Mandibular Advancement vs Home Treatment for Primary Snoring: A Randomized Trial

(SNORE-LESS)

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A Introduction

A1 Study Abstract

Introduction: Snoring is a problem affecting nearly 40% of the adult population and which leads to adverse health outcomes in the participant and sleeping partner. Despite the large number of people affected, insufficient research exists in the published medical literature documenting treatment effectiveness for primary snoring. Contrary to this, a large amount of research exists on effective treatment for sleep apnea; from this comes our understanding of the treatment effectiveness for snoring. The goal of this study is to determine whether Mandibular Advancement Devices (MAD) are an effective treatment for primary snoring when compared to conservative therapies.
Methods: This study will consist of a randomized control trial of adult participants with non-apneic snoring. Participants will be recruited from an academic medical center and randomized into either conservative therapy that is medicated nasal rinses, external nasal dilator, mouth taping, and lateral positional therapy or Mandibular Advancement Device. Participants and their sleeping partner will be evaluated at baseline and at follow up with a modified Clinical Global Impression (CGI) Scale. At baseline, they will be evaluated with a CGI-Severity scale, and at follow up with a CGI-Improvement scale. The primary outcome is the Snoring Clinical Global Impression Scale-Improvement for the sleeping partner. Secondary outcomes include change in the Epworth Sleepiness Scale (ESS) in the participant, change in ESS in the sleeping partner, CGI-I Scale for the participant, change in the SNORE25 for the participant, and change in SNORE25 for the sleeping partner.

A2 Primary Hypothesis

We hypothesize that the Mandibular Advancement Device (MAD) will result in a clinically meaningful, statistically significant difference in the modified Snoring CGI-I Scale when compared to the conservative therapy for participants with non-apneic snoring as measured by their sleeping partner.

A3 Purpose of the Study Protocol

The purpose of the study is to assess the efficacy of two popular treatments in adults with non-apneic snoring — mandibular advancement device versus conservative therapy (medicated nasal rinses, external nasal dilator, mouth taping, and lateral positional therapy). Knowledge gained will help guide treatment practice. In doing so, physicians will be able to offer evidence-based options to inform patients when they present with non-apneic snoring, a medically minor, but socially impactful pathology.

B Background

B1 Prior Literature and Studies

Snoring is a nearly ubiquitous problem in American life. The pathophysiology of snoring is related to resistance to airflow in the upper airway during sleep and exists on a spectrum between the extents of snoring and sleep apnea. At the lowest end of the scale exists snoring, in which transient obstruction of the upper airway increases resistance in the upper airway, requiring more negative pressure by the lower airway to maintain airflow. This increase in pressure creates faster and more turbulent flow, leading to inspiratory narrowing and vibration of the upper airway but does not lead to hypoxic episodes or changes in vital signs with OSA[1,2].

It is well understood that obstructive sleep apnea leads to systemic effects such as hypertension and sleepiness[3]. However, the consequences of primary snoring are less well studied. Several investigators established that hypertension, ischemic heart disease, and all-cause mortality are not related to nonhypoxic snoring[4–7]. However, primary snoring is associated with an increase in carotid artery atherosclerosis independent of OSA[8,9]. Cognitive complaints and morning headaches are also increased in persons with snoring, however this association did not control for apneic vs non-apneic snoring[10]. Snoring also affects the sleeping partner substantially. In patients with sleep apnea, their partner has a worse quality of life and more sleepiness compared to a couple in which neither partner has sleep apnea. In addition, the non-apneic sleep partner's qualify of life improved when the patient's sleep apnea was treated[11,12]. This indicates an impact of snoring on the health of both the patient and their spouse, and could be a cause of marital discomfort[13,14].

Yet despite snoring affecting up to 40% of the population, rigorous studies on how to treat isolated snoring have not been completed[15,16]. Currently available conservative measures consist of weight loss, lateral sleep positioning, nasal rinses, and external nasal dilators. Surgeries do exist to correct or reduce snoring. The primary surgery currently recommended is the Uvulopalatopharyngoplasty (UPPP), which removes tissue from the soft palate and tonsillar pillars. The current studies on the effect of body position on apneic and non-apneic snorers show conflicting and inconclusive results[17–19]. Mandibular advancement devices (MAD) show consistent improvements in sleep quality for patients with sleep apnea; however, their effect on patients with primary snoring remains less well known. One systematic review by Micheline et al. looked at MAD for the treatment of primary snoring with or without sleep apnea. However, in the included studies, none of the 18 papers had a primary snoring definition that corresponded to snoring without apneic spells. One of the 18 papers reported treatment effectiveness on patients with primary or non-apneic snoring; however, this included only 8 cases of patients with non-apneic snoring and did not provide a definition for what qualified as primary non-apneic snoring. Although MAD therapy could potentially treat primary snoring, the researchers concluded future studies needed to occur for a definitive answer[20].

B2 Rationale for this Study

As outlined in the Prior Literature and Studies section, an important gap exists in the current knowledge — What therapy is available to patients who have snoring bothersome enough to warrant an evaluation by an ENT specialist, but not bad enough to qualify as sleep apnea and warrant CPAP trial? Previous research has not evaluated treatments for primary snoring but has instead extrapolated findings from treatments for sleep apnea. This study will address the gap in knowledge for what treatments are effective for primary snoring.

C Study Objectives

C1 Primary Aim

The primary aim is to evaluate the efficacy of a mandibular advancement device (MAD) vs conservative treatment for adults with non-apneic snoring. We hypothesize that adults with non-apneic snoring treated with a MAD will experience a greater reduction of snoring as measured by the *Clinical Global Impression – Improvement* (*GCI-I*) Scale response of the sleeping partner.

C2 Secondary Aim

The secondary aim is to evaluate the effectiveness of treatment of snoring on the sleeping partner's sleep quality as measured by the *CGI-I* scale, the *Epworth Sleepiness Scale* (*ESS*), and a modified *Symptoms of Nocturnal Obstruction and Related Events* (*SNORE-25*) questionnaire.

C3 Rationale for the Selection of Outcome Measures

Primary Outcome:

Clinical Global Impression of Improvement Scale (CGI-I) - Partner: To address the primary aim, the primary outcome measurement is the CGI-I Scale in the sleeping partner. The CGI-I will pose the question "Overall, how do you rate the response to snoring treatment?", with 7 response options including: *Very Much Improved*, *Much Improved*, *Minimally Improved*, *No Change*, *Minimally Worse*, *Much Worse,* and *Very Much Worse*. The CGI-I is adapted from a previously validated measure commonly used in psychiatric studies, and is a self - report scale[21]. Participants will be measured after completing 4 weeks of their respective intervention. As snoring primarily effects the sleeping partner, the sleeping partner's responses will be the primary outcome measurement. A sleeping partner who rates the response to treatment as either *Very Much Improved* or *Much Improved* will be graded as a responder to treatment. The percentage of responders to non-responders will be compared between the two treatment arms.

Secondary Outcomes:

1. **CGI-Improvement Scale - Participant:** The CGI-I will be administered to the participant in the same method as described above.
2. **CGI-Severity (CGI-S) Scale - Partner and Participant:** The CGI-Severity Scale poses the question "On average, how much of a problem does your [partner's] snoring pose?" The 5 response options will include: no problem, mild problem, moderate problem, severe problem, problem as severe as it can be. It will be measured both at baseline and after treatment. In addition, the CGI-S will be measured by the sleeping partner on a daily basis both before and after treatment.
3. **Epworth Sleepiness Scale (ESS) - Partner and Participant:** The ESS is a commonly used measure to evaluate the propensity to of a participant to fall asleep in 8 everyday scenarios "in recent times". The participant rates each situation on a scale of 1-7, with 1 being least likely to fall asleep and 7 being the most likely[22]. When used as an outcome, the ESS shows similar outcomes for participants with sleep apnea when compared to CPAP[20]. De Meyer et al. conducted a systematic review of studies looking at the minimal clinically important difference (MCID) of the ESS, and found a range between 2 and 3. It calculated the exact MCID as being 2.4, and found the scale has a good internal and external validity[23]. As a conservative value, we will use 3 as the MCID in this study. The ESS will be collected both at the baseline and at follow up, and a change in the ESS will be calculated.
4. **Symptoms of Nocturnal Obstruction and Related Events (SNORE-25) - Partner and Participant:** The SNORE-25 is a modification of the Obstructive Sleep Apnea Patient-Oriented Severity Index (OSAPOSI) which includes 25 total items of symptoms with possible scores ranging from 0 to 5, with high scores indicating greater sleep-disordered breathing—related health burden[24]. For the sleeping partner, we will administer a modified form of the SNORE-25 which preserves the intent of each of the questions but changes the wording to refer to effects of the participants snoring on the sleeping partner's life.
5. **Pittsburgh Sleep Quality Index (PSQI) - Partner and Participant:** The PSQI is a self-rate questionnaire which assess sleep quality and disturbances over a 1-month time interval. It is composed of 19 items which contribute to 7 different component scores: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global sum of these components > 5 signifies poor sleep quality with a sensitivity of 89.6% and a specific of 86.5%[25]. The PSQI will be taken at baseline and at follow up.

D Study Design

D1 Overview

This study is a randomized control trial with an active control group. Once participants are enrolled in the study, all baseline measures and demographic information will be recorded by the participant and their sleeping partner (*Demographics*, *DemographicsPartner*, *BaselineData*, and *BaselineDataSleepingPartner*). After the baseline measures are recorded, participants will be randomized to receive either MAD or the standard conservative therapy. The MAD arm will consist of participants given a fitted mandibular advancement device that they will wear for the length of the study. The device will be fully fitted by the maxillofacial physician who specializes in maxillofacial prosthodontics, and is an expert at the fabrication of mandibular advancement devices. The standard home therapy will include daily use of medicated nasal rinses, external nasal dilator, mouth taping, and lateral positional therapy and will function as our active control group.

For those randomized to the MAD, we will arrange a meeting with the maxillofacial physician to initiate the process of fitting the device. After the device is fully fitted, which will take 4 weeks, the participants will initiate the 4-week intervention.

For those who are randomized to the standard conservative therapy, it will begin with a medicated nasal rinse (Neti-cort – nasal saline lavage with Mometasone), which will take 4 weeks to achieve therapeutic effectiveness for improved nasal breathing. After the 4 weeks of Neti-cort therapy, the standard therapy group will begin their intervention for 4 additional weeks as well. Participants in the standard home therapy will have access to an instructional video library which will correctly demonstrate how to implement the home therapies.

The sleeping partners will receive a text message each morning from the day of enrollment until study completion. The content of the text message will be the CGI-S and the sleeping partner will respond to the text message each morning.

Participants will use the intervention nightly for a period of 4 weeks after which an end of study visit will occur. At the end of study visit, all post-intervention outcomes will be recorded.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Participants will be recruited based on the following inclusion criteria:

- Age ≥ 18
- Report of snoring
- Prior polysomnogram (PSG) within the past 60 months showing AHI < 5 and no more than 10% gain in body weight since the prior polysomnogram
- Possess a sleeping partner who sleeps in the same room as the participant for >= 4 nights a week and who can report outcomes
- Access to the internet
- Ability to follow up within 1 month after adequate fitting of MAD or 4 weeks of Mometasone

Inclusion criteria for the sleeping partner:

- Age ≥ 18
- Possess a sleeping partner who sleeps in the same room as the participant for >= 4 nights a week and who can report outcomes
- Access to the internet

2.b Exclusion Criteria

Individuals will not be allowed to participate in this study if they meet one or more of the exclusion criteria:

- Significant hypoxemia as defined as SaO2 below 89% for ≥ 12% of the total nocturnal monitoring time
- Inability to wear a MAD defined as missing more than 50% of their dentition or their dentition is not in good condition.
- Prior intolerance of MAD
- Current treatment for OSA
- Concurrent use of sedatives or > 2 alcoholic drinks per night
- Chronic nasal obstruction due to structural anatomic defects, nasal polyps, or history of unresponsiveness to nasal rinses.

Sleeping partners do not have any exclusion criteria defined for this study.

2.c Ethical Considerations

This study relies on participation of human subjects. Informed consent will be obtained in person for each participant at the baseline visit to ensure their safety, minimize risk, and ensure full confidentiality. All assessment will be conducted via HIPAA-compliant online surveys using REDCap. We are asking the participant to engage in an intervention; however, they are not the ones solely benefitting from it as their partner is also expected to benefit.

2.d Subject Recruitment Plans and Consent Process

We plan to enroll 30 participants and 30 sleeping partner participants for each arm of the trial: 120 participants, or 60 pairs, in total. Recruitment will be done at the Washington University Department of Otolaryngology-Head and Neck Surgery outpatient clinics, the Washington University Sleep Medicine Center, and advertisements through Volunteer for Health, Washington University School of Medicine's Research Participant Registry. At each of these physical locations, the recruitment flyer will be posted inviting patients to participate and contact the research team. Additionally, due to the focus on virtual research at this time, we will also use website postings to share the trial. The website posting will be a virtual reproduction of the flyer already provided. The study population will consist of snorers who do not have sleep apnea. Control and experimental populations will be identical.

If needed, we will search the electronic medical record system for patients who have been seen at Washington University's Sleep Medicine Center for patients who have had a previous PSG that resulted in exclusion of a diagnosis of sleep apnea. To determine this, we will access the diagnostic codes, laboratory data, and doctor's notes to

identify potential subjects. These potential participants will then be contacted, made aware of the study and asked if they would like to be screened for potential participation in the study. Contact will occur through the telephone, following the IRB approved recruitment scripts -*Telephone* or *Letter.*

Potential participants meeting inclusion criteria will be invited to enroll, and will have as much time as needed to consider participation and contact the research team for a start of study visit. After participants are invited to enroll, and verbally agree to participate, a meeting of the study participant, the Principal Investigator (PI), and research coordinator (RC) or a Research Assistant (RA) will be arranged for a start of study visit. Formal enrollment will consist of the subject and their spouse being given a REDCap identifier ID in the REDCap database. After this, consent materials will be given and reviewed with the patient.

Informed consent will be obtained at the start of study visit prior to any research activity. To minimize the possibility of coercion or undue influence during the consent process, patients will be given the option to read through and sign the consent with the RC or alone. We will also remind the patient prior to the consent process that their ability to receive care will not be impacted by the presence or absence of consenting to the study, and that if they do consent, they can withdraw at any time. To minimize the coercion to finish the study, the participants will be reminded that if they do not finish the study, they will still be compensated on a pro-rated basis for the previously completed steps.

All assessments will be conducted either in person or virtually via HIPAA-compliant online surveys at baseline and then throughout the study course virtually or over the telephone.

2.e Randomization Method and Blinding

Participants will be randomized according to computer-generated code to receive either the mandibular advancement device or standard at-home therapy. Dr. Kallogjeri will provide the randomization table to the co-investigator, Patrick Ioerger.

Due to the nature of the randomization process, blinding during the data collection phase will not be possible as the primary researcher will have to coordinate a specific initial visit with either the maxillofacial physician or Dr. Piccirillo, the otolaryngology specialist. Participants cannot be blinded either as the treatment modalities differ in a way which makes adequate blinding not possible. Dr. Piccirillo will be blinded to randomization. Prior to data analysis, Dr. Kallogjeri will blind groups as “A” and “B” so that the team will not know which intervention corresponds to A and B throughout both the data analysis and manuscript writing process.

2.f Risks and Benefits

Mandibular Advancement Device. Risks of the Prosomnus sleep and snore device include drooling, temporomandibular disturbances, tooth pain, TMJ disturbances, and movements of the teeth that can change a person’s bite. All these risks are uncommon and resolve after cessation of use. These risks will be minimized using a morning

repositioning device each morning after the Mandibular Advancement Device is worn. Benefits of the device include a reduction in snoring intensity and severity.

Standard At-Home Conservative Therapy:Mometasone nasal rinse, mouth taping, nasal strip, lateral positional therapy. Risk of *Mometasone* include systemic absorption of the topical glucocorticoid rinse and risk of aggravating cataract and glaucoma. Risk of the *mouth taping* and *nasal strip* include skin irritation from the adhesive. Risk of *lateral positional therapy* include shoulder and hip pain during the day after sleeping.

Benefits of both treatment interventions include a reduction or cessation of snoring, leading to an improvement of quality of life for both the participant and their sleeping partner.

The consent process informs a volunteer about the study, indicates that participation is voluntary, and that he/she has the right to stop at any time. Risks are listed in the informed consent form and described orally during the consent process.

2.g Early Withdrawal of Participants

Participants may withdraw at any point in the study. The Principal Investigator can also withdraw a participant at his discretion if he determines the participant is not using the intervention correctly, for failure to adhere to the intervention, or for undermining integrity of the study.

If a participant decides to withdraw from all components of the research study, the investigator will discontinue all the current and scheduled research activities in the study.

2.h When and How to Withdraw Participants

A participant can withdraw consent for the study at any time. Participants will be allowed to end participation in the study at any point should they desire. All participants will have an exit interview to ascertain any adverse effects and discuss the reason for ending participation. The study team will follow them for safety reasons up to 30 days after stopping use of the study intervention.

2.i Data Collection and Follow-up for Withdrawn Participants

If a participant has ended participation, the only data that will be collected are the data from the exit interview and the data collected prior to withdrawal. There will not be any other follow-up or data collected from these subjects.

Data collected up to this point will not be used in the analysis, and further data will not be collected from these participants.

D3 Study Intervention

3.a Description

3a.1 Interventional Arm

The Mandibular Advancement Device for this study will be the ProSomnus Sleep Device. It is a sleep device intended to reduce nighttime snoring and mild to moderate Obstructive Sleep Apnea in adults by holding the lower jaw forward during sleep. This

position prevents the tongue and throat from collapsing into the airway, preventing obstruction. The amount of protrusion is determined by the device's arches or by the expansion screws within the device itself. A dentist prescribes the device at an initial visit where the amount of advancement is also determined. From there, the device can be advanced manually by the participant, either through inserting the next upper or lower arch in the series of arches, or by manually adjusting the screws in the device. This is done incrementally until the prescribed advancement is achieved. Since the device can be adjusted by the participant, only an initial visit is required for fitting.

3a.2 Conservative treatment arm

The conservative treatment will consist of four different interventions used simultaneously.

Mometasone nasal rinse. Mometasone is an anti-inflammatory corticosteroid used for a variety of conditions. Among respiratory tract conditions, Mometasone is used for COPD, nasal polyps, asthma, chronic sinusitis, and allergic rhinitis. A nasal sinus saline irrigation (aka "Neti-Pot") type system will deliver the Mometasone to the participant's sinuses. For participants randomized to the conservative treatment arm, daily use of nasal lavage with mometasone will be required. Each nasal rinse will contain 2 mg of Mometasone in a 240 ml Nasal Sinus Rinse kit. The Mometasone rinse will have minimal systemic effects, as previous studies with topical steroid rinses have shown no adverse outcomes[26,27].

External nasal dilatory therapy. External nasal dilatory therapy consists of a stiffened adhesive strip (a "breathe-right" strip) applied externally across the nasal alae nightly. The goal is to retract and stabilize the nasal alae, dilating the anterior nasal vale and encouraging nasal breathing.

Mouth taping. Participants will receive a package of Johnson and Johnson Band-Aid Woven Adhesive Bandages (1" x 3") tape and instructed to apply it vertically over the upper and lower lips at the columella. This encourages the participants to breathe through their nose instead of their mouth and decrease snoring amount.

Lateral positional therapy. Lateral positional therapy consists of interventions to encourage lateral sleeping (i.e., "snore" ball, hugging pillow), which reduces the anatomical obstructions of snoring.

3.b Treatment Regimen

3b.1 Interventional arm

After the device is fitted by the maxillofacial physician, the participant will take the device home and wear it during sleep for a period of four weeks.

3b.2 Conservative treatment arm

Participants in this group will undergo a nightly medicated nasal rinse consisting of 240 ml nasal saline lavage with 2mg Mometasone. This mometasone nasal rinse will occur for a 4-week period prior to beginning the other three conservative therapy interventions. After the 4-week period of the mometasone nasal rinse the other three

conservative therapy interventions (external nasal dilator, mouth taping, and lateral positional therapy) will begin and occur simultaneously each night as described above.

3.c Method for Assigning Participants to Intervention Groups

The participants will be assigned using permuted block randomization in a 1:1 allocation between two arms: the MAD intervention and the conservative therapy intervention.

3.d Preparation and Administration of Study Intervention

The MAD will be delivered to the participants during the initial visit with the maxillofacial physician. Participants will self-insert the device nightly during the trial.

For the conservative therapy arm, the participants will be supplied with a roll of Johnson and Johnson Band-Aid Woven Adhesive Bandages 1" x 3", one box of Breath-Right strips (either small, medium, or large), and one Neti-Pot. The participants will receive their topical glucocorticoid prescription through the mail from AdvancedRx, which is a compound pharmacy in Fort Washington Pennsylvania that specializes in nasal delivery of medications.

3.e Participant Compliance Monitoring

There will be check-ins with the study participants every two weeks conducted through the participant's preferred communication method (i.e., phone call or video call) to answer questions and ensure participants are adhering to protocol requirements. Participants will be asked to keep a paper calendar for daily notes of side/adverse effects and study barriers. The paper calendar will be mailed back to the RA after study completion, or a photo of the paper calendar will be sent attached to an email to the RA. Treatment compliance data and rates of side effects will be collected in the two groups. Collection of compliance will occur through a nightly log of compliance, which the participants will receive via REDCap from the research team and fill out throughout the study.

3.f Prior and Concomitant Therapy

Participants will not qualify for the study if they are on any concomitant therapy for snoring not assigned by the study team. Participants who have tried prior therapy for the treatment of snoring will be eligible for the study. Information will be gathered on their use of prior or current therapies when determining study eligibility.

3.g Packaging

All packing of material will consist of the consumer packaging for all interventions except for the Mometasone. AdvancedRx will ship the participants the Mometasone via UPS or FedEx delivery directly to the participant's home.

3.h Blinding of Intervention

The Principal Investigator will conduct a pre-randomization visit with all participants in which he will explain both interventions to the participants and conduct a physical

exam. The physical exam will ensure the participants are in adequate physical health to tolerate both interventions and lack nasal polyps, temporomandibular joint disorder, and structural abnormalities. After this, the Principal Investigator will leave the visit and the other members of the study team will randomize the participants. This blinds the Principal Investigator to the intervention.

Before data analysis begins, Dr. Kallogjeri will download the data and anonymize the data into "A" and "B" groups. Only Dr. Kallogjeri will know which group belongs to which. The research team will then proceed with data analysis.

3.i Receiving, Storage, Dispensing and Return

All conservative therapy interventions will be stored on site in the Outcomes Lab in compliance with the manufacturer recommended storage procedures. Products will be dispensed to the participants during the baseline visit if in the conservative therapy group, or at the Maxillofacial physician meeting if in the MAD group. Return of all dispended interventions is not expected.

E Study Procedures

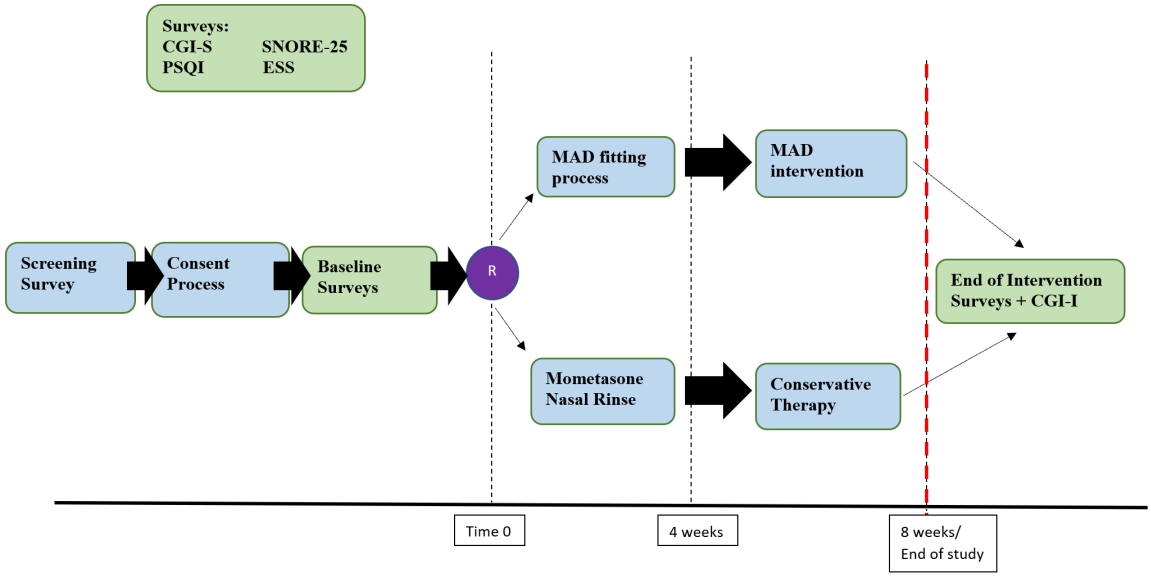
E1 Screening for Eligibility

Individuals who reach out with interest in the study after seeing the approved study flyer or who have contacted RA for participation in similar studies for which recruitment has ended will be asked to complete an online screening questionnaire to ensure initial inclusion criteria is met. Interested individuals are also free to directly fill out the Screening Survey in REDCap through a QR code or link before contacting the RA.

Following initial eligibility confirmation, the RA will contact the individual to schedule a baseline visit at the Center for Advanced Medicine (CAM) building in the department of Otolaryngology – Head and Neck Surgery as well as obtain a copy of the patient's previous PSG study to ensure an AHI of < 5. At the screening/baseline visit, participants will be provided with an e-consent form through REDCap. The RA will offer each person the option to review the consent form independently or with the RA. Once the participant electronically signs the consent form, the RA will review it and sign. The REDCap software will automatically email the participant a copy of their completed form.

E2 Schedule of Measurements

Following the recruitment period and successful enrollment, baseline survey completion and randomization of participants will occur. The timeline for measurements can be seen below:



*R = Randomization

E3 Visit 1

At the baseline study visit, The RC or RA and the participant and sleeping partner will complete the demographic information and baseline measures. This includes the baseline CGI-S scale, the ESS, and the SNORE-25 or the modified SNORE-25. Then randomization of the participant will occur. Participants randomized to the MAD will be scheduled to meet with the maxillofacial physician, ideally within two weeks of randomization, to be fit with the MAD. Participants randomized to the conservative therapy will be given a roll of Johnson and Johnson Band-Aid Woven Adhesive Bandages 1" x 3", one box of Breath-Right strips (either small, medium, or large), and one Neti-Pot. The participants will receive their topical glucocorticoid prescription through the mail from AdvancedRx.

E4 Maxillofacial Visits

Participants randomized to the Mandibular Advancement Device arm of the trial will undergo additional visits with the Maxillofacial Physician. The first visit will be setup after the baseline study visit to occur within 2 weeks of the consent process. At the first visit, the maxillofacial physician will educate the participant on the device, explain the treatment plan to the participant, and take a molding of the participant's teeth at this meeting. After this, the molding and measurements will be sent to ProSomnus to have the device made, which will take 7-10 days. Once the device is received by the Maxillofacial office, a second meeting will occur. At this meeting, the maxillofacial physician will ensure the device is correct size and shape and will not create undue pain or discomfort, review proper use of the device, including self-titration of the degree of jaw protrusion, and proper care of the device. These meetings will occur during the 4-week pre-intervention period as outlined in section F2.

E5 Daily Check-ins

Every morning the sleeping partner will receive a text message asking them to complete the CGI-S for the sleeping partner (*CGI-S Sleeping Partner).* They will respond via their telephone to the single question prompt until the end of the study.

E6 Visit 2

At the end of study, all the Visit 2 - End of Study outcome measures will be presented to the participant via REDCap. The End of Study measures include the CGI-I scales, the CGI-S scale, the ESS, and the SNORE-25 or modified SNORE-25. This will occur asynchronously through email surveys distributed through the Washington University REDCap server or through a scheduled telephone call depending on the participant's preference. Both the participant and the sleeping partner will complete this step. Participants will also return their compliance sheets at this time.

E7 Safety and Adverse Events

7.a Safety and Compliance Monitoring

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring committee comprised of Dr. Piccirillo, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event (UAE) will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

Participants who experience serious adverse effects with therapy will be removed from the study. Participants with serious adverse effects will be instructed to call 911, seek immediate medical care and discontinue all further treatment.

7.b Definitions of Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)).

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.

An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Serious adverse events (SAEs) are special cases of an adverse event where adverse outcomes are severe. SAEs include the following events:

- Death of any of the participants associated with a clinical trial.
- An event which can lead to life-threatening complications or put the life of participants at risk because of participation in a clinical trial.
- Events that result in such a condition where the participants may require immediate hospitalization or increase the duration of hospitalization.
- Any events that lead to a permanent or temporary physical disability in the body of the participants. Any sort of incapacity is also regarded as SAE.
- Any events that lead to any type of congenital abnormalities. It also includes any cases of birth defects resulting from the clinical trials.
- Any events where an investigator or team of investigators finds feel that it can lead to significant hazards.

7.c Classification of Events

7c.1 Relationship

An AE or SAE may or may not be causally related to the study intervention. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the intervention and the AE (e.g., the AE occurred shortly after the participant received the intervention). For all AEs, it is the responsibility of the Principal Investigator who examines and evaluates the participant to determine the relatedness of the event to the study intervention.

7c.2 Severity

Severity refers to the intensity of a specific event and is a matter of individual clinical judgment.

- Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe; or medically significant but not immediately life- threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening; urgent intervention indicated.
- Grade 5: Death related to an AE

7c.3 Expectedness

An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in this protocol or on the informed consent or is not listed at the specificity or severity that has been observed; or, if an investigator

brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.d Data Collection Procedures for Adverse Events

All adverse events and suspected adverse reactions are collected from 'source documentation' and the research coordinator will abstract the events. Documentation can be within Washington University Epic medical records, but at times, the research coordinator will also need to have the participant send outside source documentation.

7.e Reporting Procedures

The Principal Investigator (PI) will be responsible for ensuring participants' safety daily and for reporting Serious Adverse Events and Unanticipated Problems to the Institutional Review Board (IRB) as required.

All SAEs will be reported immediately to the Principal Investigator upon identification.

7.f Adverse Event Reporting Period

All AEs and unanticipated problems will be reported to the IRB in a prompt and timely manner to protect other subjects from avoidable harm. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem. For this study, unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event. Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by the Research Coordinator and the Principal Investigator knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

E8 Study Outcome Measurements and Ascertainment

Participants and sleeping partners will complete the following forms using REDCap after completing the intervention:

1. Clinical Global of Impression of Improvement Scale
2. Clinical Global of Impression of Severity Scale
3. Epworth Sleepiness Scale
4. Symptoms of Nocturnal Obstruction and Related Events
5. Pittsburgh Sleep Quality Index

F Statistical Plan

F1 Sample Size Determination and Power

To date, there is no study reporting the rate of response in participants using MAD. Due to lack of preliminary data and effect size, estimates of the sample size for this study will be determined based on feasibility. We propose a pilot study with a total sample size of 60 subjects (snorers only). The sample size of 60 subjects is feasible, given the incidence of primary snoring prevalence in America, which is estimated at 40-50%[15]. Using a 33% drop out rate, we estimate that the sample size of 60 subjects randomized in a balanced way between the two treatment groups will provide us with 40 evaluable cases. We hypothesize that the rate of the responders in the MAD group will be 20% higher than the rate of responders in the active control group. If the rate of response in the control group is 30%, the sample size of 20 subjects per group will allow us to estimate a 95% confidence interval around the rate difference between groups with a margin of error of 30%.

F2 Interim Monitoring and Early Stopping

Due to the size of the study and the nature of a pilot study, we will not be participating in early stopping or interim monitoring of the participants.

F3 Analysis Plan

A Per Protocol analysis will be used for the primary analysis of the data. Descriptive statistics will be used to describe the characteristics of participants in the 2 study groups. Responder rate difference will be calculated as shown below:

Responder Rate:

$\text{Reponder}_{\text{Conservative}}$ / $\text{Total Participants}_{\text{Conservative}}$

$\text{Reponder}_{\text{MAD}}$ / $\text{Total Participants}_{\text{MAD}}$

Responder Rate Difference:

$\Delta_{\text{Responder Rate}} = \text{Responder}_{\text{Conservative}} - \text{Responder}_{\text{MAD}}$

95% confidence interval around the difference will be calculated and reported. Chi square test or Fisher's exact test will be used to compare categorical level outcomes between the 2 study groups, including the difference in Responder Rate. Effect sizes and 95% CIs will be reported for each comparison. For secondary outcomes, independent samples t-test or its non-parametric equivalent Mann-Whitney U test will be used to compare continuous level outcomes between the 2 study groups. Median or mean difference and CI will be calculated and reported according to the test being used. The role of potential confounders will be explored in multivariate analysis using logistic regression or GLM. All statistical analyses will be conducted in SPSS 28 (IBM Corp., Armonk, NY).

F4 Missing Outcome Data

All attempts will be made to minimize the occurrence of missing outcome data through adherence to the principles of Good Clinical Practice and the reduction of the complexity and number of assessments. It is assumed that all missing data will be at random. As this is a small pilot study, no computational techniques will be employed to adjust analyses for missing data.

F5 Unblinding Procedures

After all data analysis and charts, tables, and graphs are created, unblinding will occur. Dr. Kallogjeri will break the blind and all placeholders in the manuscript and graphics will be replaced with the corresponding intervention.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Procedures are in place to curb risks of breaches in confidentiality and privacy. These procedures include: 1) formal training protocols centered on the maintenance of confidentiality for all study team members; 2) a password-protected computer file that contains the identity of participants, corresponding ID numbers, and contact information; 4) secure storage for identified data forms such as completed questionnaires; and 5) communication with study team via secure email, phone line, or tele-video call.

Only members of the study team will have access to the electronic research files. All research data files will be stored on secure Washington University servers with computer, network, and database-level passwords that will only be accessible to study team members. No participant identifying information will be revealed in any publications or presentations.

Case report forms will be created as electronic documents and stored within each study participant's electronic file. Original hard-copy source documents will be electronically scanned and stored in the participant's electronic file and stored in a locked file cabinet.

G2 Records Retention

All records will be retained for a minimum of six years after completion of the study and closure with the WU IRB. Data will be stored for contribution to future research studies. Contribution for future use is optional for participation in the study

H Study Administration

H1 Participant Payment

Participants will be provided a Forte/Advarra debit card. They will receive $30 for completing each set of surveys associated with the study. As such, a participant may receive $60 total. This will be payable to the participant upon completion of the study. If participants do not complete all requirements, they will be paid proportionally for the work they have completed. Participants will be able to keep all items received as part of their respective treatment arm. The sleeping partner will be paid an additional $25 for responding to > 80% of the texts. If they respond to > 50% of the texts the will receive $10. If the sleeping partner's response rate is <50% they will not be compensate for the texts.

H2 Study Timetable

Participants will be in the study for a total of eight weeks. Given the volume of patients seen at the Adult Division of the Department of Otolaryngology-Head & Neck Surgery and the Sleep Medicine Center for assessment of snoring, we anticipate it will take one year to complete enrollment, intervention, and analysis.

Months												
	1	2	3	4	5	6	7	8	9	10	11	12
Enrollment and Baseline Assessment												
Randomization												
Pre-intervention period												
4 week intervention treatment												
End of participation assessment												
Data analysis and Manuscript preparation												

*Pre-intervention period is the 4-week period prior to the intervention where the MAD will be adjusted or the Mometasone nasal rinse is ongoing.

I Publication Plan

We plan to analyze accumulated data throughout the month of May 2023 and publish the results by the end of June 2023. This data includes the analysis of the CGI-I, CGI-S, SNORE-25, and ESS as well as a discussion of the potential adverse effects associated with Mandibular Advancement device and standard therapy for treatment of non-apneic snoring.

J Attachments

J1 Informed consent documents

J2 Patient education brochures

- Nasal Saline irrigations with Mometasone
- Prosomnus User Manual
- SNORE-LESS conservative therapy patient instructions

J3 Questionnaires or surveys

- Screening Survey
- Demographics
- Demographics Sleeping Partner
- Baseline Data
- Baseline Data Sleeping Partner
- CGI-S Sleeping Partner
- Follow Up Data
- Follow Up Data Sleeping Partner
- Completion Data

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