Novel Myofunctional Water Bottle to Reduce OSA and Snoring study

NCT05371509

11October2024

Mayo IRB#: 22-001883

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Protocol version: 11OCT2024

Specific Aims: There is a clear unmet need to provide alternative, first-line solutions for both obstructive sleep apnea (OSA) and primary snoring. Most people suffering from OSA are currently not receiving treatment with estimates of 80% undiagnosed (23 million Americans) and 40% non-adherence to the gold standard treatment, continuous positive air pressure among diagnosed patients. This has serious implications for overall health resulting in increased daytime sleepiness and comorbidities of hypertension, heart disease, diabetes, and depression. The OSA undiagnosed population alone contributes to an estimated cost burden of $30 billion from comorbidities and mental health, $26.2 billion from motor vehicle accidents, $6.5 billion from workp lace accidents, and $86.9 billion from lost productivity, with a total cost burden to the US of $149.6 billion each year [1]. Although most people are undiagnosed, indicators such as snoring can be found in up to 94% of OSA patients [2] and habitual snorers (snoring ≥ 3 nights/week) with bed partners often seek treatment for their snoring. Low risk, low burden, and affordable solutions that are easily administered to OSA patients and primary snorers open new treatment paradigms to reduce the overall harm from these conditions. Oropharyngeal exercises are a promising therapy for motivated patients and have shown, on average, to reduce apnea hypopnea index (AHI) by 14.3 points and snoring by more than 50% [3,4]. Despite their efficacy, all exercise regimens need to be performed regularly and in a measurable way, factors that limit their widespread adoption. **There is a significant opportunity for a simplified device that can effectively deliver oropharyngeal exercise therapy in less burdensome, measurable, and more acceptable ways to increase patient adoption and adherence.**

Unmet Need: To address the problem of adoption and adherence, we will develop and clinically test our proposed myofunctional therapy (MT) nozzle that simplifies the oropharyngeal exercise regimen for OSA patients and primary snorers. Swallowing is a complex motion that requires activation and coordination of most oropharyngeal muscles that are also involved in maintaining patency of the upper airway. By providing resistance and repetitions during the oral phase of swallowing, most muscles of the tongue and soft palate can be effectively exercised [5].

Solution: Our novel MT nozzle delivers targeted oropharyngeal exercises through daily use of a reusable water bottle (Figure 1). This device is designed to deliver daily therapy by simply drinking one or two bottles of water making it a simple, easy, and effective method to adopt and adhere to oropharyngeal exercises. Our proposed MT nozzle has low risk and low burden making it a promising adjunct and/or first-line solution for OSA and primary snoring once efficacy is established. This user-centric design and unique connection of the therapy with a biologically driven action of drinking water greatly increases the probability of long-term adherence to oropharyngeal therapy.

Figure 1: MT Nozzle & Reusable Water Bottle

Specific Aims:

Aim 1: Characterize, develop, and test pre-production MT Nozzles. We will characterize key therapy design features and develop a pre-production MT nozzle model for testing. The MT nozzle will be designed and manufactured to fit on a commercially available reusable water bottle. The preproduction model using production grade silicone materials will be tested using pre-established design and safety requirements.

Milestone: Finalize MT nozzle and fit with a reusable water bottle that meets design requirements.

Aim 2: Conduct feasibility study in human subjects. We will conduct a randomized, non-significant risk (NSR) device study that will assess adherence and quality of life after two months use of the MT nozzle water bottle vs. control for mild-moderate OSA patients. Secondary outcome measures will compare changes in myofunctional assessment, AHI, oxygen saturation (SpO2), and snoring intensity/percentage using a clinically validated and commercially available home sleep apnea test (*WatchPAT™ One*). Myofunctional measurements will be conducted at day 0 and day 60 using an Iowa Oral Performance Instrument and a myofunctional assessment score. Water consumption will be standardized across subjects through fitting of the MT nozzle and standard nozzle on commercially available water bottles that are Bluetooth enabled to measure water consumption (*Hidrate Spark™*). A questionnaire such as SAQLI (Sleep Apnea Quality of Life Index) will be used to measure QOL. Participants' significant others will be asked to complete a bed partner survey as applicable.

Milestone: Conduct NSR device feasibility study with MT water bottle vs control that assesses adherenceto therapy and quality of life after two months of use in mild to moderate OSA patients. Additionally, collect information on changes in snoring, OSA and myofunctional measures.

Our proposed nozzle is a novel, low risk, low burden, and low cost myofunctional device that will be clinically tested for feasibility with mild to moderate OSA patients. A future Phase II project would focus on further therapy optimization and conducting a larger more inclusive clinical trial with emphasis on efficacy. This proposed work has the potential to create a new therapy platform for patients to easily improve their OSA and snoring.

Inclusion Criteria:

- Diagnosis of mild to moderate obstructive sleep apnea with Apnea Hypopnea Index 5-29 events/hour confirmed within last 2 years with an in-lab diagnostic polysomnography or home sleep apnea test.
- Ownership of a smartphone and willingness to use a smartphone application to automatic log daily water intake.
- Willingness and ability to discontinue the currently prescribed OSA treatment for at least 3 days prior to testing.
- Age greater than or equal to 18 years.
- Participants willing to travel to the Rochester area for the Speech and Language Pathologist exam

Exclusion Criteria:

- Significant weight change (10% change in body weight in Kg) from the time of the OSA diagnosis until the study initiation.
- Persistent excessive daytime sleepiness (Epworth Sleepiness scale > 10), despite treatment of OSA
- Significant medical comorbidities requiring restricted oral fluid intake – **decompensated** heart failure, end stage renal disease, end stage liver disease, hyponatremia **(S. Na <130 mg/dl)**, nocturia **> times/night.**
- Significant mental health comorbidities including history of psychogenic polydipsia, obsessive-compulsive behavior, **current** suicidal ideation and uncontrolled anxiety.
- Unable or unwilling to participate in study procedures.
- Previous upper airway surgeries significantly modifying upper airway anatomy.
- Known congenital or acquired diseases significantly affecting upper airway anatomy.
- BMI >40 kg/m^2.
- Currently treating OSA with hypoglossal nerve stimulator.

Significance: There is a clear unmet need to provide alternative, first-line solutions for both obstructive sleep apnea (OSA) and primary snoring. Most people suffering from OSA are currently not receiving treatment, with estimates of 80% undiagnosed (23 million Americans) and 40% non-adherence to the gold standard treatment, continuous positive air pressure (CPAP), among those diagnosed. This has serious implications for overall health resulting in increased daytime sleepiness and comorbidities of hypertension, heart disease, diabetes, and depression. The undiagnosed population alone contributes to an estimated cost burden of $30 billion from comorbidities and mental health, $26.2 billion from motor vehicle accidents, $6.5 billion from workplace

accidents, and $86.9 billion from lost productivity, with a total cost burden to the US of $149.6 billion each year [1]. The aging population in addition to increases in obesity will only make this problem worse [6]. Although most people are undiagnosed, indicators such as snoring can be found in up to 94% of OSA patients [2] and habitual snorers (snoring ≥ 3 nights/week) with bed partners often seek treatment for their snoring. Low risk, low burden, and affordable solutions that are easily administered to OSA and primary snoring sufferers open new treatment paradigms to reduce the overall harm from these conditions.

Current available OSA treatments are effective but have high burdens due to difficulty of administration and high costs resulting in low adherence, especially among patients with primary snoring. The first-line gold standard treatment, CPAP, is highly effective but has a non-adherence rate of 40% and outright refusal rate of 20% for OSA patients, with even worse adoption and adherence for those with primary snoring [1,7]. Alternatives such as mandibular advancement devices have a higher rate of adherence than CPAP. They are considered less effective and 80% of patients have minor short-term side effects and 15% of patients have long-term side-effects such as bite changes [8]. Oropharyngeal exercises, focused on increasing strength and endurance of tongue, soft palate, and pharyngeal dilator muscles, have been shown to be a safe and effective treatment for motivated snorers and patients with mild to moderate OSA. Various studies show, on average, a decrease in apnea hypopnea index (AHI) by 14.3 events/hour and reduction in snoring by more than 50% [3,4]. Although positive results have been demonstrated, a major barrier to the adoption of and adherence to oropharyngeal exercises is the time and effort burden associated with having to learn and practice the multitude of exercises required daily. None of the current treatments are reimbursed by insurance for primary snoring, resulting in out-of-pocket costs for patients in the hundreds to thousands of dollars. Many snorers with possible undiagnosed OSA are led to easy, cheap snoring solutions that are often less efficacious for their snoring, thus adversely affecting long term treatment acceptance.

The efficacy of oropharyngeal exercises for the treatment of sleep related breathing disorders is based on the fact that these disorders are caused by “double hit” from (i) increased resistive loading of the upper airway by mechanical factors such as obesity, and (ii) absent compensatory neuromuscular responses. Thus, improving neuromuscular responsiveness of these upper airway muscles can compensate for anatomical causes and treat majority of the snorers and also serve as either first-line or adjuvant treatment in up to 36% of patients with OSA who have altered neuromuscular responses of the upper airway during sleep as the primary cause of their OSA [9]. Several randomized clinical trials have demonstrated efficacy of various oropharyngeal exercise protocols for treatment of snoring and sleep apnea. However multiple exercises are required to be learned and practiced daily which makes the therapy burdensome. Current protocols have been developed by researchers at the University of Sao Paulo, Brazil who started with 15 oropharyngeal exercises [10] then simplified them down to six [11] but still require a trained myofunctional therapist to administer. A new app-based oropharyngeal exercise regimen called *Airway Gym* was created to increase exercise participation by eliminating the time-consuming effort of having in-person sessions with a speech or myofunctional therapist. The exercise regimen, based on the original six exercises of the Brazilian protocol, showed AHI reduction on average from 25.8 to 14.1 per hour, yet still only demonstrated adherence rate to the therapy of 75% [12]. Another digital solution, *Soundly*, developed by our collaborator from University of Minnesota, simplified the oropharyngeal exercises further and implemented a gamified app-based myofunctional therapy regimen that mainly targeted the genioglossus muscle of the tongue by using vocalizations and found a 22% mean reduction in snoring rate over 60 decibels [13]. The app-based delivery and use of gamification is very innovative; however, both app therapies still take upwards of 15 minutes of focused exercises each day and not all patients own or enjoy using a smartphone each day. The therapy may be manageable at first; however, it will likely become burdensome overtime with low probability of long-term adherence except for those who are the most motivated. **A major obstacle to patient adoption and adherence exists, creating a demand for a simplified device that can effectively deliver oropharyngeal exercise therapy in less burdensome and measurable ways.**

To address the problem of adoption and adherence, we will develop and clinically test an innovative myofunctional therapy (MT) nozzle and associated reusable water bottle to simplify the oropharyngeal exercise regimen and can easily be administered to both OSA patients and primary snorers. The **scientific premise** of this project is that natural tongue suction, tongue compression against palate, and swallowing movements activate most of the muscles targeted with oropharyngeal exercises, allowing the therapy burden to be reduced by utilizing the biologically driven action of drinking water. There are three main goals to

our therapy. **Goal 1:** Tighten muscles in throat and soft palate to reduce vibration and collapsibility. This is achieved by increasing daily swallows. **Goal 2:** Tighten genioglossus muscle to reduce/prevent tongue from falling back in throat while sleeping. This is achieved by both the tongue suction and tongue press. **Goal 3:** Promote tongue on roof of mouth with light suction and nasal breathing while at rest. This is achieved by exercising the intrinsic tongue muscles during the tongue suction and exercising most of the tongue muscles during the tongue press against the roof of mouth. Swallowing is a complex motion that requires activation and coordination of most oropharyngeal muscles including those involved in maintaining upper airway patency [4]. By providing resistance and promoting repetitions during the oral phase to pharyngeal phase of the swallow, most of the oropharyngeal muscles exercised in the previously mentioned Brazilian protocol are activated (**Table 1**).

Table 1: Comparison of Our Therapy to the Standard Six Exercises Utilized in the Brazilian Protocol

Brazilian Protocol [11]	Main Effects of Exercise	REMastered Sleep Myofunctional Therapy (Tongue Suction, Tongue Press, Swallow)
Tongue suction to hard palate	Activates intrinsic muscles, raises tongue to roof of mouth, activates genioglossus.	The tongue suction activates same muscles by utilizing the tongue to create negative pressure to suck water into mouth.
Tongue tip slide backwards	Exercises hyoid, hyoglossus, and genioglossus.	Tongue suction, tongue press, and swallowing exercises the hyoid, hyoglossus, and genioglossus.
Tongue on bottom of mouth	Exercises hyoid and genioglossus.	Tongue suction, tongue press, and swallowing exercises the genioglossus and hyoid.
Saying ‘ah’	Exercises soft palate to reduce vibration of tissue.	Swallowing blocks off nasal cavity to prevent water flow into nose by raising soft palate.
Bilateral chewing with tongue on palate	Works most tongue muscles by using tongue to move food side to side.	Tongue press activates similar muscles of the tongue but without the side to side motions.
Buccinator outward press	Targets buccinator. Unclear if this would have any effect on snoring and/or OSA.	The buccinator has slight activation during the swallow.

[redacted] This creates the potential for tens of millions of OSA sufferers, primary snorers, and bed partners to get better sleep resulting in reduced comorbidities, less daytime sleepiness, improved emotional and relationship health, and reduction of the $149 billion yearly cost burden associated with untreated and undiagnosed OSA.

[redacted]

Our simplified exercise regimen greatly reduces the burden of having to learn and practice multiple exercises daily and will lead to greater patient adherence and adoption. The innovative therapy delivery system embeds the oropharyngeal exercises into the biologicallydriven action of drinking water, which minimizes the intrinsic and/or extrinsic motivation needed to exercise each day. The myofunctional therapy nozzle and water bottle delivery system, if proven effective, has the potential to be state-of-the-art and paradigm changing for providing adjunct or alternative treatment option for OSA and primary snoring.

We created an innovative myofunctional therapy nozzle that allows the user to repeatedly perform the tongue suction, tongue press, and swallow exercise movements while also providing targeted resistance to train and improve tongue, soft palate, and pharyngeal muscle strength and endurance **(Figure 2)**. Key design features of the nozzle promote proper tongue swallowing position and tongue suction motion and resistance during the preparatory and oral phase of the swallow. The nozzle then provides resistance as the tongue compresses the nozzle against the hard palate through the transition of the oral and pharyngeal phases of the swallow. The device promotes 20-50% more daily swallows by limiting water bolus size for each swallow. The device is designed to deliver daily therapy by simply drinking one or two bottles of water (30oz – 60oz), making it simple to keep track of daily therapy. The nozzle is engineered to utilize natural biomechanical motions of the tongue and prevent improper exercise motions, which makes it easy to use with minimal instruction or attention.

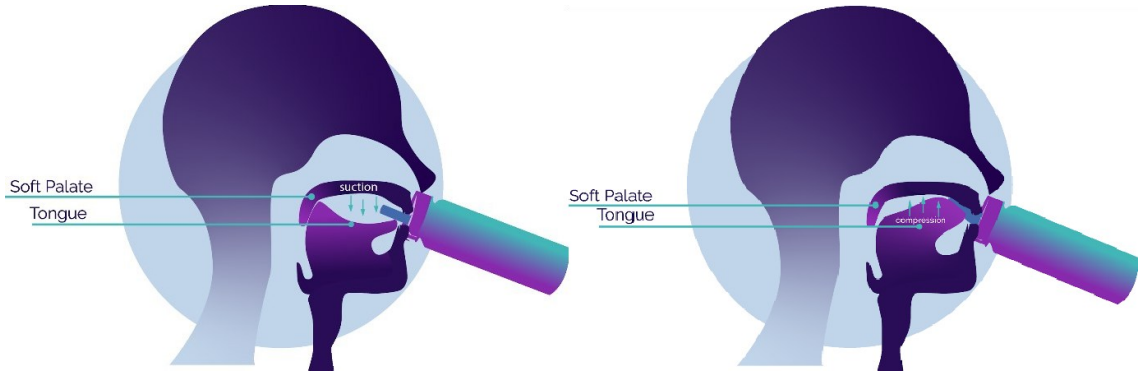

Figure 2: Depiction of Tongue Suction (left) and Tongue Press (right) Motions.

Our technology has created an oropharyngeal exercise device that has low risk and low burden and can be easily administered to reduce primary snoring and obstructive sleep apnea severity. The user-centric design and unique connection of the therapy with a biologically driven action greatly increases the probability of long-term adherence to the therapy regimen. Our solution has the potential to create a new therapy option for physicians to manage their patients' OSA and snoring.

Approach: In this SBIR Phase I project we will characterize, develop, and test a novel myofunctional therapy nozzle that can be used with a commercially available reusable water bottle and conduct a feasibility study comparing the device vs. a normal water bottle nozzle control to assess adherence and quality of life (QOL) for mild to moderate obstructive sleep apnea patients after two months of device use. Secondary outcome measures will compare changes in myofunctional assessment, AHI, oxygen saturation (SpO2), and snoring intensity/percentage. Successful outcomes of this Phase I project will be a myofunctional therapy nozzle with characterized key therapy related design variables that has shown feasibility and improved adherence.

Preliminary Work: Usability Study: A prototype myofunctional therapy nozzle and water bottle were developed and used to conduct a product usability study with snorers over the summer of 2020 to assess likeability, one-month adherence, and subjective snoring improvement. Participants were recommended to drink one 880mL bottle of water a day (water amount could be adjusted if was too easy or too difficult) five days a week and keepa daily log. Subjective bed partner reported snoring data was collected through survey pre- and post-use of device over one month. Participants had two feedback interviews conducted through virtual video call: initial impressions after a few days of use and feedback after one month of use. An anonymous survey was provided after one month to measure the customer satisfaction score (CSAT). 37 subjects participated in the study and completed one month of device use. 27 participants were included in the snoring analysis and 35 participants in the tiredness analysis. 8 participants were excluded from the snoring analysis because they did not have a bed partner that could provide snoring feedback, or they used a device while sleeping, such as a mouth guard or CPAP, that would interfere with the results. 2 participants were excluded from both the snoring and tiredness analysis based on non-compliance using the device (1 participant) and using the device with the goal to help with jaw clenching (1 participant).

Snoring Results: The one-month assessment showed 88% adherence, the overall satisfaction of the product was 80% measured by CSAT, and 93% reported subjective improvements in reducing snoring intensity, occurrence, and/or impact. Bedpartner reported median snoring intensity decreased from "somewhat loud" to "soft or quiet", overall snoring occurrence decreased, and median snoring impact reduced from "moderate" to "a little bit" after one month of device use. Although this was a one-month study, some participants continued use beyond the study period and reported additional snoring improvements after two months of consistent device use. The initial feedback interviews revealed participants liked the device, thought it was comfortable to use, the effort to drink was not a problem, it was easy to use it while doing other tasks such as while working or watching tv, and enjoy the concept of doing something during the day (positive biofeedback) that may have lasting effects rather than having to sleep with a device each night. The therapy levels chosen worked for most participants with only some opting to go to lower or higher levels of resistance. Some participants reported additional improvements in swallowing, nasal breathing with tongue on roof of mouth positioning during day that carried over into night, and increased tongue strength and endurance.

Tiredness Results: 12 of the 35 participants (34%) self-reported improvements in tiredness after one month of device use, although the study recruited snorers and did not intend to measure tiredness improvement. Participants described more restful sleep or decreased tiredness, less headaches, reduced awakenings in the middle of the night, and less fogginess in the morning – symptoms that appear more indicative of OSA than typical snoring. One severe OSA patient reported further tiredness benefit with use of MT nozzle water bottle as adjunct to already compliant CPAP therapy. Ten of the participants that reported benefit in tiredness have not been diagnosed with OSA. These improvements in tiredness could be a result of improving the symptoms of undiagnosed OSA given the high undiagnosed rate in the general population.

Rigor and Reproducibility: The scope of work will be done with good engineering, laboratory, and clinical practices. Data collected in lab notebooks will be dated and signed by operator. Early engineering design work and characterization testing will not require validated test systems unless deemed necessary. Design verification testing against the requirements outlined in Aim 1 will require proper test method validation as defined per our company's quality system unless there is justification that it is not required. This consists of normal engineering controls such as calibration and Gage R&R to show the test is accurate, repeatable, and reproducible.

Aim 1. Design, develop, and test pre-production MT Nozzles: There are 4 main design requirements that need to be met before the device is ready for a clinical study. There are 2 therapy requirements, 1 durability requirement, and 1 safety requirement. Initial design testing and characterization will be conducted using food-grade silicone and 3D printed molds. Designs will be optimized for all the requirements and manufacturability before finalizing the design and moving to preproduction. Preproduction injection molded medical-grade silicone parts will be used for design verification testing to prove metrics of success. *Note: The target value of the therapy requirements mentioned in Aim 1.a & 1.b are a range because tongue strength and endurance have a wide range of variation throughout the population [14]. Requirement values will be chosen within our desired range and similar to our previous usability studies; however, further optimization of the therapy resistance levels is expected in a Phase II project.*

1.a) Build Nozzle with Consistent Radial Compression Force: The therapy compression force requirement range of our nozzle was based on numerous dysphagia studies in the literature that utilized the Iowa Oral Performance Instrument (IOPI), in combination with qualitative testing. The IOPI is a commonly used tool to assess tongue strength and endurance by compressing a bulb against the hard palate with the user's posterior or anterior tongue. We will correlate compression force to IOPI pressure measurements by compressing an IOPIbulb with a force load cell and test stand. The force compression range will be 0 – 100kPa measured by the IOPI[15]. The max compression distance of 100 kPa will be determined by measuring the distance from touching without compression and compressing until the IOPI reads 100kPa. 5 – 10 compression distances within the minand max range will be measured by recording the data point on both the IOPI and the compression load cell at each distance. This test will be repeated until the data is sufficient to understand the relationship. The therapy requirement will be adjusted from IOPI pressure to compression force measured by load cell using the correlation equation determined. Nozzle Radial Compression Characterization testing will be conducted by varying silicone stiffness (durometer) and wall thickness associated with the nozzle. The mold design can be easily iterated upon with CAD software and 3D printing to test varying wall thicknesses. Silicone stiffness can be varied by selecting different durometer grades of silicone used. A load cell and motorized test stand will be used to radiallycompress the nozzle at a set speed, to mimic the normal speed of swallowing [16,17]. The force data will be analyzed to determine the max radial compression force before the inflection point where the silicone inner walls are touching, and the silicone material is being compressed.

Metric of Success: 30 nozzles will be manufactured within +/- 10kPa (IOPI measurement that will be correlatedto radial compressive force) of the desired radial compression force requirement as measured by radial compression testing.

Alternatives: If nozzle is built consistently but there is a mean shift outside of tolerance range, it will be determined the nozzle radial compression forces are adequate for the usability study. If the variability exceeds the accepted tolerance range for the 30 nozzles, parts can be scrapped so that at least 20 are available for the feasibility study in Aim 2. If this cannot be met, the manufacturing process, design, and specification tolerance will be evaluated for further optimization to produce the 20 study nozzles.

1.b) Control Nozzle Outlet Flow Resistance: Initial therapy investigation has determined that amount of nozzle outlet flow with externally applied negative pressure is an important therapy requirement to promote proper tongue movement. We will design and test our nozzle to pass flow requirements tested at external negative pressure. After nozzle designs are finalized, they will be put through flow testing at negative pressure. A modifiedvacuum chamber will be used to create set negative pressures external to the nozzle. The nozzle will be attached to a tube that runs outside of the vacuum chamber that is attached to a container with water. The water containerweight will be measured before and after and the time will be recorded to determine the flow of water through the nozzle at external pressure of -10kPa, -20kPa, -30kPa, and -40kPa (determined as a max value from previous testing). This will be repeated 3 times for each of the nozzle designs and each external pressure level.

Metric of Success: Build 30 nozzles within 20% of desired outlet flow at applied external negative pressure measured with change in water container weight before and after divided by the time elapsed.

Alternatives: If the variability exceeds the accepted tolerance range for the 30 nozzles, parts can be scrapped so that at least 20 are available for the feasibility study in Aim 2. If this cannot be met, the manufacturing process, design, and specification tolerance will be evaluated for further optimization to produce the 20 study nozzles.

1.c) Perform Nozzle Durability Testing: A cyclic wear test will be created by using a peristaltic pump mechanism. A peristaltic pump has roller arms with bearings that are controlled to either a set distance or set force. A motor is used to rotate the roller arms in a circular movement. The nozzle will be attached on the inlet end and placed against a hard race wall. The roller arms will move in a circular motion repeatedly compressing and stretching the nozzle. The test will be designed to exceed the compression forces or cycles that the nozzle would see in normal use based on compression force data from normal swallows [17], and the number of cycles and force estimated to be seen in normal use for full compression of the device as determined from above force testing. We estimate that less than 200,000 cycles would be seen in one year of use. Ten nozzles will undergo durability testing. The cyclic testing will have periodic stop points to check for nozzle wear. A visual inspection under microscope will be used to inspect for tears at the outlet holes and any other observable wear on the nozzle. Pictures will be taken during each cycle inspection and abnormalities will be noted. The functional test for flow through the outlet holes at different negative pressures and radial compressive force testing will be performed at each level and at the end to see if any functional changes occur with cycles.

Metric of Success: Create therapy nozzle that passes visual wear inspection, functional water flow test requirements, and radial compressive force requirements (Aim 1.a & 1.b), after 200,000 compressive cycles.

Alternatives: If the nozzle design does not meet the durability requirements mentioned above, the mid-point analyses will be used to determine at approximately what number of cycles the nozzle fails. This will be used to estimate the expected life of the product. If this is less than 2 months, this may affect the device feasibility study that we will conduct in Aim 2. To overcome this, multiple nozzles will be given to participants to replace the nozzle after a predetermined period.

1.d) Develop Nozzle to Water Bottle Connection Interface: The nozzle to water bottle connection requirement is important to allow users ability to detach the nozzle for cleaning or replacement while also minimizing the riskof the nozzle inadvertently detaching during use and becoming a potential choking hazard. Engineers will work to develop a simplified connection system to connect our silicone nozzle to the *Hidrate Spark*™ water bottle forthe clinical feasibility study defined in Aim 2. Thirty water bottles will be measured with a caliper on predetermined key connector features. If no adequate connection features on the water bottle exist, the water bottle lid will be modified. The water bottle connector interface will be recreated in CAD and the nozzle connector will be designed to match this interface. A mold will be 3D printed and the nozzle with connector interface will be molded. The nozzle release force will be tested by increasing tensile load until the nozzle disconnects. The tensile load will be recorded, and this will be repeated three times on the same part and performed on ten other water bottle andnozzle connector combinations. If any of the nozzles fail the requirement, the nozzle connector interface will be redesigned and retested. An additional qualitative test will be performed where the operator manually removes the nozzle from the water bottle. This will be timed, and the operator will rank difficulty to remove as acceptableor unacceptable. If nozzles take longer to remove than 10 seconds and/or scores are unacceptable, nozzle connection will be redesigned for easier removal.

Metric of success: Nozzle securely attaches to *Hidrate Spark*™, the commercially available water bottle used in clinical feasibility study and meets tensile load and removability requirements as determined by connector usability testing.

Alternatives: If nozzle does not meet connector requirements, additional design features could be added i.e. adding a latch or cinch. If the nozzle is too difficult to remove, alternative methods of cleaning the nozzle could be developed.

Aim 2. Conduct feasibility study in human subjects: The goal of Aim 2 is to conduct a feasibility study of the MT nozzle water bottle vs. a normal nozzle (placebo) water bottle in mild and moderate OSA patients. Dr. Umesh Goswami and Dr. John Park, sleep medicine experts at the Mayo Clinic, will oversee the study. An experienced speech language pathologist (SLP), will perform myofunctional assessment at study entry and after approximately two months of device use to determine if the device is delivering the desired oropharyngeal exercises. 43 participants will be recruited from Mayo Clinic Sleep Disorders Center in Rochester, MN who underwent polysomnography (PSG) or home sleep apnea test (HSAT) within last 2 years and are diagnosed with mild to moderate obstructive sleep apnea (AHI 5-29/hour). Potential participants will be contacted by a member of the Pulmonary Clinical Research Unit (PCRU) to gauge interest in the study. Those interested in participating will be asked to come to Mayo Clinic for enrollment or may enroll via a virtual visit and sign a consent form electronically. REMastered Sleep will provide randomized kits to the PCRU for each enrolled participant containing a clinically validated disposable home sleep apnea test (WatchPAT™ ONE), a smart water bottle with Bluetooth connectivity (Hidrate Spark™), and either an MT nozzle or a placebo nozzle with an instruction sheet on how to use and clean the water bottle and the provided nozzle. Each person who enrolls at Mayo Clinic will receive a kit during the visit. Those enrolled virtually will have kits shipped to their homes. Study IDs will be assigned by the study team at Mayo Clinic.

Prior to the first visit with SLP, each participant will complete a QOL questionnaire such as SAQLI (Sleep Apnea Quality of Life Index). If the participant has a significant other, the significant other will be asked to complete a bed partner survey. Participants will receive these surveys through their email or they may be distributed via paper at the first SLP visit. These surveys will be reviewed by the study coordinator or the PI within 48 hours of completion. The participant will undergo baseline myofunctional measurements conducted with SLP. The myofunctional assessment test includes upper airway and oral exam to calculate a myofunctional assessment score and assess tongue strength and tongue endurance using the Iowa Oral Performance Instrument (IOPI).

Following this, the participants will conduct the home sleep apnea test using the provided WatchPAT™ ONE device for baseline measurements of pAHI (PAT Apnea Hypopnea Index), pRDI (PAT Respiratory Disturbance Index), SpO2 measures – ODI (Oxygen Desaturation Index), nadirSpO2 and T90 (Total sleep time < 90% SpO2), and snoring (intensity and percentage of night with snoring). If the subject has completed a WatchPAT clinically at Mayo Clinic within the last 3 months, the baseline WatchPAT is not required to be sent to the participant as the clinical data is accessible and will still be valid.

The measurements of the myofunctional assessment score, home sleep apnea test and questionnaires will be repeated at day 60 (± 5 days) after enrollment. Participants will have 15 days to complete the questionnaires after the 60 day visit.

To wash-off the remnant effects of the standard of care (SOC) OSA treatment on their upper airway, participants who are actively using CPAP, mandibular advancement device, or sleep positioning device, would be asked to discontinue the SOC treatment use for 3 nights prior to the baseline and end-of-study testing. The participants will be enrolled in the study on a rolling basis and the study coordinator will hand out randomized kits containing either MT nozzle (intervention group) or the placebo nozzle (control group), 20 participants each, as described above. The participants, PI and SLP will remain blinded to the group assignments. The study coordinator will be unblinded to group assignments. The placebo nozzle will be made out of the same silicone material and resemble the MT nozzle in appearance but will not have the resistance component to provide myofunctional exercises. The smart water bottle with Bluetooth connectivity (Hidrate Spark™) will automatically log each participant's daily fluid intake through the provided nozzle via a compatible smartphone application and share the fluid intake data with the study personnel. All participants will be suggested an intake of approximately 1.2 liters of water per day using the provided water bottle (equivalent of drinking two 20 Oz water bottles). At the

time of study conclusion, the participants will be invited to participate in a survey interview to assess the usability of their assigned devices and record changes they have noticed. This survey will be developed after the study enrollment starts but before participants would need to complete the survey. A modification will be submitted to the Mayo Clinic IRB when the survey becomes ready. Subjects will be reimbursed for their time as described in the Budget Justification section. The participants may continue to use the MT nozzle, smart water bottle and its accompanying smartphone application after the study completion if they choose to without any additional study data collection. The participants in the placebo nozzle group will be provided with the MT nozzle for personal use upon request after the completion of the study. The human subject study will be approved by Institutional ReviewBoard (IRB) at Mayo Clinic Rochester. Statistical analysis methods are described in the Statistical Design and Power Section.

Metric of Success: Adherence is greater than 50% in the therapy group. There is statistically significant changein QOL of the therapy group compared to control group after 60 days of therapy.

Alternatives: If adherence is not greater than 50%, participants will be interviewed to understand what could be improved. If there are no statistically significant changes in QOL, sample size will be reviewed along with, AHI, SpO2, snoring measures, and the final survey interview to assess if there was notable improvement reported between the therapy and the control groups. More emphasis will be put on the analysis of the myofunctional assessment to look for trends to inform improvement of therapy and/or patient selection.

Timeline:

Specific Aims	Month					
	1-2 months	3-4 months	5-6 months	7-8 months	9-10 months	11-12 months
1) Characterize, Develop, and Test Pre-production MT Nozzles						
1.a) Build Nozzle with Consistent Radial Compression Force	■	■				
1.b) Control Nozzle Outlet Flow Resistance	■	■				
1.c) Perform Nozzle Durability Testing		■	■			
1.d) Develop Nozzle to Water Bottle Connection Interface			■			
2) Conduct Clincial Feasibility Study						
IRB Approval & Recruit Patients	■	■	■			
Conduct Clinical Feasibility Study				■	■	
Analyze Study Results					■	■
Submit Final Report						■

Anticipated Outcomes: Successful outcomes of this Phase I project will be a characterized low risk, low burden, and low cost myofunctional therapy nozzle that has demonstrated feasibility for mild to moderate OSA patients.

Future Work: A future Phase II project would focus on further therapy optimization and conducting a larger clinical study with a more inclusive population of OSA patients, including children with OSA and snoring, with emphasis on efficacy of the device in treatment of snoring and mild-moderate OSA.

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