected at O1. At both time points, we will collect participant's body weight and reassess changes to medical or medication history. Participants will complete the perceived preference, FOSQ, ESS, Chalder Fatigue, SF-36 and side effects questionnaires. After the analysis of final adherence data, treatment adherence will be compared to initial results of the discrete choice experiment and the perceived preference questionnaire. We will then assess health outcomes depending upon the adherence results found. Participants will have an appointment with the sleep physician who will go over the results with the participant and recommend an ideal treatment regimen. All participants will receive continuing support from the clinicians involved in the study after the trial is finished.

Adherence: will be measured by the smart chip embedded in the mandibular advancement appliance (sensitivity 0.98, data not published yet) or in the positive airway pressure machine. The adherence will be measured by hours per night and nights per week. This data will be assessed at every visit (except baseline visit and visits following washout periods). **Apnea–hypopnea index** (events/hour) to measure intervention efficacy (at baseline, T1, and T2) will be calculated with manual readings of a portable sleep study device (cardio-respiratory) together with the sleep diary including date, approximate time of falling asleep, time awake in the middle of the night, and time woken up for total sleep time estimation (Stardust III Sleep Recorder Philips Respironics; comparison of Stardust level III with full-night polysomnography showed an intraclass correlation co-efficient for AHI of 0.89[38]). Based on adherence and AHI, the mean disease alleviation will be calculated for each therapy. **Symptoms** will be measured at baseline, T1, T2, O1, and O2 using the following: (1) FOSQ to assess the impact of sleep apnea on everyday activities and the related impact of treatment. FOSQ test-retest reliability is alpha = 0.95 and scoring internal consistency is r = 0.90.[45] (2) ESS questionnaire will be used to evaluate self-reported daytime sleepiness with a good internal consistency (Cronbach's alpha statistic = 0.74 to 0.88 in four different groups of subjects).[40] (3) Chalder Fatigue Scale will assess self-reported mental and physical fatigue with a high degree of internal consistency.[41] (4) SF-36 health survey will assess general quality of life/health status. Its reliability co-efficient median is 0.85.[46] (5) The participant preference described by the OSA treatment decision aid tool[29] will be collected only while participants are naïve to treatment at baseline, and the results will then be compared to treatment objective adherence at T1, T2, O1, and O2. (6) **Patient preference:** subjective intervention preference questionnaire that was previously used in patients who tried both PAP and MAS interventions[32] will be used at baseline, at T1, T2, after disclosure of the results and at O1 and O2. (7) Side-effects questionnaire: will be used to report the side effects of PAP and MAS at the end of the adaptation and titration period for each appliance and at T1, T2, O1, and O2.

2.10 Will health service research issues be addressed?
The objective measurement of participant adherence to PAP and MAS will help improve treatment protocols, long-term general health-related quality of life, and perhaps decrease morbidity/mortality. Although positive airway pressure is considered to be the first line of treatment and the gold standard in obstructive sleep apnea, approximately 46–83% of patients discontinue therapy at long-term follow-up.[47,48] MAS have also been shown to be effective.[21] However, there is a paucity of information on objective adherence with this appliance; only a few studies report a subjective adherence of 79–84%.[24] In this proposed trial, quality of life measures will be assessed to compare these interventions in order to help develop practice guidelines and health policies based on objective adherence and mean disease alleviation, both at the individual and the population levels.

2.11 What is the proposed sample size and what is the justification for the power calculations?
To detect an average difference of 1 hour of adherence between the two treatments requires 36 participants to complete both portions of the cross-over study. This calculation assumes a Type 1 error of 0.05 (2-sided), power of 85%, and a within-person standard deviation of 2.0.[22] One hour is the minimum clinically important difference for an impact on ESS and quality of life.[16] We anticipate a 10–15% dropout rate during the cross-over study, thus we would need to recruit 42 participants for the cross-over study. Assuming 25% of the participants will not proceed to the trial after the titration phase, we anticipate recruiting 54 to 60 participants to the trial.

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place?
The planned recruitment rate is 10 participants per centre per year, over the enrollment period of 2 years. It can be estimated that the prevalence of OSA is 10% in the adult population, both genders combined. All three centres are located in dense urban areas, ranging from 516,600 to 1.65 million inhabitants. Based on our combined previous experience in our academic and hospital-based centres, we estimated that the randomization screening ratio is 0.2 (1 participant randomized for every 5 participants screened). Moreover, it has been estimated that only 10% of participants invited to a clinical trial will actually consent to participate.[49] Thus the calculated community potential enrollment rate[49] is 43 participants/month/centre (using the smallest urban population among the three sites). Our planned recruitment rate is hence considered conservative and feasible.
The recruitment will be organized similarly to previously successful clinical research studies on OSA completed at each of the participating centres. Participants will be recruited from hospital-based and private sleep clinics, in addition to university-based and private dental clinics. Either a research team member or a graduate student will then conduct an introductory interview over the telephone with each potential participant to describe the study and to assess major inclusion. Potential eligible participants will be invited to the research clinic for an information and screening visit. Preliminary screening for inclusion/exclusion criteria will be done by a clinician; following this, eligible and interested potential participants will be invited to read and sign the informed consent form. They will be given the opportunity to ask questions or ask for clarification, in addition to taking the form home for further consideration. If the recruitment rate is slower than anticipated in any of the centres, participants from the general population close to the centre will be recruited through advertisements in local newspapers and targeted media outlets. Based on previous experience with this recruitment method, 40% of these responders will be eligible for participation. This bi-level and wide-ranging recruitment strategy will allow the trial to reach the planned annual recruitment rate for the first 2 years.

2.13 What is the likely rate of loss to follow-up?

We anticipate a 10 to 15% dropout rate for the cross-over study. This rate is consistent with an Australian study using a similar design.[21] The expected dropout is minimized as participants who complete the cross-over portion of the study will receive both interventions for future use.

2.14 How many centres will be involved?

Three centres across Canada will be involved to increase the number of participants and the generalizability of the results. All centres have extensive clinical and research experience in sleep medicine, sleep apnea, and dental sleep medicine. All steps of the trial will be carefully standardized between centres and we will conduct statistical analysis to assess possible variability between centres. The centres are at the University of British Columbia, Université de Montréal, and Université Laval.

2.15 What is the proposed type of analyses?

Continuous data will be summarized as mean (sd) or median (P25,P75) if the data is skewed. Categorical data will be summarized as frequency (percent). **Primary analyses:** average adherence (hours/night over 4 weeks) and AHI between the two treatments will be compared using a linear mixed model (LMM) that includes fixed effects for treatment (PAP/MAS), period (1/2), sequence (PAP/MAS, MAS/PAP), AHI severity category and centre, and a random effect for participant.[50] A global statistical test will be employed to compare the two treatments with regard to FOSQ, ESS, and fatigue.[51] Point and interval estimates for group differences will be determined. **Secondary analyses:** Interchangeable adherence and SF-36 scores will be compared using an LMM as above. **Exploratory analyses:** The analysis of the treatment usage phase will compare the outcome for the preferred device of the treatment efficacy phase (T1 and T2) to those observed at O1 and O2. The model will include fixed effects for time (T1, T2, O1, O2), participant preference, and AHI severity category. Subjects will be included as a random effect. The dependent variable is objective adherence. These analyses will be performed under the responsibility of the statistician (P. Rompré). Only final analyses are planned once the trial is complete, without interim analyses, due to the nature of the outcome measures and the duration of the trial.

2.16 Has any pilot study been carried out using this design?

Two studies completed by the research team have acquired pilot data, shown feasibility, and demonstrated the importance of the proposed trial. The aim of the first study was to better understand participants' perspectives and preferences regarding PAP and MAS for OSA treatment[52] (Appendix 9). This was a qualitative study with four focus group sessions of 22 participants treated with PAP or MAS. Results suggested that matching treatment with participant preference could achieve greater therapy adherence, and thus greater health outcomes. The second study assessed the feasibility of using PAP interchangeably with MAS. Nineteen (19) OSA patients (AHI ≥ 10 events/hour) who were compliant with PAP (≥ 4 hours/night) for at least 3 months were adjusted with MAS. Following the next 3 months at home with both treatments to be used at their discretion, patients completed a treatment usage, sleepiness, and preference questionnaire. Results showed that 85% of patients used MAS, sleepiness was further improved compared to PAP alone, and 56% of patients preferred MAS in comparison to 31% who preferred PAP and 13% of patients who reported no preference.[32]

2.17 Potential weaknesses and associated resolution.

The proposed project has a long-term design, increasing the possibility of high dropout rates. To overcome this, we have planned a three-centre trial to optimize participant supervision and decrease the burden in each centre. To reduce clinical practice variability between centres, Dr. Almeida will visit the other two centres and will see some participants with the corresponding dentists and research assistants. During the study, regular standardization will continue to be done via telephone and video calls. The disclosure of treatment outcomes is prone to bias; thus we plan to have a standard lay language written report, to minimize influences of the dentist or physician over the participant's decision prior to the treatment usage phase. These letters will always be written in conjunction by Drs. Fleetham and Almeida. Finally, portable sleep recorders (cardio-respiratory) instead of polysomnography will be used. Every participant will have had at least one PSG prior to the study (inclusion criteria) and this will be correlated to the baseline portable monitoring. All further treatment efficacy evaluations will be assessed comparing only the results from the portable sleep monitor (level III) to avoid measurement bias.

3. Trial Management

3.1 What are the arrangements for day-to-day management of the trial?

The co-ordinating team for this multi-centre trial will be led by the nominated principal applicant, Dr. Fernanda Almeida, and centralized at the University of British Columbia. A dedicated trial manager will co-ordinate the day-to-day management of the trial, such as ethics, recruitment, protocol, data management, and troubleshooting across all participating centres. Standardization between all three participating centres will be ensured by following the current best clinical practice guidelines for both MAS and PAP interventions, in addition to regular on-line audio/video conference calls with the entire research team. Furthermore, a thorough initial standardization session will be held before the start of the trial. A trial statistician (P. Rompré supervised by P. Brasher) will be responsible for the treatment sequence arm allocation randomization and final statistical analyses.

3.2 What will the proposed role of each principal applicant and co-applicant proposed be?

The multidisciplinary research team includes junior and senior investigators with successful past and present collaborations from three highly regarded Canadian universities. The nominated principal applicant, **Fernanda Almeida**, DDS, MSc, PhD, has pioneered research on the dentofacial side-effects of oral appliances and PAP therapy. Moreover, she has participated in developing protocols and establishing ground-breaking knowledge in a variety of areas related to dental sleep medicine. The Faculty of Dentistry at the University of British Columbia has worldwide leaders in the field of oral appliances and the treatment of snoring and OSA with extensive publication records. The co-principal applicant, **Nelly Huynh**, PhD, has completed various studies in dental sleep medicine and sleep apnea. The Faculty of Dental Medicine at the Université de Montreal is also a worldwide leader in dental sleep medicine research, with extensive and significant publications on sleep disorder-related pain, sleep bruxism, the placebo effect, morning headaches, and trauma. ***Both principal applicants will have a role*** in protocol development, study coordination, participant recruitment, data management and entry, budget planning, statistical analyses strategy, interpretation of results, graduate student training, and knowledge translation (reporting to professional societies and collaborating on guideline development). Co-applicants: **John Fleetham**, MD, a pulmonologist specialized in sleep disorder medicine at UBC, has published more than 100 papers and 15 book chapters, mainly on different aspects of sleep disordered breathing. **Najib Ayas**, MD, MPH, a pulmonologist specialized in sleep disorders medicine at UBC, focuses his research on the public health and safety consequences of sleep apnea and sleep deprivation. **Nick Bansback**, PhD, is an Assistant Professor in the School of Population & Public Health (SPPH). He has been developing patient decision aids and has developed methods to make it easier for patients to choose options congruent with their preferences. He also has extensive experience with economic evaluations. **Alan Lowe**, DMD, PhD, from UBC, is one of the leading authorities in the world on the use of oral appliances for the treatment of sleep disordered breathing. He holds three patents in the field and has published 135 articles and 14 book chapters. **Gilles Lavigne**, DMD, PhD, from UdeM, is a world expert on dental sleep medicine such as sleep bruxism, morning headaches, and sleep-related pain. **Frédéric Series**, MD, a pulmonologist specialized in sleep disorders medicine at ULaval, has extensive experience in clinical studies on sleep-disordered breathing pathophysiology and cardiovascular consequences. **Jean-François Masse**, DDS, from ULaval, is board-certified from the

American Academy of Dental Sleep Medicine and has published various clinical trials on dental sleep medicine. ***Co-applicants will have a role*** in protocol development, participant recruitment, interpretation of the results, and knowledge translation activities. Moreover, each co-applicant will contribute their expertise and experience to the proposed RCT.
Student researcher: **Mona Hamoda**, BDS, MSc, MHSc from UBC will have a role in developing forms, data collection and managing diferent aspects of the study.
The collaborators are **Patrick Arcache**, DDS, and **Luc Gauthier**, DDS, MSc, both dentists with extensive expertise in dental sleep medicine and sleep-disordered breathing. ***They will have a role*** in participant recruitment and data collection. **Pierre Rompré**, MSc, is the statistician at the Faculty of Dentistry, UdeM, and ***will have a role*** in randomization, data verification, and statistical analyses. The steering committee will be composed of the Clinical Assembly Chair of Sleep-Disordered Breathing of the Canadian Thoracic Society (Dr. Robert Skomro), a member of the Canadian Sleep Society (dental group), one principal investigator, and one participants' representative. This committee will meet virtually every 6 months to review all aspects of the proposed study, including participant safety and any reported side-effects, and insure that the trial is conducted according to good clinical practices in clinical trials and scientific integrity.

3.3 If participation in this study is provided at no cost to the participants, why do they need to provide a security deposit cheque at the start of the trial?

Participants will be able to get their PAP and MAS appliances at no cost to them during the study and keep them after the study is over. Additionally, participants may withdraw from this study at any time without giving reasons. However, if they choose to enter the study and then decide to withdraw at a later time, they will be required to return their PAP, MAS appliance, sleep monitor, oximeter (i.e. any appliance(s) that they have at the time of withdrawal).
We are provided 60 appliances (20 in each centre) of each kind (CPAP and MAS) for this trial. We require 60 participants to complete the trial and if participants withdraw and do not return the appliances, the research team will need to purchase replacement appliances at an extra cost for the new participants who will replace the participants who dropped out.
Therefore, at the beginning of the trial. The participant will leave a security deposit cheque worth $800 with a member of the research team and the participant will receive written confirmation from the research team member that the security deposit cheque has been received by them. This cheque will be stored in a locked cabinet inside a locked office of one of the research team members.
The security deposit cheque will be returned to the participant immediately upon completion of the trial or upon withdrawal from the trial if the appliances are returned. Hence, the cheque will ONLY be cashed in case of non-returned appliances or damaged appliances.
If a participant fails to show up to the trial visits without any prior notice and without returning the appliance(s), there is a standard procedure that will be followed before the research team cash their cheque: a member of the research team will try to contact the participant 3 times over a period of 3 month, if the research team member does not get any response then she/he will try to contact the emergency contact person whose name and number will be provided to us by the participant at the beginning of the trial.
If a participant is interested in being part of this trial but could not provide an $800 cheque, the participant will need to sign a letter indicating that he/she is responsible for returning the appliances and that members of the research team will seek appropriate action to retrieve these appliances if not returned by the participant.

4. Significance

OSA is a very common problem affecting millions of Canadians and only a very small percentage of these patients are currently receiving treatment. Untreated OSA results in an increase in motor vehicle crashes, decrease in productivity, and increased cardiovascular morbidity and mortality. Unfortunately today, long-term adherence to treatment in OSA is poorly understood. We believe that understanding participant adherence and respecting their informed decisions will improve the management of patients with OSA. The long-term benefits of treatment strategies for OSA are that they can improve quality of life and reduce healthcare costs. The current proposed trial will provide enlightenment on the importance of treatment adherence in long-term effectiveness, improve awareness of the impact of participant preference on treatment adherence as well as the role of offering two therapies to be used interchangeably. This trial is in line with modern approaches of medicine, evidence-based, and patient-centered to achieve a higher improvement in health outcomes. A greater understanding of treatment adherence will accelerate changes to health policies, improve access to care, help develop clinical applications refining patient-centered decisions, and improve the effectiveness of OSA treatment across Canada.

5. Visit Schedule

Visit 1 (Baseline visit):
During this visit, a research team member will collect data such as medical history, socio-demographic, and anthropometric (weight, height) variables, and the participant will be required to fill out the following questionnaires: quality of life (OSA specific) using FOSQ, daytime sleepiness using ESS, Chalder Fatigue Scale, general health using SF-36, treatment preference (PAP, MAS, either, neither) and the OSA treatment decision aid tool. Dental impressions, 2 x-rays and intra-oral photographs will be taken at this visit. In addition, the participant will be trained on how to set up his/her at home sleep recording device and how to record on the sleep diary.
At the end of this visit, the participant will be randomized to the titration/adjustment of PAP/MAS or MAS/PAP.

Sleep study: The participant will receive the sleep recording device at visit 1 and perform the overnight sleep study at home, the following day a courier service will pick up the sleep recording device from the participant and send it back to the research lab for data assessment and interpretation.

Visit 2 (Treatment adjustment visit):
In visit 1, the participant was randomized to the titration/adjustment of PAP/MAS or MAS/PAP.
For PAP: The participant will be given his/her PAP machine and a technician will adjust the mask in this visit. The machine will be in auto mode during the first week of use. After 1 week of use, the participant will receive a follow up phone call from the sleep technician and the sleep technician will also assess the data from the PAP machine and adjust the pressure via internet. The participant will come back to the clinic <u>1 month</u> after using the PAP machine.
For MAS: The participant will have the custom titrable appliance inserted by a trained dentist and he/she will use the appliance at home for one week and adapt to it before titration begins. The participant will need to come back to the clinic 1 <u>week</u> after this visit.

Visit 3 (1st treatment adjustment and titration):
Titration for PAP: The participant will NOT need to come to the clinic for this visit. After 1 week of PAP use, the sleep technician will assess the pressure data and set-up the upper pressure bound to the 90th percentile via internet. In addition, the sleep technician will call the participant to trouble-shoot any problems.
Titration for MAS: After an initial 1 week adaptation period, the MAS will be checked by the dentist at this visit for fit and comfort and adjustments will be made if necessary. Mandibular advancements of

0.1 mm per day will start until the maximum of 55 advancement turns has been reached or the maximum comfortable mandibular advancement is achieved.
The first advancement turn will be done in the clinic and the remaining turns will be done by the participant at home. The participant will be shown how to turn the screw on the appliance at this visit and he/she will turn the screw at home starting on the day following this visit.
If at any time during the titration period the participant could not tolerate any further advancement; he/she will be instructed to temporarily stop the advancements for a few days and then try again.

Visit 4 (Treatment adjustment/titration follow up visit):
Titration for PAP and MAS: After one month of appliance use the participant will come back to the clinic for follow up. At this point, the participant has been using this appliance for 1 month and will use it for another month. In this visit, the participant will be given a choice of whether he/she would like to pick up the oximeter from the clinic a few days before the end of the two month titration period or if he/she would like it to be delivered to him/her via courier service.

Oximeter: Shortly before the end of the 2 month titration period, the participant will receive an oximeter to use overnight with his/her appliance to ensure that adequate titration has been achieved. Objective improvement is defined as an ODI < 5. The participant will bring the oximeter with him/her to visit 5 and the results of the oximetry will be assessed in visit 5.

Visit 5 (Return of first treatment/dispense of second treatment):
At this visit, if optimum titration has been achieved, the participant will return the first appliance and he/she will fill out a side effects questionnaire. The participant will be given the second appliance to start its adjustment and the remainder of this visit will be the same as described in visit 2, next visit will be visit 6.
If the oximetry data assessed during this visit shows that optimum titration was not achieved during the standard 2 month titration period (i.e. ODI < 5 has not been achieved), a 1 month of further titration is required. The participant will further titrate the appliance until visit 5.1 and again the participant will be given a choice on whether he/she would like to pick up the oximeter from the clinic a few days before the end of this 1 month extra titration period or if he/she would like it to be delivered to him/her via courier service. The participants will use the oximeter overnight with the appliance towards the end of this extra 1 month of titration.
Hence, the participant will use the 1st appliance for an extra month and come back for visit 5.1

Supplemental visit 5.1 (if needed):
The participant will return the oximeter at this visit and results of this extra month of titration will be assessed. If optimum titration has been achieved, the participant will return the first appliance and he/she will fill out a side effects questionnaire. The participant will receive the second appliance to start its adjustment and the remainder of this visit will be the same as described in visit 2, next visit will be visit 6.
If optimum titration has not been achieved yet, a second extra month of titration will be required. Again the participant will be given a choice of whether he/she would like to pick up the oximeter from the clinic a few days before the end of this extra titration period or if he/she would like it to be delivered to him/her via courier service. The participant will use the oximeter overnight with the appliance towards the end of this extra titration period and he/she will come back for visit 5.2.

Supplemental visit 5.2 (if needed):

Oximetry data will be assessed and the participant will return the first appliance, as the maximum of 4 months of titration has been reached. The participant will also complete a side effects questionnaire then he/she will be given the second appliance to start its adjustment and the remainder of this visit will be the same as described in visit 2.

Visit 6 (2nd treatment adjustment and titration):
Titration for PAP: The participant will NOT need to come to the clinic for this visit. After 1 week of PAP use, the sleep technician will assess the pressure data and set-up the upper pressure bound to the 90th percentile via internet. In addition, the sleep technician will call the participant to trouble-shoot any problems.
Titration for MAS: After an initial 1 week adaptation period, the MAS will be checked by the dentist at this visit for fit and comfort and adjustments will be made if necessary. Mandibular advancements of 0.1 mm per day will start until the maximum of 55 advancement turns has been reached or the maximum comfortable mandibular advancement is achieved.
The first advancement turn will be done in the clinic and the remaining turns will be done by the participant at home. The participant will be shown how to turn the screw on the appliance at this visit and he/she will start turning the screw at home starting on the day following this visit.

Visit 7 (Treatment adjustment/titration follow up visit):
Titration for PAP and MAS: After one month of 2nd appliance use, the participant will come back to the clinic for follow up. At this point, the participant has been using the 2nd appliance for 1 month and will use it for another month. During this visit, the participant will be given a choice of whether he/she would like to pick up the oximeter from the clinic a few days before the end of the two month titration period or if he/she would like it to be delivered to him/her via courier service.

Oximeter: Shortly before the end of the 2 month titration period, the participant will receive an oximeter to use overnight with the appliance to ensure that adequate titration has been achieved. Objective improvement is defined as an ODI < 5. The participant will bring the oximeter with him/her to visit 8 and the results of the oximetry will be assessed in visit 8.

Visit 8 (End of titration phase and return of appliance):
At this visit, if optimum titration has been achieved, the participant will return the first appliance and he/she will fill out a side effects questionnaire. If the oximetry data assessed during this visit shows that optimum titration has not been achieved during the standard 2 month titration period (i.e. ODI < 5 has not been achieved), a 1 month of further titration will be required. The participant will further titrate the appliance until visit 8.1 and again the participant will be given a choice on whether he/she would like to pick up the oximeter from the clinic a few days before the end of this 1 month extra titration period or if he/she would like it to be delivered to him/her via courier service. The participant will use the oximeter overnight with the appliance towards the end of this extra 1 month of titration.
Hence, the participant will use the 2nd appliance for an extra month and come back for visit 8.1

Supplemental visit 8.1 (if needed):
The participant will return the oximeter at this visit and results of this extra month of titration will be assessed. If optimum titration has been achieved, the participant will return the appliance and he/she will fill out a side effects questionnaire. If optimum titration has not been achieved yet, a second extra month of titration will be required. The participant will be given a choice of whether he/she would like to pick up the oximeter from the clinic a few days before the end of this extra titration period or if

he/she would like it to be delivered to him/her via courier service. The participant will use the oximeter overnight with the appliance towards the end of this extra titration period and he/she will come back for visit 8.2.

Supplemental visit 8.2 (if needed):
Oximetry data will be assessed and the participant will return the first appliance, as the maximum of 4 months of titration has been reached. The participant will also complete a side effects questionnaire.

After adaptation to both therapies (2-4 months for each therapy), the participant will return the second appliance to the clinic (either in visit 8, 8.1 or 8.2), for a one week washout period before the start of the trial.

Cross over trial:
Visit 9 (Beginning of clinical trial phase):
In this visit, the participant will be randomized again to the order of treatment (PAP/MAS OR MAS/PAP) and he/she will be given his/her designated treatment at this visit. Changes in participant's medical and medication history will also be recorded. The participant will be given a new sleep diary to fill in during this first month of the trial. In addition, the participant will be reminded how to set up the home sleep recording device that will be used for one night towards the end of this 1 month trial period. The participant will be given a choice on whether he/she would like to pick up the sleep monitor from the clinic a few days before the end of the one month period or if he/she would like it delivered to him/her via courier service.
If the participant is randomized to MAS and he/she could no longer tolerate the final advanced position that had been reached at the end of the MAS titration period, the dentist will need to set back the MAS 1 mm. To compensate for this 1mm set back, advancement will be resumed during the trial period.

Sleep study: The home sleep recording device will be sent to the participant via courier service or the participant will pick it up from the clinic. After completing the at home overnight sleep study, he/she will be expected to return the sleep monitor to the clinic when he/she comes in for the clinic visit that has been scheduled to take place on the day following the overnight sleep study (visit 10).
Visit 10 (End of first month of clinical trial phase):
This visit is scheduled to take place after using the PAP or MAS appliances for 1 month and the day following the overnight at home sleep study. The participant will return the sleep monitor and data will be downloaded from the appliance being used. A research team member will also collect the sleep diary and the participant's body weight, as well as reassess changes to the medical or medication history. The participant will be required to fill out the following questionnaires: FOSQ, ESS, fatigue, SF-36, treatment preference and side effects. After this visit the participant will be required to stop treatment for a 1 week washout period.

Visit 11 (Start of second appliance use):
After the wash out period, the participant will switch to the other treatment and will be given his/her second treatment device at this visit. The participant will be given a new sleep diary to fill in during this second month of the trial. In addition, the participant will be reminded how to set up the home sleep recording device that will be used for one night towards the end of this 1 month trial period. The participant will be given a choice on whether he/she would like to pick up the sleep monitor from the clinic a few days before the end of the one month period or if he/she would like it delivered to him/her via courier service.

If the participant is randomized to MAS and he/she could no longer tolerate the final advanced position that had been reached at the end of the MAS titration period, the dentist will need to set back the MAS 1 mm. To compensate for this 1mm set back, advancement will be resumed during the trial period.

Sleep study: The home sleep recording device will be sent to the participant via courier service or the participant will pick it up from the clinic. After completing the at home overnight sleep study, he/she will be expected to return the sleep monitor to the clinic when he/she comes in for the clinic visit that has been scheduled to take place on the day following the overnight sleep study (visit 12).

Visit 12 (End of clinical trial phase):
This visit is scheduled to take place after using the second treatment for 1 month and the day following the overnight at home sleep study. The participant will return the sleep monitor and data will be downloaded from the appliance being used. A research team member will also collect the sleep diary and the participant's body weight, as well as reassess changes to the medical or medication history. He/she will be required to fill out the following questionnaires: FOSQ, ESS, fatigue, SF-36, treatment preference and side effects questionnaires.
At this visit, the participant will go home with both treatments and will be allowed to use either treatment exclusively, alternating, or even in combination. He/she will also be given a new sleep diary to record.

Visit 13 (Disclosure of the results):
After all results from the cross over trial have been assessed and interpreted, a written letter containing these results will be discussed with the participant by a research team member. All letters will be written by Dr. Almeida and Dr. Fleetham. The participant will be required to fill out a treatment preference questionnaire at this visit.

Observational trial:
Visit 14: After 1 month of using the treatment/treatments of choice, the participant will come to this visit. Data will be downloaded from both appliances and sleep diary will be collected. We will collect body weight and reassess changes to participant's medical or medication history. The participant will complete the treatment preference questionnaire, FOSQ, ESS, Chalder Fatigue, SF-36 and side effects questionnaires.

Visit 15: After 6 months of using the treatment/treatments of choice (5 month from the last visit), the participant will come back to the clinic. Data will be downloaded from both appliances and a research team member will collect participant's body weight and reassess changes to medical or medication history. The participant will be required to fill out the following questionnaires: FOSQ, ESS, fatigue, treatment preference, side effects and SF-36.

End of trial: After trial completion, the participant will continue to receive support from the dentists and physicians and he/she will still be able to come to the clinic for follow up visits. The participant will be also able to meet with the sleep physician who will go over the results and will recommend an ideal treatment regimen for him/her.

REFERENCES

1 AlGhanim N, Comondore VR, Fleetham J, et al. The economic impact of obstructive sleep apnea. Lung 2008; 186:7-12
2 Sassani A, Findley LJ, Kryger M, et al. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep 2004; 27:453-458
3 Tarasiuk A, Greenberg-Dotan S, Brin YS, et al. Determinants affecting health-care utilization in obstructive sleep apnea syndrome patients. Chest 2005; 128:1310-1314
4 Peppard PE, Young T, Barnet JH, et al. Increased Prevalence of Sleep-Disordered Breathing in Adults. Am J Epidemiol 2013 Epub ahead of print
5 Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. Sleep 2004; 27:934-941
6 Otsuka R, Ribeiro de Almeida F, Lowe AA, et al. The effect of oral appliance therapy on blood pressure in patients with obstructive sleep apnea. Sleep Breath 2006; 10:29-36
7 Itzhaki S, Dorchin H, Clark G, et al. The effects of 1-year treatment with a herbst mandibular advancement splint on obstructive sleep apnea, oxidative stress, and endothelial function. Chest 2007; 131:740-749
8 Trzepizur W, Gagnadoux F, Abraham P, et al. Microvascular endothelial function in obstructive sleep apnea: Impact of continuous positive airway pressure and mandibular advancement. Sleep Med 2009; 10:746-752
9 Chan AS, Lee RW, Cistulli PA. Dental appliance treatment for obstructive sleep apnea. Chest 2007; 132:693-699
10 Sadatsafavi M, Marra CA, Ayas NT, et al. Cost-effectiveness of oral appliances in the treatment of obstructive sleep apnoea-hypopnoea. Sleep Breath 2009; 13:241-252
11 Sabaté E, WHO Adherence to Long Term Therapies Project., Global Adherence Interdisciplinary Network., et al. Adherence to long-term therapies : evidence for action. Geneva: World Health Organization, 2003
12 Burkhart PV, Sabate E. Adherence to long-term therapies: evidence for action. J Nurs Scholarsh 2003; 35:207
13 Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep 2011; 34:111-119
14 Parish JM, Miller BW, Hentz JG. Autotitration positive airway pressure therapy in patients with obstructive sleep apnea who are intolerant of fixed continuous positive airway pressure. Sleep Breath 2008; 12:235-241
15 Sutherland K VO, Tsuda H, Marklund M, Gagnadoux F, Kushida CL, Cistulli PA. Efficacy and Effectiveness of oral appliance therapy for Obstructive Sleep Apnea. J Clin Sleep Med 2014; 10:215-227.
16 Gagnadoux F, Fleury B, Vielle B, et al. Titrated mandibular advancement versus positive airway pressure for sleep apnoea. Eur Respir J 2009; 34:914-920
17 Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of CPAP versus Oral Appliance treatment for Obstructive Sleep Apnea: A Randomised Controlled Trial. Am J Respir Crit Care Med 2013; 187:879-887
18 Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004; 170:656-664
19 Grote L, Hedner J, Grunstein R, et al. Therapy with nCPAP: incomplete elimination of Sleep Related Breathing Disorder. Eur Respir J 2000; 16:921-927

20 Vanderveken OM, Dieltjens M, Wouters K, et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax; 68:91-96
21 Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2013; 187:879-887
22 Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. Thorax 1994; 49:263-266
23 Lowe AA, Sjoholm TT, Ryan CF, et al. Treatment, airway and compliance effects of a titratable oral appliance. Sleep 2000; 23 Suppl 4:S172-178
24 Vanderveken OM, Dieltjens M, Wouters K, et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax 2013; 68:91-96
25 Bansback NJ, Anis AH, Marra CA. Patient reported outcomes for rheumatoid arthritis: where are we and where are we going? J Rheumatol 2008; 35:1482-1483
26 Ferguson KA, Ono T, Lowe AA, et al. A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. Thorax 1997; 52:362-368
27 Ferguson KA, Ono T, Lowe AA, et al. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. Chest 1996; 109:1269-1275
28 Engleman HM, McDonald JP, Graham D, et al. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002; 166:855-859
29 Pelletier-Fleury N, Gafni A, Krucien N, et al. The development and testing of a new communication tool to help clinicians inform patients with obstructive sleep apnoea syndrome about treatment options. J Sleep Res 2012; 21:577-583
30 Krucien N, Gafni A, Fleury B, et al. Patients' with obstructive sleep apnoea syndrome (OSAS) preferences and demand for treatment: a discrete choice experiment. Thorax 2013; 68:487-488
31 Stacey D, Bennett CL, Barry MJ, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2011:CD001431
32 Almeida FR, Mulgrew A, Ayas N, et al. Mandibular advancement splint as short-term alternative treatment in patients with obstructive sleep apnea already effectively treated with continuous positive airway pressure. J Clin Sleep Med 2013; 9:319-324
33 Anandam A, Patil M, Akinnusi M, et al. Cardiovascular Mortality in Obstructive Sleep Apnea Treated with Continuous Positive Airway Pressure or Oral Appliance: an Observational Study. Respirology 2013; 18:1184-1190
34 Almeida FRB, N. Long-Term Effectiveness of Oral Appliance versus CPAP Therapy and the Emerging Importance of Understanding Patient Preferences. Sleep 2013; 36:1271-1272
35 Lim JLTJFJWJJ. Oral appliances for obstructive sleep apnoea (Review) The Cochrane Library 2009:1-69
36 Blackman A, McGregor C, Dales R, et al. Canadian Sleep Society/Canadian Thoracic Society position paper on the use of portable monitoring for the diagnosis of obstructive sleep apnea/hypopnea in adults. Can Respir J 2010; 17:229-232
37 Gauthier L, Almeida FR, Arcache P, et al. Position paper by Canadian dental sleep medicine professionals on the role of different health care professionals in managing OSA and snoring with oral appliances. Can Respir J 2012; 19:307-309
38 Santos-Silva R, Sartori DE, Truksinas V, et al. Validation of a portable monitoring system for the diagnosis of obstructive sleep apnea syndrome. Sleep 2009; 32:629-636
39 Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. Sleep 2009; 32:915-919

40 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14:540-545
41 Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993; 37:147-153
42 McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31:247-263
43 Arnardottir ES, Janson C, Bjornsdottir E, et al. Nocturnal sweating--a common symptom of obstructive sleep apnoea: the Icelandic sleep apnoea cohort. BMJ Open 2013; 3
44 Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012; 8:597-619
45 Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997; 20:835-843
46 McHorney CA, Ware JE, Jr., Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994; 32:40-66
47 Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008; 5:173-178
48 Wolkove N, Baltzan M, Kamel H, et al. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. Can Respir J 2008; 15:365-369
49 Harper BD. Projecting realistic enrollment rates. Monitor 2004; 18:15-18
50 Jones B KM. Design and analysis of cross-over trials. New York: Chapman & Hall 1989
51 Sankoh A DAR, Huque M. Efficacy endpoint selection and multiplicity adjustment methods in clinical trials with inherent multiple endpoint issues. Statist Med 2003; 22:3133-3150
52 Almeida FR, Henrich N, Marra C, et al. Patient preferences and experiences of CPAP and oral appliances for the treatment of obstructive sleep apnea: a qualitative analysis. Sleep Breath 2013; 17:659-666