PAP-OAT-CBTi-COMISA Trial: a Pilot Study

POCC Trial: a Pilot Study

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Summary of rational, objectives, protocols, timeline and requirements for the POCC Trial: a Pilot Study

The POCC Trial: a Pilot Study v 3.2

POCC Trial: a Pilot Study. Dr. John Viviano BSc DDS D ABDSM Sleep Disorders Dentistry Research and Learning Centre. Dr. Sherif Elsaraj BSc MSc DMD PhD, McGill University, Jewish General Hospital, Department of Dentistry, A024; Researcher, Centre de recherche en medecine psychosociale du CISSS de l'Outaouais, Hull Hospital. Dr. James Macfarlane BSc MSc PhD FAASM

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POCC Trial: a Pilot Study

Executive Summary:

Recent literature documents the high prevalence of co-morbid insomnia and OSA (COMISA). PAP adherence for patients suffering with COMISA is 30% lower than OSA alone, approximately 35% a year post prescription. This leaves approximately 2/3's of diagnosed patients unmanaged for their OSA, and as a result, likely to have difficulty managing their Insomnia. In contrast, oral appliance therapy (OAT), which has a similar Mean Disease Alleviation (MDA) to PAP, experiences a very high adherance, in the 90% range for non-COMISA patients. **The question we cannot currently answer is, "Does high OAT adherence position it as the preferred treatment alternative for patients suffering with COMISA?"**

Pilot Study Main Objective:

To evaluate the clinical utility of OAT in COMISA patients by assessing the effectiveness of OAT in patients suffering with COMISA, that are resistant or intolerant to PAP therapy.

INTRO to PAP-OAT-CBTi-COMISA Trial (POCC Trial)

This document summarizes a pilot **study to evaluate the clinical utility of oral appliance therapy in combination with CBTi for management of COMISA**. Two studies are proposed: a Pilot Trial, and a Full Trial (POCC Pilot Trial, POCC Full Trial)

a) "**Pilot Trial**: **A patient management protocol with formal care pathway.** This is not a randomized trial. The goal is to offer the protocol to consecutive patients in Ontario sleep clinics. There are no significant risks to participants, with potential gains in formalized care, systematic scheduling and compiling of patient-centred and laboratory outcomes; in addition, the participants who complete all steps will have cost savings related to their treatment of sleep apnea. There is no 'experiment' strictly speaking (there is no control condition nor randomization) but the formalized sequence of offering OAT after a prescription of PAP is not a universally implemented for the care of OSA or more specifically COMISA and there are benefits from documenting the results of this protocol. Our intention is to publish in Abstract and Poster form **ASAP**. (Mid to late 2025), followed by a full journal publication. We are applying for a Panthera research grant (submission deadline August 30, 2024) to help fund expenses for this pilot study.

b) **Full Trial**: will have a longer timeline and will be designed to answer many more unknowns and to withstand the most rigorous of scientific scrutiny. This will require more significant funding and submission for a higher-level Grant. All discussions for the Full Trial are in the preliminary stage and study objectives, protocols, choice of oral appliance and CBTi delivery, and individuals invited to participate are all open for discussion. Once the team is assembled and the study protocol is finalized, a research grant proposal will be written and submitted for the Full study.

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Rational and Overview: POCC Trial Project

COMISA, which refers to co-existing insomnia and obstructive sleep apnea (OSA), is a highly debilitating disorder with a general population prevalence of 6% **[1]**. Up to 50% of people with OSA have insomnia and 40% of people with Insomnia have OSA **[2]**. These disorders are likely bi-directionally related. Insomnia may be caused by obstructive events, and greater frequency and duration of awakenings from increased sympathetic activity, and OSA may be worsened by insomnia, via hyper-arousability, reducing stable sleep and reducing the respiratory arousal threshold. PAP use has been associated with a reduction in insomnia in some patients **[3]** and is currently the standard of care for patients suffering with COMISA. Conversely, Cognitive Behavioural Therapy for insomnia (CBTi) has been associated with a small decrease in OSA severity, probably because it consolidates sleep periods and reduces sleep-wake transitions to improve airway stability. **[4]**

Studies using the NHANES 2005-2008 data, sleep health heart study data and the Wisconsin Sleep Cohort data, have reported that COMISA is associated with cardiovascular disease and a 50-70% increased risk of All-Cause Mortality **[5, 6, 7]. Neither insomnia alone nor OSA alone were associated with increased mortality risk.** These studies suggest that ***"future research should investigate mechanisms underpinning COMISA and the effectiveness of different treatment approaches to reduce mortality risk for this common condition".*** **[7]**

PAP is very effective in normalizing OSA. **[8]** However, it suffers from very poor adherence to therapy, with 50% dropping out of treatment after a year, and 83% dropping out of treatment at 5 years. **[9, 10, 11]** Unfortunately, PAP adherence for patients suffering with COMISA is even lower. Patients with COMISA experience a 30% reduction in initial PAP acceptance and use PAP therapy for approximately 2-hours less per night, compared to those with OSA alone. **[12, 13, 14, 15]** Consequently, PAP therapy may not be the most suitable "first-line" treatment for COMISA, as it is often rejected, used sub-optimally, and discontinued over time. This results in both disorders remaining untreated and causing significant health risks. The literature provides little to no guidance regarding alternative therapies for COMISA patients with documented intolerance to PAP use.

Oral appliance therapy (OAT) is not as efficacious at eliminating OSA but has a well-documented high adherence to therapy. Vanderveken documented the Mean Disease Alleviation (MDA) for both PAP and OAT be approximately 50% **[16].** The lower efficacy to eliminate all the OSA seems to be balanced by the much higher adherence rate associated with OAT, resulting in a similar MDA.

The pre-existing issue of less than optimum PAP adherence is exacerbated by co-existing Insomnia. The question is, could the pre-existing favourable adherence associated with OAT provide an advantage and more favourable outcomes for patients suffering with COMISA that have difficulty tolerating PAP?

A very recent clinical trial of 31 patients with COMISA (58% male) and 25 patients with OSA alone (51% male) reported that OAT was associated with improved OSA severity and insomnia symptoms **[17].** In a separate cohort of 12 patients with COMISA, OAT was also associated with improved markers of cardiovascular health. The authors concluded that OAT can be an effective tool for managing COMISA patients, with significant positive impact on respiratory and insomnia related therapeutic outcomes as well on the reduction of cardiovascular risk, as documented by the positive impact on the autonomic balance.

In a recently published case series involving three patients with mild OSA and chronic severe insomnia, aPAP therapy with no treatment for insomnia resulted in one patient experiencing a modest improvement in somatic arousal, insomnia severity, and fatigue, but two patients could not tolerate aPAP therapy. In contrast,

a mandibular advancement device with no treatment for insomnia resulted in prolonged, complete resolution of somatic arousal, chronic insomnia, and fatigue as well as management of their OSA. **[18]**

This is a patient management protocol with a formal care pathway. It is not a randomized trial of such a pathway. The goal is to offer the protocol to consecutive patients in Ontario sleep clinics. There are no significant risks to participants, with potential gains in formalized care, systematic scheduling and compiling of patient-centred and laboratory outcomes; in addition, the participants who complete all steps will have cost savings related to their treatment of sleep apnea. There is no 'experiment' strictly speaking (there is no control condition nor randomization) but the formalized sequence of offering OAT after a prescription of PAP is not a universally implemented for the care of OSA or more specifically COMISA, this Pilot study will document outcomes associated with offering OAT for patients suffering with COMISA, if they prove intolerant to or refuse PAP. **This trial is particularly important as the absence of data regarding outcomes with this protocol currently results in many of these patients remaining unmanaged whatsoever.**

Patients with COMISA experience significantly lower rates of PAP acceptance and use compared to those with OSA-alone. Considering the high prevalence and mortality risk associated with unmanaged COMISA, alternative treatment approaches are required. Initial evidence suggests that OAT may be a favourable therapy in patients with COMISA, which will be more acceptable to patients, and reduce symptoms of both insomnia and OSA. To date, no previous study has investigated combinations of OAT and CBTi in patients with COMISA. Therefore, more research is required to investigate the real-world clinical utility of OAT paired with CBTi for the management of COMISA. This will be the focus of the PACC Pilot Study. THE POCC Trial (pilot study) describes a clinical management protocol aimed at improving the care of patients with OSA, insomnia, and particularly those with overlapping conditions like COMISA (co-morbid insomnia and OSA). This non-randomised trial aims to investigate a novel management model for COMISA, combining CBTi, PAP therapy, and OAT;

Objective: To evaluate the clinical utility of OAT in the management of patients suffering with COMISA in a formal patient management protocol offered to consecutive patients in Ontario sleep clinics.

Nature of the Study: This is not a randomized controlled trial but a formal care pathway protocol. There is no experimental component involving control conditions or randomization.

Risk and Benefit: There are no significant risks to participants.
Potential benefits include:

- Formalized guidance-based care and systematic scheduling.
- Compilation of patient-centered and laboratory outcomes.
- Cost savings for participants who complete all steps of the protocol.

Protocol Details:

- The protocol involves offering Oral Appliance Therapy (OAT) after the prescription of Positive Airway Pressure (PAP) therapy for patients that refuse/cannot tolerate PAP.
- This sequential approach is not universally implemented for the care of Obstructive Sleep Apnea (OSA) or COMISA, however, it is aligned with AASM and AADSM guidance.

Target Population:

Consecutive patients from enrolled Ontario sleep clinics who are diagnosed with COMISA. **This protocol aims to streamline and enhance patient care while providing measurable benefits without the complexities and risks associated with experimental studies.**

Primary Outcome:

- **Evaluate effect of Oral Appliance Therapy (OAT) in COMISA patients** by assessing the effectiveness of OAT in patients suffering with COMISA (Co-morbid Insomnia and Sleep Apnea), that are resistant or intolerant to PAP therapy.

Secondary Outcomes:

- **Impact of Insomnia Symptoms on Adherence to PAP or OAT.** This outcome focuses on whether insomnia symptoms affect how well patients adhere to PAP or OAT. **(does insomnia, or specific insomnia symptoms, predict or worsen PAP or OAT use?)**
- **What fraction of participants who did not continue PAP are adequately managed with OAT, and what fraction will not continue any treatment (no PAP, no OAT)**
- **The effect of OAT on improving insomnia symptoms**
- **The presence of a dose-response relationship between OAT use, and improvements in insomnia symptoms.**
- **Evaluate the integration of OAT into Current Models of Care for COMISA Management**: Outcomes examine how OAT can be successfully incorporated into existing treatment frameworks for managing COMISA.
- **Evaluate the prevalence of COMISA** in patients attending for an in-lab sleep study

Citations

1. ***Sweetman. A. et al., (2021). Prevalence and associations of co-morbid insomnia and sleep apnoea in an Australian population-based sample. Sleep Medicine. 82. 9-17.***

2. ***Sweetman A. et al. (2019) Co-Morbid Insomnia and Sleep Apnea (COMISA): Prevalence, Consequences, Methodological Considerations, and Recent Randomized Controlled Trials. Brain Sci. 2019, 9, 371.***

3. ***Sweetman. A Co-morbid Insomnia and Sleep Apnoea (COMISA): Latest Research from an Emerging Field. Curr Sleep Medicine Rep 9. 180-189 (2023).***

4. ***Sweetman A et al., Cognitive Behavioural Therapy for Insomnia Reduces Sleep Apnea Severity: A Randomized Control Trial. ERJ Open Res 2020 May 17;6(2): 00161-2020***

5. ***Lechat B. et al., The association of co-morbid insomnia and sleep apnea with prevalent cardiovascular disease and incident cardiovascular events. J Sleep Res. 2022 Oct;31(5):e13563. doi: 10.1111/jsr.13563. Epub 2022 Feb 15. PMID: 35166401.***

6. ***Sweetman A. et al., Association of Co-morbid insomnia and sleep apnoea symptoms with all-cause mortality: Analysis of the NHANES 2005-2008 data. Sleep Epidemiology 2 (2022) 100043.***

7. ***Lechat B., et al. All-Cause Mortality in People with Co-Occurring Insomnia Symptoms and Sleep Apnea: Analysis of the Wisconsin Sleep Cohort. Nat Sci Sleep. 2022 Oct 13;14:1817-1828.***

8. ***Douglas NJ, Systematic review of the efficacy of nasal CPAP. Thorax 1998;53:414–415.***

9. ***Bartlett D. et al., Increasing adherence to obstructive sleep apnea treatment with a group social cognitive therapy treatment intervention: a randomized trial. SLEEP 2013;36(11):1647-1654***

10. ***Fernanda Ribeiro de Almeida et al., Long-term compliance and side effects of oral appliances used for the treatment of snoring and obstructive sleep apnea syndrome J Clin Sleep Med 2005 Apr 15;1(2):143-52.***

11. ***Sutherland K. et al., Efficacy vs. effectiveness in the treatment of OSA: CPAP and oral appliances. Journal of Dental Sleep Medicine 2015;2(4):175–181.***

12. ***Smith S, et al., Sleep onset insomnia is associated with reduced adherence to CPAP therapy. Sleep Biol Rhythm. 2009;7:A74.***

13. ***Sweetman A, et al. Developing a successful treatment for co-morbid insomnia and sleep apnoea. Sleep Med Rev. 2017;33:28-38.***

14. ***Sweetman A, et al., Co-morbid insomnia and sleep apnea (C0MISA): Assessment and management approaches. Sleep Medicine Clinics. 2022 Dec;17(4):597-617.***

15. ***Tan D, et al. Health and treatment correlates of obstructive sleep apnoea (0SA) alone and comorbid with insomnia (C0MISA) in a community based sample. Effect of C0MISA on CPAP acceptance and use ASA Adelaide Meeting. 2022.***

16. ***Vanderveken OM. et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax 2013; 68:91-6***

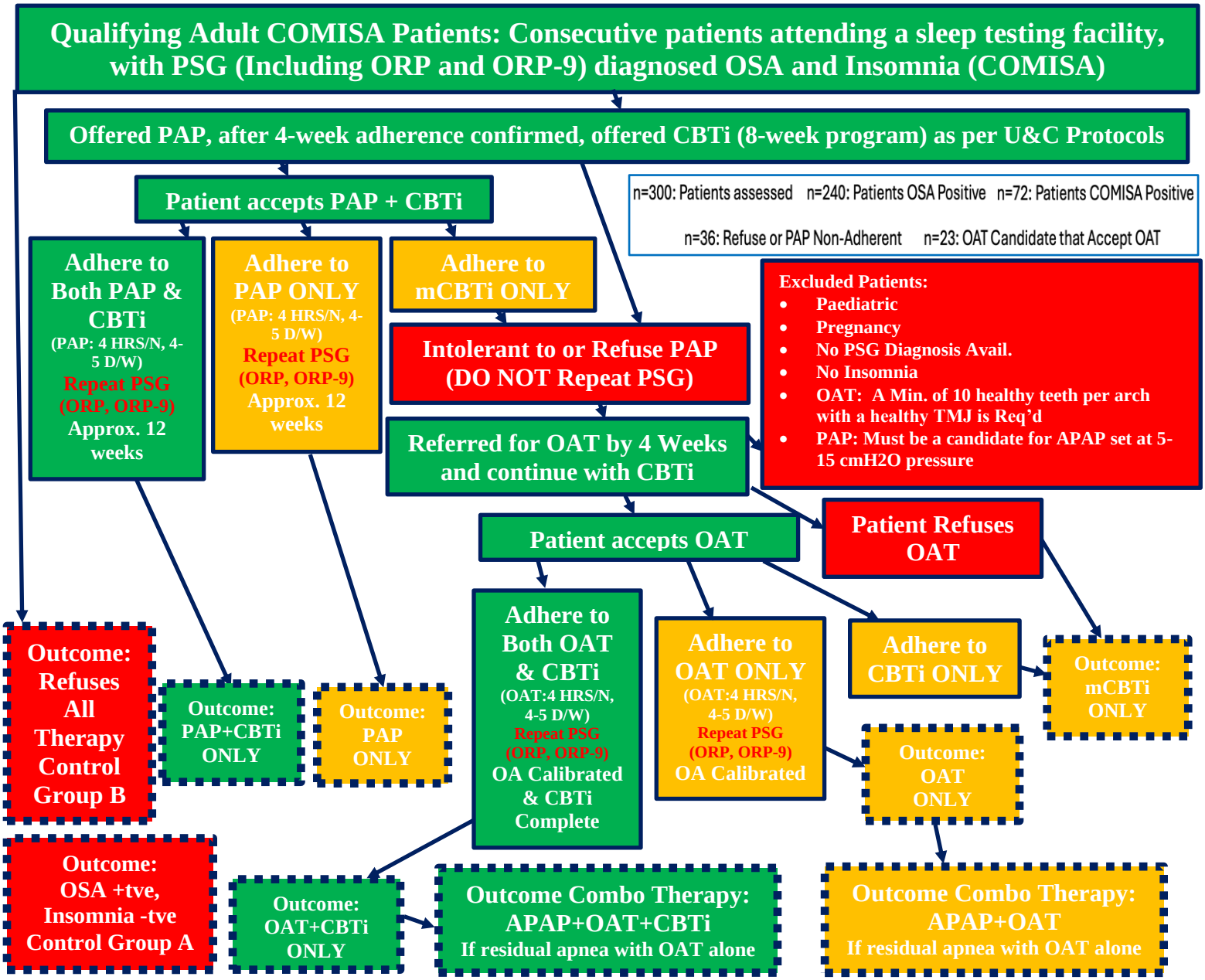
17. ***Giannasi LC., et al., Effective Treatment with mandibular Advancement Devices in Comorbid Insomnia and Sleep Apnea: A Two Step Study on Clinical, Polysomnographic, and Cardiovascular Risk. Sleep Sci 2023; 16(S 01): 001-070 DOI: 1055/s-0043-1770264 ID: 1419.***

18. ***Proothi et al. Chronic insomnia remitting after maxillomandibular advancement for mild obstructive sleep apnea: a case series. Journal of Medical Case Reports (2019) 13:252 https://doi.org/10.1186/s13256-019-2182***

"POCC Trial Pilot Study Design"

POCC Pilot Study: *Observational*

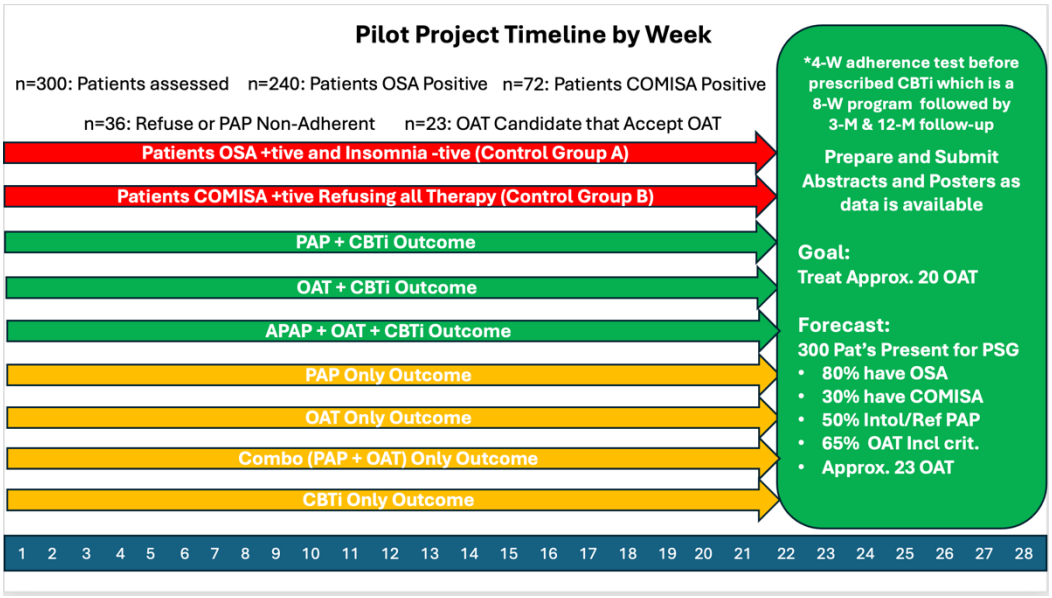
Objective is to produce valid data as quickly as possible for presentation in Abstract and Poster format at upcoming meetings: AADSM, APSS (AASM/ SRS), CHEST, etc. It is designed to document clinical utility of OAT for COMISA patients.



Analysed Cohorts:

- Control Group A (OSA +tve, Insomnia -tve)
- Control Group B (COMISA diagnosed refusing all therapy)
- PAP + CBTi (Tolerant of PAP + CBTi)
- OAT + CBTi (Tolerant of OAT + CBTi)
- Combo + CBTi (Intolerant of PAP, Residual apnea with OAT, Tolerant of PAP + OAT + CBTi)
- PAP (Adherent to PAP only, does not complete CBTi)
- OAT (Adherent to OAT only, does not complete CBTi)
- Combo PAP + OAT (Adherent to PAP + OAT only, does not complete CBTi)
- CBTi (Adherent to CBTi, Intolerant/Refused PAP, Intolerant/Refused OAT)

Pilot Threshold: Treat Approx. 20 patients with OAT n ≈300, ≈80% OSA, ≈30% COMISA, ≈50% Intolerant/Refuse PAP, ≈65% meet OAT Inclusion criteria and Accept OAT: ≈23 OAT cases



n	Description
≈300	Total Patients Assessed with PSG
≈240	(80%) Positive for OSA
≈168	(70%) Positive for OSA and Negative for Insomnia (NO COMISA) **(CONTROL GROUP A)**
≈72	(30%) Positive for OSA and Positive for Insomnia (COMISA)
?	COMISA diagnosed refusing all therapy **(CONTROL GROUP B)**
≈36	PAP + CBTi (Tolerant of PAP + CBTi)
≈23	OAT + CBTi (Tolerant of OAT + CBTi)
?	Combo + CBTi (Intol. of PAP, Residual apnea with OAT, Tol. of PAP + OAT + CBTi)
?	PAP (Adherent to PAP only, does not complete CBTi)
?	OAT (Adherent to OAT only, does not complete CBTi)
?	Combo PAP + OAT (Adherent to PAP + OAT, does not complete CBTi)
?	CBTi (Adherent to CBTi Intol./Refused PAP, Intolerant/Refused OAT)

NOTE: Questionnaires will be completed by all patients at Baseline, at treatment Endpoint, and at 3-month and 12-month after reaching treatment Endpoint.

Timeline and Protocol Management

The care pathway described in this protocol is ambitious, but necessary to achieve our goal of improving COMISA management. **Sleep Disorders Dentistry inc. (SDDi) will assume the responsibility to monitor, document and ensure completion of all Milestones and Protocols in a timely fashion.**

All patients diagnosed with COMISA will be offered a **numbered enrolment package at the time of diagnosis, and SDDi will be informed of the patient's name and contact information.** These patients will be entered onto a MASTER spreadsheet that will be used by SDDi to document those that refuse all therapy (Control Group), those that enrol in the study, and all Milestones, Endpoints, and 3- and 12-month post Endpoint follow up questionnaires.

The Case Manager's at SDDi will oversee each patient's progress until study completion at 12-months post Endpoint. Case Managers will monitor, interview, and enroll all participating patients, and from that point forward, their progress will be monitored on a spreadsheet ensuring all milestone and follow-up PSG's are scheduled and completed. If patients are non-adherent to PAP, they will facilitate a referral for OAT. SDDi will ensure all milestones are completed in a timely manner.

All appointments will be arranged as per usual and customary protocols in the Physician or Dental office the patient is attending. However, the case manager will be responsible for monitoring and coordinating appointments and ensuring that data collection is complete (pre and post treatment blood pressure measurements, etc.), monitoring adherence, and addressing any issues that arise.

Additionally, to ensure timely follow-up, and that Follow-up PSGs are completed within the timeline of the study, a Follow-up PSG should be scheduled 2 months post aPAP adherence is documented and 2 months post OAT adherence is documented. **These follow-up PSG's should be a minimum of 3 months from initiating OSA therapy with that specific treatment modality.** For the aPAP arm, if the patient fails to adhere with therapy, the PSG will be cancelled and preserved for OAT outcome assessment. By assigning case managers and ensuring dedicated resources for follow-up, we aim to facilitate the successful implementation and completion of the protocol.

SDDi Management team will monitor, facilitate and document:

- **Qualifying COMISA Patients refusing all treatment will be documented**
- **Patient Enrollment**
- **CBTi post-delivery Follow-up**
- **PAP post-delivery Follow-up**
- **PAP-CBTi Endpoint PSG scheduling and Follow-up**
- **Referral for OAT if non-adherent/refuse PAP**
- **OAT Post-delivery Follow-up**
- **OAT-CBTi Endpoint PSG scheduling and Follow-up**
- **CBTi ONLY Follow-up**
- **aPAP-OAT-CBTi Endpoint documented through aPAP report and Endpoint Questionnaires**
- **aPAP-OAT ONLY Endpoint documented through aPAP report and Endpoint Questionnaires**
- **aPAP ONLY Endpoint documented through aPAP report, PSG and Endpoint Questionnaires**
- **OAT ONLY Endpoint documented through PSG and Endpoint Questionnaires**
- **CBTi ONLY Endpoint documented through Endpoint Questionnaires**

Sleep Physicians are to follow AASM guidance and Dentists are to follow AADSM guidance in their patient Management. The Sleep Reset APP will be dispensed as per Sleep Reset Recommendations.

Safety

An important aspect of this protocol is to ensure and report on the safety of the approach. **Adverse events will be documented as the patient makes us aware of them, or they are noted by a managing clinician or attendant, and will also be specifically enquired about, and documented at treatment Endpoint and at the 3- and 12-month follow-up.**

This will include all reported symptoms or incidents, as well as incidents of recently falling asleep at the wheel while driving. Our protocols will follow current guidelines.
Phillips R et al. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open Access. 2019;9:e024537.

All consecutively tested patients that are diagnosed with COMISA will end up in an outcome group as follows:

- **(1) Control Group A (OSA +tive, Insomnia -tive) No COMISA**
- **(2) Control Group B (COMISA diagnosed refusing all therapy)**
- **(3) PAP + CBTi (Tolerant of PAP + CBTi)**
- **(4) OAT + CBTi (Tolerant of OAT + CBTi)**
- **(5) Combo + CBTi (Intolerant of PAP, Residual apnea with OAT, Tolerant of PAP + OAT + CBTi)**
- **(6) PAP (Adherent to PAP only, does not complete CBTi)**
- **(7) OAT (Adherent to OAT only, does not complete CBTi)**
- **(8) Combo PAP + OAT (Adherent to PAP + OAT, does not complete CBTi)**
- **(9) CBTi (Adherent to CBTi Intolerant/Refused PAP, Intolerant/Refused OAT)**

For patient's requiring further therapy due to refusing all therapy, or having unresolved concerns, an appropriate referral will be made as required outside the study. This patient will be considered either a "non-registered candidate (Control Group above), a "drop-out", or, if they have completed therapy as prescribed and can safely continue their study obligations regarding Endpoint, 3- and 12-month questionnaires, they would do so. Patients who discontinue PAP or OAT will be offered a second trial of PAP. If they still choose not to continue with therapy, their Endpoint will be as **Group (9)** above. This comparator group will provide valuable insights, as these patients will have presumably completed CBTi and may show measurable improvements on questionnaires.

To ensure CBTi is being provided in a safe manner, the prescribing sleep physician is promptly advised when a participant that has been prescribed CBTi, either drops out of OSA therapy altogether, or transitions early from aPAP to OAT. The sleep physician will then decide the most appropriate option regarding CBTi from the following:

1) **Continue unmodified CBTi**
2) **Remove sleep restriction from CBTi (mCBTi)**
3) **Terminate CBTi**

This will allow the sleep physician to consider important patient specific factors that vary between COMISA patients:

1) **Some are sleepy, others are not**
2) **How far the patient has progressed in the CBTi program, and their level of sleepiness at that point**
3) **Some have safety-critical activities, some do not**

If CBTi is terminated, the sleep physician may decide to re-instate it once the patient has demonstrated adherence to OSA therapy, for instance dropping aPAP and moving onto OAT. These management decisions will be recorded systematically in the research file / case report form (CRF)

Study protocols ensure a systematic approach to monitoring safety and aligns with established guidelines for reporting adverse events. Sleep physicians will maintain the ability to adjust PAP settings as part of their standard care for our patient population, ensuring treatment is tailored to individual needs. **At no time will the patient's safety be compromised for the sake of the study.**

APPENDIX I

Defining Insomnia Status:

Insomnia Severity Index (ISI) threshold to define insomnia in the presence of OSA:

- A score of 4 or more on the sum of the first 3 items plus:
    - combined with a total score of 8 or above defines at least mild insomnia
    - combined with a total score of 15 or above defines moderate insomnia.

https://www.sleepprimarycareresources.org.au/questionnaires/isi

The combination of the sub-score from the first 3 items, and the total threshold score ensures that the participant has at least a 'moderate' complaint for one of the sleep symptoms (first 3 items), and a combined score in the clinically relevant range overall (either mild or moderate threshold).

This is important because patients with OSA may report significant daytime impacts / dissatisfaction / interference because of their OSA, in the absence of any nocturnal insomnia symptoms. For instance, it is possible to score 16/28 on the ISI, by checking the most severe range on the final 4 items.

NOTE: this is not specifically a DSM-V or ICSD-3 diagnosis; the validity of this way of declaring significant insomnia will be discussed as per existing literature data.

DSM-5-TR: https://www.psychiatry.org/psychiatrists/practice/dsm

APPENDIX II

Rational for modifying the ESS Questionnaire:

- **Increased likelihood that patient understands the questions.**

ESL patients are not familiar with the verb 'to doze". In addition, the patient may think it's asking them how they feel right now. Things could be made clearer with the following subtle revision to the wording:

- **Here's how it reads now...**
  - **How Sleepy Are You? How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:*
    - *· No chance of dozing =0*
    - *· Slight chance of dozing =1*
    - *· Moderate chance of dozing =2*
    - *· High chance of dozing =3*

- ***m*ESS Modified as follows:**
  - **How Sleepy Are You? How likely are you to fall asleep in the following situations during the past 2-weeks? For each situation, decide whether or not you would have:*
    - *· No chance of falling asleep =0*
    - *· Slight chance of falling asleep =1*
    - *· Moderate chance of falling asleep =2*
    - *· High chance of falling asleep =3*

APPENDIX III

Sequence of Therapy:

- **Important considerations:**
  - CBTi uses sleep restriction/compression to increase drive to sleep.
  - Unmanaged OSA combined with sleep restriction/compression may lead to increased daytime somnolence and associated concerns.
  - Sleep Reset CBTi sleep restriction/compression begins the later part of week 1.
  - Sleep Reset CBTi program runs for 8 weeks.
  - CPAP adherance is related to adherance at end of week 4. *"Given that early adherence was a strong predictor of long-term compliance, for now, a short-term trial of CPAP therapy (of approximately 1 month) may be the best practical means to identify those at highest risk of future nonadherence to treatment"* ***Emer Van Ryswyk et al. Predictors of long-term adherence to CPAP in patients with OSA and CVD. SLEEPJ, 2019, Vol. 42, No. 10, 1-9***
  - Patients that are non-adherent to OSA therapy should use Sleep Reset CBTi with Sleep Restriction turned off. *Request "sleep restriction" schedule not be employed through Sleep Reset for safety, participants ask the coach to stop the restricted schedule, and they would get CBTi without sleep restriction. This is not ideal and will be evaluated and described as a* ***modified*** *CBTi intervention, (****mCBTi****).*

- **Delivery of OSA and Insomnia therapy should be staged as follows:**

  - **Start Date: aPAP Delivery**
  - At **4 weeks:** Confirm aPAP adherance ***(Ryswyk et al. Sleep 2019 suggests 4 weeks)***
    - **If aPAP adherent, deliver Sleep Reset CBTi**
  - At **12 weeks:** PSG to evaluate outcome for Combined aPAP + Sleep Reset CBTi

    - **If aPAP non-adherent at any point, then refer for OAT Consultation**

    - **If patient agrees to OAT, then take impressions and bite registration**

  - **Start Date: OAT Delivery**
  - At **4 weeks:** Confirm OAT adherance
    - **If patient does not proceed with OAT, deliver Sleep Reset CBTi with Sleep Restriction Turned off. (mCBTi)**
    - **If OAT adherent, deliver Sleep Reset CBTi**
  - At **12 weeks:** PSG to evaluate outcome for Combined OAT + Sleep Reset CBTi

    - **If OAT non-adherent, deliver Sleep Reset CBTi with Sleep Restriction Turned off. (mCBTi)**

  - **If PSG demonstrates residual OSA with OAT, patient to combine use of aPAP and OAT, and aPAP report used to document Efficacy and Adherence.**

APPENDIX IV

CBTi Therapy:

"Sleep Reset APP" – The company has agreed to make this online APP available at N/C for use in this study. Dispensing of the Sleep Reset APP will be performed as per the recommendations provided by Sleep Reset.

NOTE: Patients that are non-adherent to OSA therapy will use Sleep Reset CBTi with Sleep Restriction turned off. *(Request "sleep restriction" schedule not be employed through Sleep Reset for safety, participants ask the coach to stop the restricted schedule, and they would get CBTi without sleep restriction.) This is not ideal and will be evaluated and described as a* ***modified*** *CBTi intervention, (****mCBTi****).*

https://play.google.com/store/apps/details?id=com.simplehabit.nocturne&hl=en_CA&pli=1

https://apps.apple.com/us/app/sleep-reset-cbt-for-insomnia/id1529321947

APPENDIX V

Odds Ratio Product:

Overview

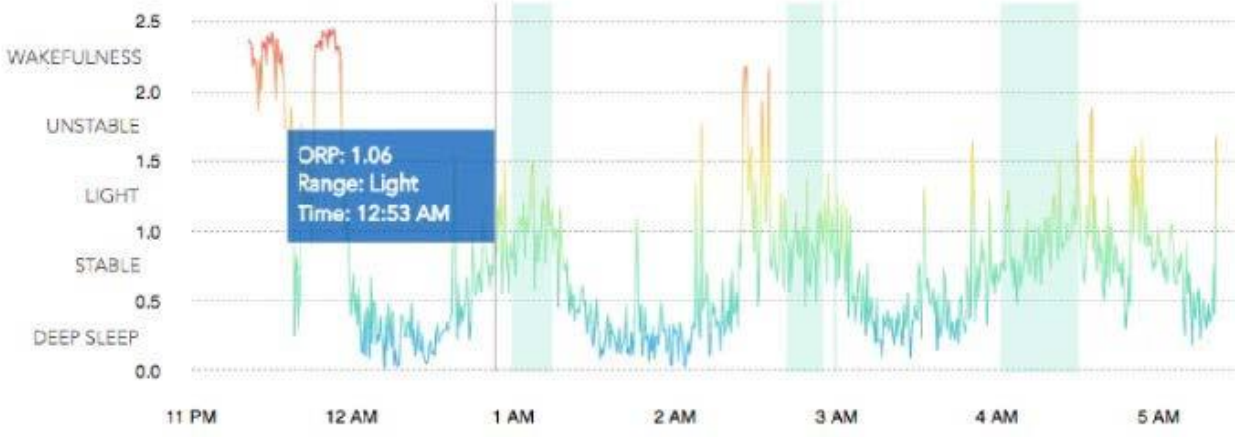
Odds Ratio Product (ORP) is a highly validated measure of sleep depth ranging from 0 (deep sleep) to 2.5 (full wakefulness). ORP uses Fast-Fourier Transform to separate the EEG into 4 frequency bands (slow-delta, fast delta+theta, alpha+sigma, beta) and assigns a power value of 0 to 9 for each frequency band in each 3-second epoch. This creates a 4-digit combination for each 3-second epoch and 10,000 potential patterns. These patterns are assessed for the probability of being asleep or awake and are then averaged across a 30-second epoch and converted to an ORP value between 0 (never occurs during stage wake) to 2.5 (never occurs during sleep).2 The outcome is a continuous and objective measure of sleep depth throughout the night. ORP is provided as an average in the entire total recording time (ORPTRT), during NREM sleep, REM sleep, or stage wake where it indicates the pressure for sleep. ORP decreases as a patient moves from wake through the NREM stages (See Figure 2). During REM sleep, higher values are associated with greater REM fragmentation. Sleep depth in any given stage varies considerably among subjects. Thus, patients with the same amount of stage 2 can have very deep or very shallow sleep overall. ORP may help identify subjects who have sleep symptoms but appear to have normal sleep architecture.

ORP-9

ORP-9 assesses sleep depth after an arousal, calculated as the average ORP in the 9 seconds post-arousal in NREM sleep. It reflects how sensitive an individual might be to disruptions in their sleep and is a promising marker of sleep disturbance. A low ORP-9 indicates that following arousal the patient can quickly (within seconds) return to a deep sleep where he/she is resistant to arousal stimuli. Conversely, high ORP-9 indicates that following an arousal, sleep lingers in a light state for long periods during which minor stimuli can re-arouse the subject. Thus, ORP-9 may be a mechanism of sleep disruption, where a combination of high ORP-9 and repeated arousals makes it difficult for the patient to achieve deeper sleep.

Note:

- The ORP-9 may not be reliable and be artificially inflated if the AHI is >60.
- Low ORP-9 is <0.7: suggests a low likelihood of sleep being easily disturbed.
- Mod ORP-9 is >0.7<1.2: suggests mod likelihood of sleep being easily disturbed.
- High ORP-9 is >1.2 < 2.5: suggests high likelihood of sleep being easily disturbed.



ORP distribution across an entire night. Green shaded boxes indicate REM sleep.

APPENDIX VI

Oral Appliance Therapy Appliance Selection:

Panthera **D-SAD Classic** and **D-SAD X3** oral appliances

- All patients will be offered a **D-SAD Classic**, unless they are not candidates due to missing teeth or poor mandibular retention, in which case they are offered a **D-SAD X3**

Oral Appliance Therapy Protocol:

The OAT protocol followed in this study will be as per usual and customary OAT protocols. The oral appliance will be fabricated at a jaw position where the jaw is noticeably forward from habitual position but still within the patients comfort so as to be able to initiate sleep. The vertical dimension will be approximately 5 mm inter-dentally to accommodate both the appliance and curve of Spee. This is in line with most bite protocols currently in use.

Jaw drop will be controlled with elastics when required.

Key symptoms will have been established and documented when completing the intake questionnaires.

Post delivery, the patient will advance their appliance (Home Calibration) until snoring and key symptoms are resolved or they cannot tolerate further advancement.

Objective testing with the Belun ring will be used to document objective reduction in OSA, or the need for further advancement, before finalizing the jaw position.

This pilot study involves a Formal Care Pathway which includes exclusively aPAP, OAT, or combined aPAP plus OAT therapy to manage OSA, but if deemed necessary or appropriate, patients may have access to adjunctive therapies such as myo-functional therapy, positional therapy, weight loss etc. after fulfilling their study obligations.

APPENDIX VII

PAP Therapy:

Patients must be candidates for APAP set at 5-15 cm H2O in order to qualify for participation in this study.

All patients in the study that use PAP will use APAP 5-15 cm H2O.

In Ontario, OHIP covers a portion of aPAP therapy and patients that have access to Extended Health Care often have the remainder covered in full. Any portion not covered by OHIP and/or available extended health care plans will be provided at N/C to the patient. **There is no financial penalty to the patient for participating in this study.**

APPENDIX VIII

Sleep-Promoting Medications:

While there has been a benefit shown with the use of sleep-promoting medications for improving CPAP compliance, CBTi produces results that are equivalent to sleep medication, with no side effects, fewer episodes of relapse, and a tendency for sleep to continue to improve long past the end of treatment. The long-term improvements result from the patient learning how to support and promote a natural sleep while remaining compliant with PAP therapy. Therefore, CBTi should be considered a first-line therapy for COMISA (when available), with sleep-promoting medication as a legitimate second line option.

This pilot study involves a Formal Care Pathway which includes exclusively CBTi therapy to manage insomnia, but if deemed necessary or appropriate, patients may have access to sleep-promoting medications after fulfilling their study obligations.

APPENDIX IX

Home Sleep Testing:

As Follow Up Study:
In the rare event that the patient uses their 2 PSG allotment, and they require a third study, they will take a NOX T3 HST.

https://noxmedical.com/noxt3s/

NOX Medical Contact: Natalie Morin
natalie.morin@noxmedical.com

We may require loaners for NOX Medical to be used for the study and returned afterwards.

For Oral Appliance Calibration:
The Belun ring will be used to aide oral appliance calibration for all study oral appliances prior to attending for the follow-up in-lab PSG studies or NOX T3 studies. Belun rings and a dedicated portal access will be provided prior to the study commencing.

At the 3-month follow-up, patients will be provided a Belun ring for 7 nights of consecutive use to document continued efficacy of therapy.

Belun Tech Contact: Maggie Lo
maglobelun@gmail.com

APPENDIX X

PAP-OAT-CBTi -COMISA Trial (POCC Trial)

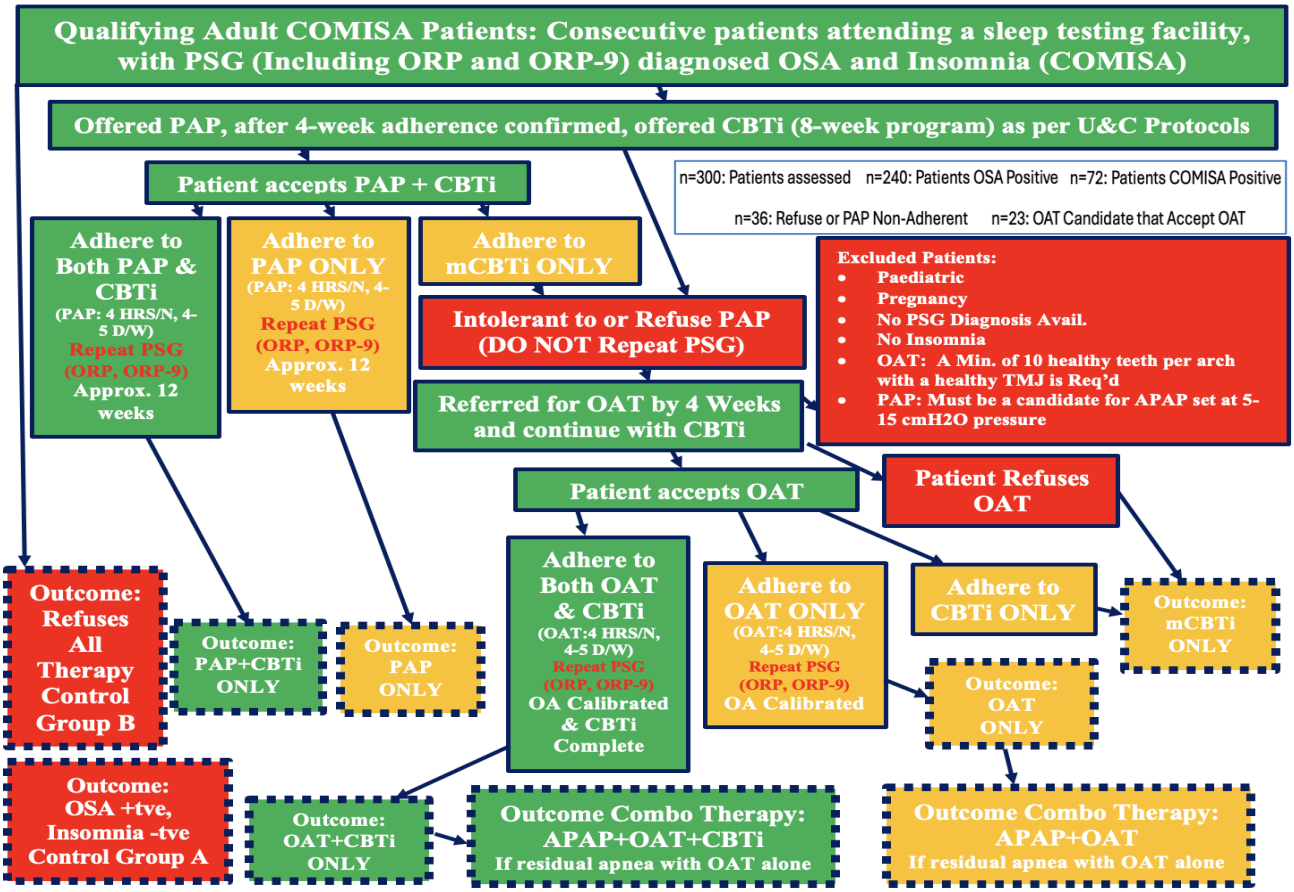
Executive Summary:

Recent literature documents the high prevalence of co-morbid insomnia and OSA (COMISA). PAP adherence for patients suffering with COMISA is 30% lower than OSA alone, approximately 35% a year post prescription. This leaves approximately 2/3's of diagnosed patients unmanaged for their OSA, and as a result, likely to have difficulty managing their Insomnia. In contrast, oral appliance therapy (OAT), which has a similar Mean Disease Alleviation (MDA) to PAP, experiences a very high adherance, in the 90% range for non-COMISA patients. **The question we cannot currently answer is, "Does high OAT adherence position it as preferred treatment alternative for patients suffering with COMISA?"**

Pilot Trial Objective:

To evaluate the clinical utility of OAT in the management of patients suffering from COMISA.

Sweetman. A. et al., (2021) Sleep Medicine, Sweetman A. et al. (2019) Brain Sci., Sweetman. A. (2023) Curr Sleep Medicine, Sweetman A et al., (2020) ERJ Open Res, Sutherland K. et al., (2015) JDSM 2015, Vanderveken OM. et al. (2013) Thorax 2013



Trial enrolment ends once 23 patients have accepted OAT. If you wish to participate as a Sleep Physician, you must commit to offering the Trial opportunity to ALL consecutive patients testing +tve for COMISA until trial ends. This involves explaining that a trial is available and providing patient a Trial Package which contains all of the information they need to make a decision. Trial administration team will be available to answer their questions and accept their consent forms. If patient enrols in Trial, the protocol described above must be followed and documented on provided "data collection" documentation.

APPENDIX XI

Summary of POCC Trial Protocols

PSG 1	Consecutive Adult Patients Attending "Enrolled Sleep Test Facility" Screened for COMISA	
Patients Testing Positive for COMISA are offered the Opportunity to Participate in POCC Trial: Provided a short video Link explaining OSA, OAT, COMISA and the project, and also written materials including Information about the Study, a Consent Form and the email to contact to advise they wish to enrol.		
Administrative Team will contact patient to answer any questions, arrange next steps, and arrange collection of signed consent and preliminary data		
Enrolled Patients will attend for U&C APAP Dispense, IF aPAP adherent at 4 weeks, THEN Dispense of CBTi		
APAP Therapy: Fees not covered by OHIP or Available Extending Health Care are provided at N/C to Patient		
PSG 2	Patients Adherent to APAP have Outcomes Assessed with Follow-Up PSG	Endpoint: APAP+CBTi, APAP Only
Patients Refusing or Non-Adherent to APAP are Offered a Referral for OAT		
NOTE: APAP Adherence determined, & Repeat PSG conducted by 12 weeks. If determined non-adherent to APAP it is IMPORTANT not to conduct an efficacy PSG until they have been referred for OAT.		
Referred Patients will attend for usual & customary consultation for OAT		
OAT Therapy: Fees not covered by OHIP or Available Extending Health Care are provided at N/C to Patient		
PSG 2	Patients Adherent to OAT have Outcomes Assessed with Follow-Up PSG	Endpoint: OAT+CBTi, OAT Only
Patients with residual apnea using OAT will be asked to wear their appliance in combination with their APAP (if they had previously failed Adherance to APAP) Outcomes of Combination Therapy assessed and documented with APAP Report.		Endpoint: APAP+OAT+CBTi, APAP+OAT Only
NOX T3	Patients Refusing or Non-Adherent to APAP & OAT have Outcomes Assessed	Endpoint: CBTi Only
Post Endpoint Questionnaires will be completed at 3- and 12-Months post reaching a therapeutic endpoint.		Endpoint:
Patients refusing all therapies		Endpoint: CONTROL GROUP

Inclusion Criteria:

- **Must Have a Level I Sleep Study with a Diagnosis of COMISA**
- **Must be a Candidate for aPAP, set at 5-15 cmH_20 pressure**
- **Must Have a Minimum of 10 healthy teeth per arch with a healthy TMJ**
- **Must be 18 Years of Age or over**

Exclusion Criteria:

- **Pregnancy**

Study Population:
(300) Adult Patients attending for Sleep Study
80% have OSA **(240)**
30% have COMISA **(72)**

APPENDIX XII

Informed Consent Form for Participation in the POCC Trial: a Pilot Study

Study Title: *PAP - ORAL APPLIANCE THERAPY – CBTi - COMISA Trial: POCC Trial: a Pilot Study*

Principle Investigators: Dr. John Viviano, BSc DDS D ABDSM & Dr. Sherif Elsaraj BSc MSc DMD PhD, McGill University, Jewish General Hospital, Department of Dentistry, A024; Researcher, Centre de recherche en medecine psychosociale du CISSS de l'Outaouais, Hull Hospital. Dr. James Macfarlane BSc MSc PhD FAASM.

Collaborators: Dr. Michael Mak MD FRCPC FCPA FAASM, Dr. Andrew Sweetman PhD, Dr. Marc Baltzan MD.

Sponsor/Funder(s): *Panthera Dental*
Sleep Disorders Dentistry Inc. Ethics APPROVAL # 240-402

Patient ID #: _____

INTRODUCTION

You are being invited to participate in a clinical trial (a type of study that involves research). This trial is a **patient management protocol with formal care pathway,** it is not a randomized trial. The goal is to offer the protocol to consecutive patients in Ontario sleep clinics. There are no significant risks to participants, with potential gains in formalized care, systematic scheduling and compiling of patient-centred and laboratory outcomes; in addition, the participants who complete all steps will have cost savings related to their treatment of sleep apnea. There is no 'experiment' strictly speaking (there is no control condition nor randomization) but the formalized sequence of offering OAT after a prescription of PAP is not a universally implemented for the care of OSA or more specifically COMISA and there are benefits from documenting the results of this protocol.

You are invited to participate in this trial because you have been diagnosed with co-existing sleep apnea and insomnia (***COMISA)***. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this clinical trial. Taking part in this trial is voluntary. Deciding not to take part or deciding to leave the trial later will not result in any penalty or affect current or future health care. You can withdraw from this trial at any time throughout the process.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

The first line standard or usual treatment for ***sleep apnea*** is positive airway pressure ***(PAP),*** which is very effective but suffers from moderate patient adherance***.*** You have been diagnosed with COMISA, patients suffering with COMISA have an adherance rate to PAP that is 30% lower than patients suffering with sleep apnea alone. Oral appliance therapy ***(OAT)*** is considered second line therapy for sleep apnea, it has a moderate level of effectiveness but has a very high patient adherance. This study is investigating whether the higher adherance rate associated with OAT also occurs in patients suffering with COMISA, perhaps making OAT a more preferred therapy for these patients.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to validate the effectiveness and adherance of OAT in helping patients suffering with COMISA that have difficulty accepting or adhering to PAP therapy. The study design investigates the usual and customary use of continuous positive airway pressure (PAP) and cognitive behavioral therapy for insomnia (CBTi) for the management of COMISA, and for those patients not tolerant to, or refusing PAP, the study design investigates the use of oral appliance therapy (OAT) along with CBTi as a second line approach.

WHAT OTHER CHOICES ARE THERE?

You do not have to take part in this study in order to receive treatment or care. Other options (in addition to the standard or usual treatment described above) may include, but are not limited to:

- PAP therapy which is provided under OHIP with a co-payment.
- CBTi through available private therapists, which is not covered through OHIP, but may be covered through extended health care.
- OAT available through qualified dentists, which is not covered by OHIP but may be covered through extended health care.
- Other research studies may also be available if you do not take part in this study.
- Surgical options such as Genioglossus Advancement, Hypoglossal Nerve Stimulator, Uvulopalatopharyngoplasty (UPPP), Maxillomandibular Advancement (MMA), Septoplasty and Turbinate Reduction, Tracheostomy, Bariatric Surgery….etc. Its essential to consult with a sleep specialist and a surgeon experienced in sleep apnea treatments to determine the most appropriate approach.
- No treatment

Please talk to your usual doctor or the study doctor about the known benefits and risks of these other options before you decide to take part in this study. Your usual doctor or the study doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

PATIENT RECRUITMENT AND QUALIFYING FOR PARTICIPATION:

Consecutive adult patients attending for a “first time”, in-lab sleep study (PSG), in participating centers diagnosed with COMISA (co-existing Sleep Apnea, and Insomnia). will be offered the opportunity to participate in this POCC Trial. Participants must have a minimum of 10 healthy teeth per arch, a functional and healthy temporomandibular joint and must be a candidate for APAP set at 5-15 cm H2O.

You have the right to know about the purposes and procedures that are used in this study and to be informed about their potential benefits, risks and any discomfort that may occur. Before you agree to take part in this study, it is important that you read the information in this consent form. You should ask as many questions as you need to in order to understand what you will be asked to do. Your participation is voluntary.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that approximately ***300 to 400*** people originating from a number of sleep testing facilities will take part in this study, the oral appliance therapy will be provided at the research site located at:

Sleep Disorders Dentistry Research & Learning Centre
10-300 5045 Orbitor Drive, Mississauga, Ontario, Canada L4W 4Y4

This study has been designed following usual and customary standard protocols for providing PAP, OAT and CBTi. Your enrollment and obligations end when the required questionnaires are completed 12 months after a final endpoint is reached in your therapy which should be within a 16-month period in most cases.

WHAT WILL HAPPEN DURING THIS STUDY?

If you decide to participate then you will be offered auto-Positive-Airway-Pressure therapy (aPAP) to manage your sleep apnea. This is the usual and customary first line therapy for sleep apnea. It is mostly covered by OHIP, and any available extended health care insurance usually covers the remainder. Any fees not covered by OHIP and/or available extended health care plans will be provided at N/C to the patient.

Once you demonstrate that you can use aPAP, you will be provided the 'Sleep Rest" APP, an online CBTi program designed to manage your Insomnia. This will be provided at N/C, a substantial savings to you.

If you are adherent to aPAP and complete the CBTi 8-week program, final questionnaires will be completed along with a final in-lab sleep study documenting effectiveness of therapy.

If you are unwilling or unable to tolerate aPAP, you will be offered oral appliance therapy (OAT), and any portion of the cost not covered by existing extended health care insurance will be provided at N/C.

Once the oral appliance is optimally calibrated, a final in-lab sleep study along with the required questionnaires will document its effectiveness. At both 3-months and 12-months after treatment ends, questionnaires will be filled out to establish continued benefits of therapy.

You will retain ownership and use of your therapy at NO COST to you provided you complete all sleep study and questionnaire requirements. If you do not complete these requirements, you will be required to return the therapy devices or pay whatever portion of the usual and customary costs that were not covered by OHIP or extended health care.

THERAPY USED IN THIS STUDY:

The aPAP therapy offered in this study will be selected by the sleep physician in a usual and customary manner following current standards of care.

The CBTi program offered in this study is called "Sleep Rest". It is an online, self-administered program designed to manage insomnia.

The oral appliance offered in this study will be either the Panthera D-SAD Classic, or the Panthera D-SAD X3, depending on which appliance is most suitable for the patient, which will be decided by the treating dentist.

WHAT IS THE STUDY INTERVENTION?

Experimental Intervention:

If you are unwilling or unable to wear aPAP to manage your sleep apnea, you will be provided OAT which is usual and customary second line therapy for management of sleep apnea.

WHAT ARE THE STUDY PROCEDURES?

- Non-Experimental Procedures

In-lab Sleep Studies will be conducted as part of this study. These sleep studies will be conducted as per usual and customary care for the management of sleep apnea. If the results show that you are not able to continue participating, the study doctor(s) will let you know. Therapeutic interventions include aPAP, OAT and CBTi application as per usual and customary protocols and in adherance with current medical guidelines.

- Experimental Procedures

The use of OAT to manage COMISA patients is considered experimental, as there is no published evidence that OAT is effective in the management of COMISA. However, OAT is usual and customary standard of care for all severities of sleep apnea for patients that cannot tolerate PAP or prefer OAT to PAP and has been used for years in patients suffering from co-existing sleep apnea and insomnia (COMISA).

- Questionnaires

You will be invited to complete several short questionnaires at the beginning of the study, after treatment endpoint is reached, 3 months after treatment endpoint is reached and 12 months after treatment endpoint is reached. If you cannot do so, we will ask you to complete them later and mail it back to us in a postage-paid envelope that will be provided to you. The research coordinator will conduct a telephone interview if you cannot return these questionnaires. You are also given the choice to complete the questionnaires online via email. The completion of the questionnaires may take an average 15 to 30 minutes.

The purpose of these questionnaires is *to understand how the therapeutic interventions and their implementation affects your quality of sleep* and collect your feedback (follow-up) as an end user of these interventions. The information you provide is for research purposes only.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Tell the study doctor about your current medical conditions.
- Tell the study doctor about all prescription and non-prescription medications and supplements, including vitamins and herbals, and check with the study doctor before starting, stopping or changing any of these.
- Tell the study doctor if you are thinking about participating in another research study
- Follow your usual and customary protocols regarding lifestyle and sleep schedule during the nights you are conducting a sleep study to document your sleep.
- *The therapy you are being provided* is for you alone and must not be shared with others.

Further, if you chose to participate in this study, you will be asked to do the following:

For both aPAP and OAT, you will be invited to complete several questionnaires both on the day that you agree to use a specific therapy, and also the day you attend for your follow-up efficacy sleep study or when it is determined that you are adherent to therapy, and the effect of therapy is established. These follow-up questionnaires will also be administered at 3 months and 12 months after the date of the final efficacy in-lab sleep study, or after it is determined that you are adherent to therapy and the effect of therapy is established. The research team will also ask you about your general health, sleep habits and sleep quality. We will do that to monitor improvements associated with therapy. The questions which are going to be asked in the study will help to identify improvements associated with regards to baseline symptoms associated with PAP, OAT and CBTi.

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

The full study intervention and obligation will be approximately 15 months, which includes reaching a therapy endpoint at approximately 3 months and filling out the required questionnaires 3 months and 12 months after an end point is reached. In order to establish an endpoint to your therapy, you will be required to attend for an in-lab sleep study to document the effectiveness of the therapy you are using. This is the usual and customary protocol followed in the management of sleep apnea.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

Your participation in this study is voluntary. Whether you accept or decline to participate in this study, your future medical and dental care and your patient-doctor relationship will not be affected in any way. You may choose to participate now and decide to stop your participation at any time. If you decide to withdraw from the study, all information obtained about you up to the point of your withdrawal will be kept in order to preserve the scientific integrity of the study.

Once enrolled, completion of study requirements is critical for the study to produce meaningful results. These requirements will not compromise you in any manner, they follow usual and customary treatment requirements for this therapy which include completing the required questionnaires and attending for the follow-up in-lab sleep studies so effectiveness of therapy can be established.

However, it is not a requirement for you to continue to use any therapy if you do not wish to. You can choose to end your participation in this research (called withdrawal) at any time for any reason whatsoever. If you choose to withdraw from the study, you will be required to return the therapeutic devices or pay whatever portion of the usual and customary costs that were not covered by OHIP or extended health care. You will be asked to complete a short withdrawal-questionnaires to help us better understand your experience.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- The study intervention does not work for you
- You are unable to tolerate the study intervention
- You are unable to complete all required study procedures

- The study doctor no longer feels this is the best option for you

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

At various visits you will be interviewed by the research assistant, physician or dentist depending on which stage of therapy you are in. If you feel uncomfortable to answer any of the questions, you are free to stop or skip that question and move on to the next one. The therapies offered in this study are the usual and customary therapies typically used to manage sleep apnea and insomnia. You will be provided disclosure and consent forms to review and sign for each therapy; PAP, OAT CBTi that explain any known side effects associated with use of those specific therapies.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

There may not be any direct benefit to you from participating in this study. However, study participation will provide you access to therapy that may not be covered by OHIP or your extended health care plan at N/C to you. In addition, this study will provide the medical and dental community with more information on COMISA treatment. The results of this study may contribute to the development of personalized programs to COMISA management.

WILL I BE PAID TO BE IN THIS STUDY?

There is no compensation for your participation. However, benefits associated with your participation include access to therapy not covered by OHIP or extended health care plans at N/C, provided you complete the study requirements which are fully explained below.

Regrading in-lab sleep studies and PAP therapy, OHIP will cover the costs of the in-lab sleep studies, and a portion of the cost of PAP therapy, extended health care plans you may have access to may cover the portions not covered by OHIP, and any amount not covered will be provided at N/C. Regarding CBTi, extended health care plans you may have access to may cover the costs of CBTi and any amount not covered will be provided at N/C. Regarding OAT, extended health care plans you may have access to may cover the costs of OAT and any amount not covered will be provided at N/C.

The expected benefit from taking part in this study is to have access to an alternative to PAP at N/C should you be unwilling or unable to tolerate PAP therapy. We hope the information learned from this study will help other people with *COMISA* in the future.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

During the study, we will be collecting data about you. We will do everything we can to ensure your data is kept private. No data relating to this study that includes your name will be released outside the researcher's office or published by the researchers. Sometimes, bylaw, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to ensure your information is kept private.

While you take part in this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file for the purpose of the research study. Only information necessary for the research study will be collected. All information obtained about you during this study will be

treated confidentially within the limits of the law. Thus, to protect your identity, your name and identifying information will be replaced with a code (numbers). The link between the code and your identity as well as the study file will be kept under the responsibility of Dr. Viviano and will be held in a locked drawer in Dr. Viviano's office at the Sleep Disorders Dentistry Research and Learning Center. No information that discloses your identity will be allowed to leave the institution.

The result of any analysis will be kept confidential and will not be placed anywhere in your file. Also, you will not be identified in any published report. A copy of this consent form will not be placed in your medical record file and a copy will be given to you.

For the purpose of monitoring this research, your research study file as well as your medical records identifying you could be checked by a person authorized by Sleep Disorders Dentistry Research and Learning Center Inc. This person is obliged to respect your privacy.

For safety purposes, and in order to communicate information that is required in order to protect your well-being, Drs. John Viviano and Sherif Elsaraj, the principal researchers of this study will keep your personal information including your name, contact information, the date when your participation in the study began and when it ended separate from the research documents.

You have the right to look at your study file in order to check the information gathered about you and to correct it, if necessary, as long as the study researcher or the institution keeps this information.

Records identifying you at this center will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be *used in analyses and will be published/ presented to the*

scientific community at meetings and in journals. This information may also be used as part of a submission to regulatory authorities around the world. You will be provided a copy of the consent form that you sign to enter the study.

After the study is done, we will still need to securely store the health data that was collected as part of the study. At Sleep Disorders Dentistry Research and Learning Center, we keep data stored for a minimum of 5 years after the end of the study.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care providers will be informed that you are taking part in a study. If you do not want your family doctor/health care provider to be informed, please discuss this with the study team.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

This is a pilot study intended to gather some preliminary data on the clinical utility of OAT in patients suffering with COMISA. Although the results of the study will be found and discussed online, there will not be any participant identifying information posted.

WHAT IS THE COST TO PARTICIPANTS?

Regarding aPAP, you are responsible for any portion not covered by OHIP or extended health care. This should be a nominal amount for most patients.

Regarding CBTi and OAT, any fees that OHIP and any available extended health care plan do not cover will be waived provided you complete the study requirements.

Should you not complete the requirements you will be required to return the therapies that have been provided or pay the usual and customary fee that was not covered by OHIP or third-party insurance.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study. You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study doctor.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. By signing this form, you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities. You will be given a copy of this signed and dated consent form prior to participating in this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about you that they didn't expect. For example, the researchers may *find out that you have another medical condition.*

If any new clinically important information about your health is obtained as a result of your participation in this study, you will be given the opportunity to decide whether you wish your physician to be made aware of that information.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your principal investigators, who are in charge of the study at this research study. That person is:

Dr. John Viviano BSc DDA D ABDSM Sleep Disorders Dentistry Research and Learning Center Telephone 905 212 7732

Or

Dr. Sherif Elsaraj BSc MSc DMD PhD, McGill University, Jewish General Hospital, Department of Dentistry, A024 Researcher, Centre de recherche en medecine psychosociale du CISSS de l'Outaouais, Hull Hospital Tel # 613-738-1763 or 204-440-0000.

For any question regarding your rights as a research participant, please contact Callie Ferreira Sleep Disorders Dentistry Inc., local commissioner of complaints and quality of service, at 905 212 7732 or info@DrViviano.com

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all.

HOW DO I INDICATE MY AGREEMENT TO BE IN THIS STUDY?

By signing below, you understand:

- You have read the above information and have had anything you do not understand explained to you satisfactorily.
- You will be taking part in the research study.
- You may freely leave the research study at any time.
- You do not waive your legal rights by being in the study.
- That the legal and professional obligations of the investigators and involved institutionsare not changed by participating in this study.

SIGNATURES

I have read the previous information, and my questions were answered to my satisfaction. A copy of this signed consent form will be given to me. My participation is voluntary, and I can withdraw from the study at any time without giving reasons. It will not affect my medical or dental care now or later. I do not give up any of my legal rights by participating in this study. I understand that I will be contacted by the research assistant at the first appointment and three months after establishing an end point in the study to complete the required questionnaires.

I confirm that:

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to my medical records and specimens as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form,
- I understand that my family doctor/health care provider may be informed of my participation in this study
- I agree to take part in this study.

Patient ID #: _____

_____ _____ _____

Signature of Participant	PRINTED NAME	Date
_____	_____	_____
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Complete the following section only if the participant is unable to read or requires an oral translation:

- The informed consent form was accurately explained to, and apparently understood by, the participant/substitute decision maker, and
- Informed consent was freely given by the participant/substitute decision maker

_____	_____	_____
Signature of Impartial Witness/Translator *(If participant were unable to read/required an oral translation)*	PRINTED NAME	Date

APPENDIX XIII

July 5, 2024

Dr. John Viviano
5045 Orbitor Drive
STE 10-300
Mississauga, Ontario
L4W 4Y4

APPROVAL # 240-402

RE: Ethical Approval for **"PAP-OAT-CBTi-COMISA Trial. (POCC Trial: a Pilot Study)"**

Dear Dr. Viviano,

Thank you for your request to review the ethical status of the above-mentioned Pilot study.

A thorough review of your proposed study demonstrates that all currently published medical guidance is being satisfied and that no patients are compromised in any manner following the stated protocols. All usual and customary aseptic and sterilization protocols are being followed in delivering therapy and appropriate safeguards are being exercised to ensure patient privacy as documented in the consent form.

This letter will confirm that we are pleased to be partnering and will support your endeavors on the aforementioned study.

We look forward to the results, and trust that they will assist in the management of patients suffering with COMISA

Should you have any questions, please contact me at any time.

Sincerely,

Callie Ferreira

John Viviano *DDS Diplomate ABDSM* - Sleep Disorders Dentistry *Research & Learning Centre*
5045 Orbitor Drive Unit 10-300, Mississauga, Ontario L4W 4Y4
Sleep@drviviano.com SleepDisordersDentistry.com ph: 905 212 7732 fx: 905 212 7736

APPENDIX XIV

Data Collection:

Name, Phone, Gender, Date Consent Signed

AHI, S AHI NS AHI RDI REM AHI Non-REM AHI ODI T90 % S Sleep SpO2 nadir SpO2 Mean ORP ORP-9	TST SOL ROL Sleep Efficiency WASO % Stage I % Stage 2 % Stage 3 % REM Sleep Efficiency Index (SEI) BMI Blood Pressure Date

Oral Appliance Bite Registration Data:

- **Vertical and Level of Protrusion**
  - **Baseline Mandibular range (Full Retrusive to Full Protrusive)**
  - **Baseline Most Advanced Protrusive Position of Comfort**
  - **Final Tested Position (Vertical and Level of Protrusion)**

Modified ESS Questionnaire:
https://nasemso.org/wp-content/uploads/neuro-epworthsleepscale.pdf

FOSQ10 Questionnaire:
https://www.serenitymedicalservices.com/wp-content/uploads/2020/01/CEREVES_FOSQ_10_ENG.pdf

SWIFT Questionnaire:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501668/

RAND Questionnaire:
https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/mos/mos_sleep_survey.pdf

ISI Questionnaire:
https://www.sleepprimarycareresources.org.au/questionnaires/isi

- **At Baseline and all endpoints:** All the above is captured with PSG and questionnaire.
- **At 3 and 12 months post reaching treatment endpoint:** Questionnaires and questions provide ongoing assessment of maintenance of outcomes, and ongoing adherence.

APPENDIX XV

Calculating COMISA Prevalence

Prevalence of COMISA:

To calculate the prevalence of COMISA (Co-morbid Insomnia and Sleep Apnea) in patients attending for an in-lab sleep study, we need several pieces of information and follow a systematic approach:

Required Information:

1. **Total Number of Patients**:
    - The total number of patients who attended the in-lab sleep study during a specific period.
2. **Number of Patients Diagnosed with COMISA**:
    - The number of patients who were diagnosed with both insomnia and sleep apnea during the same period.
3. **Criteria for Diagnosis**:
    - Clear diagnostic criteria for insomnia and sleep apnea to ensure consistency and accuracy in identifying COMISA cases.

Steps to Calculate Prevalence:

1. **Define the Study Period**:
    - Specify timeframe during which data was collected (e.g., 1 month, 6 months, 1 year).
2. **Collect Data**:
    - Gather total number of patients who attended in-lab sleep study during the defined period.
    - Identify number of patients who were diagnosed with both insomnia and sleep apnea.
3. **Calculating Prevalence**:
    - Use the following formula to calculate the prevalence:

Prevalence of COMISA = (Number of patients diagnosed with COMISA Total number of patients) × 100\text {Prevalence of COMISA} = \left(\frac{\text {Number of patients diagnosed with COMISA}} {\text{Total number of patients}} \right) \times 100Prevalence of COMISA =
(Total number of patientsNumber of patients diagnosed with COMISA)×100

Example Calculation:

Assume you have the following data:

- Total number of patients attending the in-lab sleep study: 500
- Number of patients diagnosed with COMISA: 50

The prevalence of COMISA would be calculated as follows:
Prevalence of COMISA=(50500)×100=10%\text{Prevalence of COMISA} = \left(\frac{50}{500} \right) \times 100 = 10\%Prevalence of COMISA=(50050)×100=10%

Considerations:

- **Accuracy of Diagnoses**: Ensure that the diagnoses of insomnia and sleep apnea are based on standardized and validated criteria.
- **Data Collection Methods**: Ensure consistent and reliable methods for collecting and recording patient data.
- **Study Population**: Consider any potential biases or specific characteristics of the study population that may affect the generalizability of the findings.

APPENDIX XVI

POCC Trail – Sleep Physician Protocol

***All protocols follow current published guidance, AASM and AADSM Standards**

All consecutively presenting patients that complete a PSG at your clinic as of your clinic's start date will be entered onto a spreadsheet. Those diagnosed with COMISA, that are candidates for APAP set at 5-15 cm H2O, will be provided the "POCC Trial Info Package" and provided a link to a video explaining this trial.

- **Patients refusing to consider enrolling continue with usual & customary management of COMISA (PAP & CBTi of physician's choice)**
- **Patients electing to enroll will contact a SDDi Case Manager, which will facilitate the enrollment process, after which they will attend with the Sleep Physician to continue with usual & customary management of COMISA (PAP & Sleep Reset CBTi as per Study protocols)**
- **Physician prescribes aPAP set at 5-15 cm H2O and follows up at 1 month to ensure adherence.**
- **If adherent, physician prescribes CBTi and a follow-up PSG is scheduled for 8 weeks.**
- **8 weeks post aPAP adherence confirmation and CBTi dispensing:**
    - **Adherent patients (4 hrs/n, 4-5 d/w), proceed with PSG reaching an endpoint.**
    - **Non-adherent patients referred for an OAT consultation. NO PSG CONDUCTED**
- **Physician documents COMISA status and effectiveness of OSA therapy utilized (APAP or OAT) and Sleep Reset for CBTi. The physician manages CBTi therapy as per study protocols.**
- **It is CRITICAL that the physician's office communicate with SDDi Case Management team regarding data and milestones. A spreadsheet with required data will be provided for all patients. SDDi will be responsible for administering and collecting the 3- and 12-month questionnaires. All data will be forwarded to attending sleep physician in a timely manner.**

NOTE: Dentist will report to POCC Trial referring physician

- **i) post-consultation,**
- **ii) post-delivery of OAT should the patient proceed and**
- **iii) post-withdrawal from OAT should the patient discontinue with OAT**
- **iv) post appliance optimally calibrated, so follow-up PSG can be conducted reaching an endpoint.**
- **v) post Combination therapy if residual apnea persists with OAT, reaching an endpoint.**

I, Dr. _____, (_____) Date: _____

Please Print Name ***Signature*** ***Date***

Agree to enrol as a POCC Trial Referring Physician and agree to manage all patients as per usual and customary currently published guidelines, including AASM and AADSM Standards of Practice, and will endeavour to follow the above stated timelines to the best of my ability without compromising patient care in any manner whatsoever.

APPENDIX XVII

POCC Trial – Dentist Protocol

***All protocols follow current published guidance, AASM and AADSM Standards**

All patients presenting from POCC Trial referring physicians will be provided a full consultation where it is determined if they are a candidate for OAT, which appliance design is most appropriate, with full disclosure regarding OAT, effectiveness and side effects including reviewing consent forms, if the patient decides to proceed with OAT their dentition will be scanned, a bite registration will be taken, and the appliance will be ordered.

- **Patients refusing to proceed with OAT will be referred back to the POCC Trial referring physician to review and finalize the status of their insomnia reaching an endpoint.**
- **Patients electing to proceed with OAT will be seen in approximately 2-3 weeks to deliver their oral appliance.**
- **Four weeks post oral appliance delivery adherence is documented and reported to physician. If adherent to OAT, and CBTi has not been initiated, the physician will initiate CBTi and a PSG is scheduled for 8 weeks.**
- **Patients will home calibrate their oral appliance using subjective benefit as a guide.**
- **The Belun ring will be used to objectively evaluate the final position and allow for fine tuning to a position that provides the best outcome.**
- **8 weeks Post OAT adherence confirmed and CBTi dispensing:**
    - **Adherent patients (4 hrs/n, 4-5 d/w), proceed with PSG reaching an endpoint.**
    - **Non-adherent patients are referred to POCC Trial referring Physician to follow-up on COMISA status and effectiveness of OSA therapy utilized (APAP or OAT) and of Sleep Reset for CBTi reaching an endpoint.**
- **Patients with residual AHI with OAT will be asked to wear both their appliance and APAP in combination. If the patient can adhere to combination therapy, all questionnaires will be completed documenting effectiveness of combination therapy reaching an endpoint.**

NOTE: Dentist will report to POCC Trial referring physician

- **i) post-consultation,**
- **ii) post-delivery of OAT should the patient proceed and**
- **iii) post-withdrawal from OAT should the patient discontinue with OAT**
- **iv) post appliance optimally calibrated, so follow-up PSG can be conducted reaching an endpoint.**
- **v) post Combination therapy if residual apnea persists with OAT, reaching an endpoint.**

I, Dr. _____, (_____) Date: _____

Please Print Name ***Signature*** ***Date***

Agree to enrol as a POCC Trial Dentist and agree to manage all patients as per usual and customary currently published guidelines, including AASM and AADSM Standards of Practice, and will endeavour to follow the above stated timelines to the best of my ability without compromising patient care in any manner whatsoever.

APPENDIX XVIII

STUDY BUDGET:

n ≈300 PSG Sleep Studies

≈80% OSA (240)
≈30% COMISA (72)
≈50% Intolerant/Refuse PAP (36)
≈65% meet OAT Inclusion criteria and Accept OAT (23.4)
≈23 OAT cases

- Sleep Reset APP will be provided at N/C by company **(≈72 APP Sleep Reset Registrations at N/C to patient)**
- ResMed will accept OHIP + any available extended health care re-imbursement for providing APAP therapy **(≈72 APAP at N/C to patient) This has not been agreed to. Currently, patient will be responsible for the portion not covered by OHIP and/or available Extended Health care plans.**
- OAT provided for re-imbursement available from any existing extended healthcare (usually, 1/3 patients have some level of partial coverage for OAT) **(≈23 OA at N/C to patient)**

*Study requires a minimum of 23 D-SAD or X3 oral appliances at N/C lab fee from Panthera Dental

Study Expenses:

i) Sleep Disorders Dentistry team (SDD Team): **(≈200 hrs at $30/h = $6,000)**
   a. Print, collate and distribute enrolment packages to participating sleep physicians.
   b. Guide patients through the enrollment and consent process.
   c. Conduct follow-up endpoint, and 3- and 12-month endpoint questionnaires and questions.
   d. Collect, collate, and double check all data entry.
   e. Forward patient information and reports to referring sleep specialist.

ii)
   a. Patient enrolment into study will continue until 23 patients have been scanned for an oral appliance.

NOTE: depending on timing, we will reach 23 scans and there will be patients already enrolled that will not adhere to PAP and will look to obtain an oral appliance. This may increase to above 23 the number of final appliances. By paying close attention we can manage this and ensure we don't need to go too much above 23, and actually ending up with a slightly higher number of oral appliances will make our findings more meaningful.

iii) Paper, toner, envelops for enrolment packages to recruit patients (for multiple sleep specialists) **(≈$400)**

iv) Purchase 2 Belun rings for OAT calibration along with monthly platform fee for study duration **(≈$2,400)**

v) Sundries / disposables associated with OAT, scanning, bite registration, delivery and maintenance **(≈$1,000)**

vi) NOX T3 sleep study consumables (Cannulas, belts, batteries, leads etc.) **(≈$300)**

Anticipated Budget: $10,100

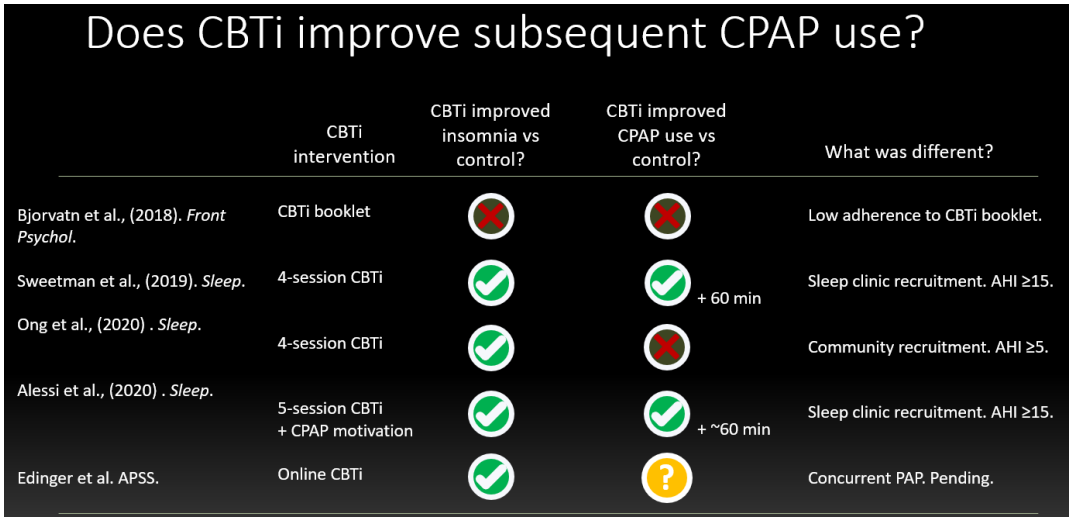
APPENDIX XIX
Considerations for Future Full Study

Timing of Therapy:

5 RCTs (one pending) have investigated whether CBTi improves insomnia and increases PAP use, compared to PAP alone. Mixed results, possibly related to the lower AHI threshold, and community recruitment (rather than sleep clinic recruitment) in Jason Ong's study.

Dr. Sweetman recommends CBTi first, however, for a research study, he suggests there is merit in using OAT alone, without contaminating the intervention with CBTi. This would allow you to understand interactions between untreated insomnia and OAT in COMISA (Does untreated insomnia impact uptake/acceptance/use of OAT? Does OAT improve insomnia severity?). Then you can add
CBTi in the full study and run it as a RCT, etc.

Staging delivery of therapy should be considered for the Full Study, but due to time and access to PSG in the Pilot Study, two options are available: i) Concurrent delivery, ii) Staggered delivery, where the patient receives PAP (OAT) first, and CBTi is delivered a set amount of time afterwards. This protocol is the safest protocol as the Sleep Restriction component of CBTi may compromise a “Sleepy” COMISA patient, and denying them OSA therapy may compromise them.



CBTi APP:

Considerations include:

1) ResMed APP Somnio

2) Sleep Reset

3) CBTi App developed by Dr. Sweetman, and 2 colleagues tailored for COMISA that could be adapted. It's currently quite "Aussie" in its delivery. https://doi.org/10.3389/frsle.2024.1355468

Type of Sleep Study:

For the Full study, it will be important to acknowledge that the majority of sleep studies done in Canada and the world are home sleep apnea tests (HSAT). This could be acceptable for the larger Study if recruitment is problematic. The important point would be that if HSAT is done at entry, then it is also done at follow-up.

Compliance Chip:

For the Full study, incorporation of a compliance chip into the oral appliance would allow a more complete understanding of the disease alleviation associated with oral appliance therapy allowing a more realistic comparison to the disease alleviation associated with aPAP therapy.

POCC Trail: a Pilot Study

Viviano JS. BSc DDS ABDSM, Elsaraj S. BSc MSc DMD PhD, MacFarlane J. BSc MSc PhD FAASM, Mak M. MD FRCPC FCPA FAASM, Sweetman A. PhD Baltzan M. MD

"The Beginning of Something Great"

JSV