Study Title: Midline traction versus bilateral thrust oral appliances: A randomized controlled trial to determine superiority for improving upper airway function and sleep quality.

NCT03219034

Study Protocol and Statistical Analysis Plan, November 14, 2019

IRB Application (Human Research) (Version 1.4)

1.0 General Information

***Please enter the full title of your study:**

Midline traction versus bilateral thrust oral appliances: A randomized controlled trial to determine superiority for improving upper airway function and sleep quality.

***Please enter a reference or other description for this study. This field is required, but will not be referenced by the staff. It is for your use:**

RCT on oral appliance design for improving sleep
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List departments associated with this study. If the study is funded, please associate it with the correct A&M System member.:

Primary Dept?	Department Name
◉	**TAMHSC** - *Health Science Center* - College Of Dentistry

3.0 Assign key study personnel (KSP) access to the project

3.1 *Please add a Principal Investigator for the study:

Emet Schneiderman

3.2 If applicable, please select the Research Staff personnel. Please note if you do not find the personnel needed, please contact the iRIS support line at 845-4969. IRB Note: These personnel will need to sign off on the initial application submission.

A) Additional Investigators

Bender, Steven
Additional Principal Investigator
Hui, Jason
Co-Investigator
McCann, Ann
Co-Investigator
Schramm, Preetam
Co-Investigator
Wilson, Phillip
Co-Investigator

B) Research Support Staff

German, Zohre
Study Coordinator
Marques De Moura, Pollyana
Grad Student
Newton, Margaret
Research Assistant

3.3 *Please add a Study Contact:

Bender, Steven
German, Zohre

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor:

3.5 Please select the Designated Department or Supervisor Approval(s)(not required for Animal Use Protocol):

Opperman, Lynne
Department Chair

For IRB and IBC, add the name of the individual authorized to approve and sign off on this protocol from your Unit (e.g. the Department Chair or Dean).

3.6 If applicable, please select the Administrative Assistant(s)(i.e., Designee) Note: These personnel will not need to sign off on the initial application submission.Please do not use for IRB applications.

4.0 Request to the Human Research Protection Program :: Please Select ONE of the options below.

Version 11.14.2019

4.1 I am conducting Human Subjects Research, and I want to proceed to the regular application.

○ Yes ○ No

Which IRB reviews your research?

○ TAMU IRB
○ Dentistry IRB

4.2 I am requesting a determination - is my project human subjects research?

○ Yes ○ No

4.3 I am requesting to defer to an external IRB (that is not IRB TAMU or IRB Dentistry).

○ Yes ○ No

4.4 I am requesting a "Delayed Onset" of human subjects research determination.

○ Yes ○ No

4.5 A non-Texas A&M researcher is requesting to use people at Texas A&M as human subjects (staff use only).

○ Yes ○ No

5.0 Information Requested to Make a Determination

5.1 Information

Describe the Project (include objectives, procedures, and how results will be used):

Who will you collaborate with (site/person)?

Funding Source

View Details	Sponsor Name	Sponsor Type	Funding Through	Contract Type:	Project Number	Award Number
No Sponsor has been added to this Study						

If the funding is a grant or contract, are you the primary awardee?

○ Yes ○ No

Attach the grant, contract or any other relevant documents that will be needed to make a determination (protocol).

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

6.0 External IRB Review

6.1 Details

Name of External IRB:

What is the TAMU personnel's role in this study?

Please indicate the study sponsor here (if applicable):

View			Funding	Contract	Project	Award

Details	Sponsor Name	Sponsor Type	Through	Type:	Number	Number
No Sponsor has been added to this Study						

IRB authorization agreement (call the IRB staff at 979.458.4067 if no agreement exists).

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

Attach approval letter from external IRB:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

Initial approval date by external IRB:

Last date of approval period by external IRB:

External IRB supporting documents (consent form, recruitment materials, protocols, ect).

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

7.0 Information Requested to Determine a "Delayed Onset" of Human Subjects Research

7.1 Information Requested

Funding Source:

View Details	Sponsor Name	Sponsor Type	Funding Through	Contract Type:	Project Number	Award Number
No Sponsor has been added to this Study						

If the funding is a grant or contract, is the primary awardee Texas A&M University/Agency?

○ Yes ○ No

Will you be issuing subawards?

○ Yes ○ No

If Yes, then list institutions:

Describe the human subjects portion of the project (include objectives, procedures, and how results will be used):

Will there be any other collaborations (site/person)?

Attach the grant or contract, or any other relevant documents (protocols) that will be needed to make a determination.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

8.0 NON TAMU person requesting to use TAMU-associated people as human subjects

8.1 Human Subjects Research - not engaged details

Name of External Organization Conducting Study

Attach the protocol or other relevant information including IRB approval from external organization.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

9.0 Study Personnel Qualifications

9.1 Study Personnel Qualifications

Select the Study Personnel from the list created earlier in the application. Then provide the qualifications and role information for that study personnel selection as applicable to this study.

Study Personnel	Qualifications	Role in Study and Duties delegated by PI
No records have been added		

9.2 External Site or Study Personnel Please list the study personnel on your study who are not associated with Texas A&M. Additional documentation and agreements may be needed for these individuals.

Will an external site review the research?

○ Yes ○ No

If yes, what is the name of the external site?

Name	Institution	Telephone	E-mail	Role
No External Personnel has been added to this Study				

Name (from above)	Briefly describe how the person will participate in human subjects research activities	Experience, training, education for these activities	Most recent CITI /alternative training date
Clinical Research Coordinator - TBA	Coordinate patient contact, data collection &		

	management		

The IRB only needs education or CITI certificate for external personnel if there is no other IRB reviewing the research or if they are a part of the TAMU team.

10.0 Texas A&M University Human Research Protection Program Project Application Form

Study Introduction

10.1 Application Checklist

The following checklist is a guide for researchers regarding supporting documents that must be considered for and/or uploaded with this application for review and approval before use.

- Informed Consent Document
- Information Sheet
- Waiver of HIPAA Authorization
- Parental Permission Form/Minor Assent Form
- Recruitment materials (i.e. flyers, emails, advertisements, telephone scripts, social media posts)
- Site Authorization Letter (for study conduct and/or access to administrative records)
- Survey/Questionnaire/Data Collection/Abstraction Forms
- Grant Applications (cover to cover), required if funded or grant submitted
- Instructions
- Protocol Investigator's Brochure (for clinical trials only)
- Case report form (for clinical trials only)
- Device Manual (if using an approved or investigational device)
- Thesis/dissertation proposal
- Waiver of parental permission/minor assent form
- Letter of cultural evaluation for international research (link to SOP)
- IRB approvals from collaborating institutions
- Any other documents related to the research
- CVs for all investigators when proposed activities are more than minimal risk
- CITI training for all personnel

10.2 Proprietary Information

This protocol includes confidential and/or proprietary information to be protected from disclosure.

○ Yes ◉ No

10.3 Is this research funded?

Please identify your funding source, if applicable.

View Details	Sponsor Name	Sponsor Type	Funding Through	Contract Type:	Project Number	Award Number
No Sponsor has been added to this Study						

Please provide the name of the PI on the funding/grant if it is different from this IRB application.

Will funds from Qatar be used to fund this research?

○ Yes ◉ No

**** If the response to this question is Yes, then approval by an IRB in Qatar may also be required.***

10.4 Has an entity conducted a scientific peer-review of this research?

○ Yes ○ No

If Yes, please specify:

TAMCD Sleep Research Advisory Group

10.5 Fee for Service Information

Is a company providing contract services associated with this research in which no company personnel are considered collaborators in the research (will not receive professional recognition or included in presentations or publications about the research)?

○ Yes ◉ No

If yes, please provide the name of the company and the contact name.

If a contract exists for this study, was the fee for service information included in the primary award information?

○ Yes ○ No

If yes, please provide a copy of the contract.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

10.6 Is this project part of a dissertation, thesis, or record of study?

○ Yes ◉ No

If available, please attach the proposal under Other Study Documents at the conclusion of the application. If not yet available, submit it as an amendment form when available.

11.0 Study Scope

11.1 Research Classification

Select all that apply:

- ☐ Social/Behavioral
- ☑ Biomedical
- ☐ Both
- ☑ Clinical Trial
- ☐ Other, specify

For Social/Behavioral Research, select all that apply.

- [ ] Questionnaire/Survey
- [ ] Observation (investigator observing participants)
- [ ] Retrospective study of records existing at time of this application
- [ ] Exposure to some type of stimulus or intervention (includes device or substance)
- [ ] Participant observation (investigator acts as participant)
- [ ] Interview
- [ ] Focus Group
- [ ] Other, specify

11.2 Vulnerable Populations

Identify any vulnerable populations that will be included in the study:

- [ ] Children (for example, in Texas, under 18)
- [ ] Pregnant women, human fetuses, neonates
- [ ] Individuals with physical disabilities
- [ ] Individuals with cognitive disabilities
- [ ] Economically or educationally disadvantaged persons
- [ ] Prisoners
- [ ] Other (for example, individuals with psychiatic disorders, emotional/social impairments, depression, etc.)
- [x] No Vulnerable Populations will be included.

If Other, then please explain:

Describe additional safeguards planned to protect the rights and welfare of vulnerable subjects:

If a subject transitions into one of the vulnerable populations (pregnant women or cognitively impaired), will the study procedures place them at any additional risk?

- ○ Yes
- ◉ No

If a subject becomes incarcerated (including awaiting sentencing, court-mandated treatment, or in prison), contact the IRB immediately.

Please justify the use of vulnerable/special populations.

12.0 Project Overview - Protocol Section Begins Here

12.1 Project Summary

In the space below, provide a summary of the project. Include information about background and rationale for the study including preliminary data, purpose, objectives, specific aims, and research questions. Character limit: 5,000 (applies to first box).

See Research Designs & Methods Below.

Procedures Involved:

In the space below, Describe and explain the study design. Provide a description of all research procedures being performed and when they are performed.

List each procedure or test and how often the procedure or test will occur for each participant.

Include a procedure schedule or table of events, if applicable - clinical studies.

Describe: All source records that will be used to collect data about subjects. This includes surveys, scripts, recordings and data collection forms; all test articles including dietary supplements, drugs and devices used in the research and the purpose of their use, and their regulatory (FDA) approval status.

☐ Drugs
☐ Devices
☐ Supplements

Significance:

This study will compare the effectiveness of the two leading designs of oral appliances (OAs) for treating moderate to severe obstructive sleep apnea (OSA) in adults. The effectiveness of OAs in patients with OSA has come under question since different designs have been lumped together, for example when comparing OAs to continuous positive airway pressure (CPAP) mask therapy. Percent improvement in the apnea hypopnea index (AHI) has ranged from 53 to 90%, therefore it will be of great value to identify the most effective design to guide sleep practitioners and patients.

Subjects, enrollment, recruitment, inclusion and exclusion criteria, and informed consent:

Texas A&M University College of Dentistry
CLINICAL TRIAL STUDY PROTOCOL

Title: Midline traction versus bilateral thrust oral appliances: A randomized controlled trial to determine superiority for improving upper airway function and sleep quality.
Short Title: RCT on oral appliance design for improving sleep
Principle Investigator: Emet Schneiderman PhD, **Co-Principle Investigator:** Steven Bender, DDS

Co-Investigators: Jason Hui, DDS, Ann McCann RDH, PhD, Preet Schramm, PhD, Duane Wilson, DDS

Sponsor: Baylor Oral Health Foundation, Airway Management Inc.

Projected duration of study – July 1, 2017 to April 30, 2018

I.ABSTRACT

Background and Significance

Sleep breathing disorders which includes obstructive sleep apnea (OSA) snoring, has an estimated prevalence of 3 – 7% of the adult US population.[1] OSA subjects experiencing chronic sleep debt and intermittent nocturnal hypoxia are more prone to health risks that includes carbohydrate metabolism imbalance, immune and endocrine dysfunction (Table 1).[2] Continuous positive airway pressure (CPAP) is the American Academy of Sleep Medicine (AASM) treatment recommendation for this highly prevalent disorder.[3] However, approximately 30% of OSA patients do not tolerate CPAP.[4]

Alternative treatment options for OSA include surgical interventions, mandibular advancement splint also referred to as oral appliance (OA) therapy, tongue retaining and hypoglossal nerve stimulating devices, but these have debatable efficacy in moderate and severe OSA. Efficacy differences in OA therapies treatment of moderate and severe OSA could be related to OA design variations although this hypothesis has not been tested.

Hoekema et al. (2007b) used a custom-fitted midline traction (MT) OA and found large improvements in Epworth Sleepiness Scale (ESS) scores, oxygen saturation levels, Quality of Life, Short Form (SF)-36 scores and the apnea hypopnea index (AHI) in a randomized control trial (RCT) in severe OSA subjects. [5] Three other RCT studies from

Hoekema (2007a, 2008a, 2008b) and two other reports also used the same MT-device in moderate and severe OSA patients. [6-10] AHI improvements ranged from 80 to 90% (mean 85%). In contrast, several studies in moderate and severe OSA patients using bilateral thrust (BT) design failed to demonstrate an AHI reduction <10 events/hour although showing >50% AHI reduction (mean 55.4%; range 53 – 57%) from baseline conditions. [13-19]
Of the OA studies considered in the American Academy of Dental Sleep Medicine (AADSM) practice guidelines, four (67%) used a MT OA, compared with only one (14%) in seven studies that used BT OA in severe OSA subjects (Table 2).[20] The mean pre-OA AHI was 40.1 events/hour that reduced to a mean 5.7 events/hour post-treatment in the MT OA reports. The single BT OA study in severe subjects had a pre-treatment AHI equal to 30 events/hour that reduced to 14 events/hour at post-OA treatment.

Purpose: The two prominent OAs used in treating obstructive sleep apnea (OSA) differ in their designs, MT versus BT. From a clinical perspective, it is important to know which design is superior and should be the 'treatment of choice' for improving airway function and sleep quality. These two designs differ in their protrusive mechanisms that are categorized in general under four main types: bilateral compression, bilateral traction, midline compression and midline traction. Although the two designs considered in this proposal have undergone the most rigorous testing individually, well controlled 'head-to-head' trials as proposed here have not been conducted to determine their efficacy within a single test population.

Patients/Methods: Adults (n=44) with moderate to severe OSA diagnosed by polysomnography (PSG) or home sleep test (HST) within the previous year, who are using CPAP therapy, will be recruited and selected to enter the study. The study duration will be approximately nine months and each patient is expected to participate in the study for nine consecutive weeks. The first 4-weeks involve using one of either MT or BT OAs followed by 1-week washout period, then 4-weeks using the second OA. Home sleep recordings will be collected at T_1-first OA start; T_2-end first OA; T_3-second OA start; T_4-end second OA. The primary outcome measure will be the respiratory disturbance index (RDI).

Table 1: Examples of sequela associated with OSA in adults.

Health Consequences	Adult
Excessive daytime sleepiness	√
Reduced Quality of Life	√
Accidents (i.e. occupational, motor vehicular)	√
Hypertension	√
Cardiovascular disease	√
Obesity	√
Neuromuscular disorders	√
Sleep quality	√
ADHD	√
Learning difficulty; Cognitive impairment; Dementia; Alzheimer's Disease	√
Behavior problems	√
Sleep-walking	√
Hormonal & metabolic problems	√
Bruxism	√
Depression	√
Impotence	√

Table 2: Select oral appliance studies using midline traction and bilateral thrust

Device	Study	post AHI	pre AHI	#pts		% improvement
TAP -MT	Hoekema2007a	3.2	20.4	20	Moderate	84%
TAP - MT	Hoekema2007b	5.2	50	9	Severe	90%
TAP - MT	Hoekema2008a	4	31	12	Severe	87%
TAP - MT	Hoekema2008b	7.8	39.4	51	Severe	80%

TAP - MT	Holley 2011*	8.4	30	497	Severe	72%
TAP - MT	Ghazal 2009	7.9	22.2	48	Moderate	64%
Somnodent - BT	Deane 2009	12	27	22	Moderate	56%
Somnodent - BT	Gotsopoulos 2002	12	27	73	Moderate	56%
Somnodent - BT	Gotsopoulos 2004	12	27	67	Moderate	56%
Somnodent - BT	Mehta 2001	14	30	28	Severe	53%
Somnodent - BT	Naismith 2005	12.2	26.9	73	Moderate	55%
Somnodent - BT	Phillips 2013	11.1	25.6	126	Moderate	57%
Somnodent - BT	Sutherland 2011	12	26.9	39	Moderate	55%

Abbreviations: TAP – MT, Thornton appliance positioner – midline traction; BT, bilateral thrust.

II. Formulation of the Problem – Introduction

Obstructive sleep apnea (OSA) is a disease in which repetitive apnea and hypopnea (cessation and reduction in airflow, respectively) events occur during sleep because the upper airway (UA) has become blocked or narrowed (i. e. via mechanical collapse). [21] The development of UA occlusion can be related to oropharynx anatomical features and decline in pharyngeal neuromuscular activity. [22] Walsh et al. (2008) evaluated the cross-sectional area of the pharyngeal airway in OSA subjects compared with controls and found OSA subjects had smaller sized velopharyngeal cross-sectional area, longer uvulas compared with controls suggesting an abnormality in size rather than shape was an anatomical predictor of OSA. [23]

OA designs vary which could impact their efficacy in treating OSA. The therapeutic goal is a >50% reduction from baseline AHI values and <10 apnea and hypopnea events/hour.

It is important to know from a clinical perspective whether the MT or BT design is superior and should be the 'treatment of choice' for improving airway function and sleep quality. To date, no well controlled 'head-to-head' crossover trials as proposed here have been conducted in determining their AHI efficacy and impact on sleep quality.

a. Approach to the Problem: OA devices are recommended as the first-line treatment for mild to moderate OSA and second-line therapy for severe OSA. By advancing the mandible forward during sleep, OAs facilitate and maintain an increase in the oropharyngeal lumen. [23] It also decreases airway collapsibility compared with no OA intervention, to enable proper breathing.

Our intent is to perform a randomized controlled 'head-to-head' crossover trial in which the same patient uses two types of OA designs to determine their RDI efficacy and impact on sleep quality.

b. Justification: The increase in oropharyngeal space created by advancing the mandible with OAs has shown efficacy in reducing the number of apnea events, comparable AHI reduction results with CPAP [8] and improvements in secondary health benefits. [5,6,8] Furthermore, several studies provide evidence that OA compliance is greater among OSA patients using OA therapy compared with CPAP use. [20]

1. **Principle of Operation: Midline Traction Oral Appliance [11] (Figure 1) A coupling mechanism located at a single point midline, allows adjustment by incremental protraction of the mandible by the patient, see Hoekema[7].**

2. **Principle of Operation: Bilateral Thrust Oral Appliance [12] (Figure 2) A bilateral torsion adjustment mechanism constructed from surgical grade stainless steel allows for the mandible to be pushed forward. The patient can modify the amount of protrusion by adjusting the mechanism on each of the two sides, but this cannot be done while in the mouth.**

c. Investigative question

Does the MT or BT device provide greater RDI reduction to an acceptable level (<10 apnea and hypopnea events/hour of recorded sleep or >50% change) from pre-treatment values in adult patients with moderate to severe OSA?

III. Theoretical framework

The UA consists of the nasopharynx, oropharynx and hypopharynx. The oropharynx is essentially a tube of tissue derived from embryonic pharyngeal arches. Its patency is maintained by the tensor veli palatini and the genioglossus muscles. The oropharynx is that part of the pharynx (throat) posterior to the oral cavity. Its volume is constrained by the size and position of the tongue, the soft palate, uvula, tonsils, and pharyngeal muscles relative to the hard-tissue framework formed by the teeth, maxillary complex, mandible and hyoid bone. The genioglossus muscle originates at the superior genial tubercle of the mandible and fans into the substance of the tongue (intrinsic tongue muscles). The geniohyoid muscle originates at the inferior genial tubercle and inserts into the hyoid bone.

During normal breathing, swallowing and phonation, detectable physiological changes occur within the oropharynx. During wake in an upright position, the normal breathing position of the mandible is at 'rest' in a plane parallel to the maxillary plane.[23]

OSA begins with sleep onset, is commonly due to collapse of the UA and almost all patients with OSA snore.[24] At sleep onset, the UA undergoes both functional and structural changes, leading to spatially and temporally distributed sites conducive to snore sound generation.[22] Particularly in a supine sleep position, reduced genioglossus muscle tone allows the tongue to fall posteriorly towards the pharyngeal wall. Encroachment of the tongue into the airflow lumen increases airflow turbulence, thus producing soft tissue vibration and snoring sounds. Other factors also impact the airway's luminal diameter including obesity, craniofacial abnormalities like micrognathia and retrognathia, enlarged palatine tonsils and uvula, a high-arched palate, nasal septal deviation, large tongue, long soft palate and small airway lumen. Nasal valve collapse Gender differences, age and genetic factors may also have an impact on airway resistance. Sedatives can further relax the airway's musculature and alcohol's sedative effect increases snoring and apneic events. Cigarette smoking can cause inflammation within the oral cavity reducing the lumen's size. [25]

Partial closure of the airway during sleep that results in reduced airflow from 30 – 50% for ≥ 10 seconds with maintained respiratory effort and associated oxygen desaturations is defined as an obstructive hypopnea. Cessation of airflow for ≥ 10 seconds with maintained respiratory effort and associated oxygen desaturations of 2 – 4% is defined as an obstructive apnea. Both events are followed with an autonomic arousal, increase in muscle tone and resumption of breathing effort. It is the cumulative number of apneas and hypopneas divided by the number of hours of sleep that results in the AHI. [3]

An increase in oropharyngeal space created by advancement of the mandible occurs in association with inferior movement of the condyles that causes the posterior aspect of the mandible to move away from the maxilla (Christensen's phenomenon). [21] The mandible's forward movement away from the maxilla stretches and tightens the lateral walls of the pharynx with the superior constrictor muscle through attachments that includes the tongue. [21] Furthermore, this space creating forward movement allows the tongue to rest behind the upper incisors to form an air seal with the soft and hard palate that then facilitates nose breathing. [21] An OA's mechanics to move the mandible forward should increase oropharyngeal space with concomitant reduction in the number of apnea and hypopnea events through increased forward torque on the lumen's surrounding musculature.

IV. Table 3: Information about the OAs

	Midline Traction OA	Bilateral Thrust OA

Provides customized fit for each patient	√	√
Uses separate upper and lower tray pieces	√	√
Advances mandible incrementally	√	√
Advancements performed by a dental sleep specialist	√	√
Single contact point between upper and lower trays	√	
Pulls mandible forward	√	
Two contact points between upper and lower trays		√
Pushes mandible forward		√

V.Hypothesis

H_0 : The RDI will not differ when treating adults with moderate to severe (>15 events/hour) OSA between the MT and BT devices. H_A: The MT device / intervention will provide greater reduction in the RDI from pre-treatment values than the BT device in adults with moderate to severe OSA. Secondarily, proportions of responders to MT device intervention who's RDI is reduced to an acceptable level (< 10 events/hour or >50% change from pre-treatment values) is expected to be higher with MT therapy.

VI.Objectives

The main study objectives are to:

1. Quantify the RDI with each OA at the start and end of four weeks of use.
2. Compare the RDI of each OA with pre-treatment PSG determined AHI to evaluate the percent reduction.
3. Characterize global sleep quality changes associated with the use of the OAs.

We endeavor to model real-world conditions for measuring sleep by utilizing HST and recording in the subject' s own sleep environment. Based on previous research, we expect reduction in the RDI with OA use and superior response with the MT OA.

VII.Methods

a. Study type
    1. Single center, cross-over randomized control trial; superiority trial

2. Interventional comparative effectiveness research

b. Population
   1. Adults (n=44) with moderate to severe OSA.
   2. Potential study participants will be recruited by means of flyers posted at the College of Dentistry, Dallas A.W.A.K.E. office (support group for sleep apnea patients) and Dallas area sleep clinics. Online postings at clinicaltrials.gov and the College web site. Also post flyers at (1) regional hospitals and clinics, (2) city and county offices/stations (such as the Dallas Fire Department), (3) DART and other transportation offices and (4) Facebook, Twitter and similar site, (5) local newspapers and magazines, (6) local radio stations. The content of the advertisements on venues (5) and (6) will be the same as the approved flyers. Written permission will be sought from all sites at which flyers are to be posted. Data analyst and subjects will be blinded to treatment device type (i. e. sequence of use of the two OAs) and subject's identity will be coded.
   3. Controls and Controlling Confounders: Subjects serve as their own controls; their baseline polysomnography (PSG) or Home Sleep Test (HST), untreated values (from full or split night PSGs) will serve as their control values for evaluating treatment effects with each of the two OAs. The focus of the trial is on comparing OA appliance efficacy in reducing the RDI (AHI); the presentation, fitting, monitoring and adjustment of the two OAs will be the same for both arms of the study. For the operators, there will be concealed allocation of assignment of subjects to treatment.
   4. Performance Site: Texas A&M College of Dentistry, 3302 Gaston Avenue, Dallas Texas. Seventh floor room 725, two operatory clinic.

c. Inclusion criteria

OSA diagnosed adults, at least 18 years old, who have been recently diagnosed by polysomnography (PSG) or polygraphy home sleep test (HST) in the previous year and are currently being treated with continuous positive airway pressure (CPAP) having an AHI > 15 events/hour of sleep; two or more OSA symptoms (snoring, witnessed apnea or daytime hypersomnolence complaint); at least 8 teeth per arch to support either OA device; Mallampati score from I to III; Palatine tonsils – grade 0, 1, or 2; Central and mixed apnea index < 5 events /hour. Consent to study's timeline; willingness to wear home sleep test apparatus for at least 4 nights and to wear an oral appliance every night for 8 weeks; willingness to pick up and return home sleep test kits as needed.

d. Exclusion criteria

Cardiac & pulmonary disease (e.g., congestive heart failure, severe arrhythmias, COPD); central sleep apnea; comorbidities of other sleep disorders other than OSA; no active TMD or jaw muscle pain, morphological airway abnormalities, BMI ≥35; pre-existing difficulty swallowing; throat or neck related health issues; endocrine dysfunction; severe psychiatric disorders; intellectually disabled; previous OA therapy; previous ENT surgery; restrictions in jaw opening; pregnant / breast feeding or intent to become pregnant during the study; inability to provide informed consent and apply the HST recorders.

e. Table 4: Variables of Interest: Primary, Secondary and Exploratory

	Primary	Secondary	Exploratory
Variables	RDI-T_1-start-of-treatment with first OA; T_2-end-of-treatment with second OA; T_3-start-of-treatment with first OA; T_4-end-of-treatment with second OA	$T_{1\text{-}4}$ Snore count; OA compliance; Mean disease alleviation; Sleep Quality $T_{0,\,2,\,4}$ Epworth Sleepiness Scale score; Short Form-36 score Thornton snoring scale Sleep observer scale Symptom alleviation Changes in occlusion as measured by shim stock, tested before and after	T_4 OA device preference and perceptions of comfort; Development of a cost effective titration protocol with maximal patient convenience.

Mean disease alleviation is a composite measure of the reduction in RDI and OA compliance. RDI, respiratory disturbance index equals the number of respiratory events per hour of recorded time; $T_{1\text{-}4}$, time points 1-4

f. Data collection techniques to be used during sleep
    1. OA compliance
        i. This variable is determined by the number of hours that the OA device is worn per hour of sleep per night using Braebon monitors (integrated chips; Kanata, Ontario, Canada)
    2. Respiratory measures (Figure 3)
        i. Braebon polygraphy (PG) recorder for home sleep testing: airflow, respiratory effort, electrocardiogram (ECG), pulse oximetry, anterior tibialis electromyography, body position, and snore sound.

The PG unit is a category Type III sleep testing device. Manually scored sleep disordered breathing events will be categorized as apnea or hypopnea (RDI; ≥5, >15, >30 events/hour) and phenotyped as either obstructive or central type events. Mixed events will be assigned to the OSA category. The definition of apnea to be used will be a ≥90% reduction in airflow from baseline and ≥10 seconds in duration. Hypopnea will be defined as a reduction in airflow of ≥30% with an associated oxygen desaturation. The RDI will be defined as the number of apnea-hypopnea events divided by recorded hour. [3, 24]

3. Sleep quality assessment (Figure 4, 5)
    i. SleepImage (MyCardio, LLC, Broomfield, CO) recorder: ECG, actigraphy, body position, snore, ECG-derived respiration

The SleepImage system includes a sleep recorder that is clinically validated and FDA cleared to allow the non-intrusive collection of objective measures of sleep quality. The ECG-recorder with cardiopulmonary coupling (CPC) analysis collects ECG, actigraphy, snoring and body position data at a sampling rate of 600 Hz that is later filtered to sampling rates of 200, 40, 10 and 10 Hz, respectively. The ECG-recorder's sleep data are uploaded and scored automatically. CPC algorithms assess the ECG's R-wave amplitude change associated with tidal volume dynamics to derive a respiration (ECG-derived respiration) signal. The resulting sleep spectrogram, divides sleep states into "stable sleep" (0.1–0.4 Hz) and "unstable sleep" (0.01–0.1 Hz). [26] Within 0.01-0.1 Hz is the "narrow band" that identifies central-periodic type patterns (0.006–0.1 Hz) and obstructive type events primarily through a "broadband" (0.0–0.01 Hz, not fitting narrow band criteria) pattern. [27, 28] Between-treatment differences in the proportions of stable and unstable sleep will be evaluated.
Subjective measures related to the sleep experience of the subjects will also be collected using these questionnaires at T_0, T_2 and T_4 : Eppworth sleepiness scale, Quality of Life Short Form-36, version 2 and the Thornton snoring Scale.

g. Data collection

Treatment devices: TAP 1 (Airway Management Inc., Dallas, TX; MT type OA device) and SomnoDent Flex (SomnoMed, Plano, TX; BT type OA). Both OA devices will be used per manufacturers' recommendations. To insure comparability, both devices have a custom thermal acrylic liner insuring a very accurate fit. Each subject will also be custom fitted with a mandibular positioner ("AM Aligner" or "Morning Positioner") to use for up to 20 minutes after awakening in the morning; this will assist in returning the subject to his/her normal occlusion.
Appliance Acclimation: Both appliances will be adjusted / titrated to the patient's maximal comfortable protrusive position by patient in the wake state. The starting position will be determined by the patient at a comfortable position but not less than 60% as determined by the Pro Gauge. "Comfortable" is defined as the advanced mandibular position that permits the subject to sleep for ≥5 hours per night for at least 6 nights of the week. Subjects will use diaries to record appliance settings and hours of sleep on each sleep recorded or non-recorded night. Two follow-up nights (post T_1) of SleepImage recordings only will be made to track sleep quality and OA position, if further mandibular adjustments are necessary as determined by the T_1 & T_3 HST and SleepImage results.
Course of Treatment: Subjects will be randomly assigned to either the MT- or BT-first OA device as treatment for OSA. Each subject will use the first OA for 4 weeks followed by – 1 week washout period that includes using nightly their prescribed CPAP and daytime use of a mandibular positioner (for up to 20 minutes) – then another 4 weeks of active treatment with the second OA.

h. Power Analysis and Sample Size

At least 38 subjects with OSA are needed to yield a power of 0.90 with alpha = .05 and an expected Effect Size of at least a 10 point difference in the post-treatment mean RDI scores between MT vs. BT devices.Recruitment will be extended to n=44 to accommodate an estimated 20% drop-out rate. The projected numbers are based on Wilcoxon signed-rank test where the expected difference between-treatments (cross-over design) is expected to be at least 10 point difference in RDI scores.

i. Statistical analyses

Wilcoxon signed-rank test (matched pairs) for cross-over design for primary variables will be used. For dichotomous secondary variables, data analysis will use logistic regression to adjust for effects of initial severity, age, gender, BMI, ethnicity, SES, phenotypic differences, etc. t-tests and Mann-Whitney tests as needed for non-dichotomous outcomes, depending upon normality. Descriptive statistics (means, standard deviation, medians, interquartile ranges) for each outcome measure will be calculated and bar, boxplot or line graphed for each time point. Repeated measures analysis of variance, parametric or nonparametric one-way analysis of variance, as appropriate, will be used to determine if each of the outcome measures vary across the time points.

1. Handling of missing data

   For the primary study endpoint, several methods will be used, including: 1) last observation carried forward, 2) multiple imputations, and 3) imputing a missing value with the group's mean value at that follow-up and frequency.
   The set of missing data analyses will serve as a sensitivity analysis for the primary study outcomes.If the data imputation methods for a given endpoint result in disparate statistical inferences, the differences will be investigated and elucidated in the final clinical study report.

j. Right and Safety of Research Participants

The clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the Belmont Report and that are consistent with Good Clinical Practice (GCP). The laws, regulations and rules of the United States, the state of Texas and the Texas A&M University pertaining to human subjects research will be followed.The rights, safety, and well-being of the trial subjects are the most important considerations and will prevail over the interests of science and society. The available clinical information on the OA devices is adequate to support the proposed clinical trial.

Freely given informed consent will be obtained from every subject prior to clinical trial participation. All patient clinical trial information will be recorded, handled and stored in a way that allows its accurate reporting interpretation and verification. The confidentiality of records that could identify subjects will be protected, respecting the privacy, confidentiality rules and to ensure non-bias reporting requirements.

During the approximately 2-hour Visit 1, the prospective subject will be given an oral exam by one of the team dentists to insure that the dentition, periodontium, temporomandibular joints, muscles of mastication are sufficiently healthy and stable for the safe participation in the study. If determined to be sufficient, the subject will then be fully enrolled in the study and have the study and tasks explained in greater detail. Dental impressions will then be obtained as models for the fabrication of the custom oral appliances.

k. Potential risk to subjects

The minor physical risk associated with the sleep-monitoring aspects of this study are no more than those involved with standards test of bodily (physiological) functions, for example wearing a heart monitor. The oral appliances are FDA cleared and are in wide use by dental patients throughout the US. The oral appliances (OAs) are FDA cleared and are in wide use by dental patients throughout the US. The OAs may cause pain in the jaw joint and teeth, and difficulty in opening or closing the jaw; these conditions are usually temporary. In the long term, the OAs may cause changes in tooth position and in the bite (occlusion), as well as damage to the teeth and gums. What makes this experience "research" rather than "routine clinical care" is that (1) the participants are randomly assigned to one OA or the other during the two active phases of the study, and (2) additional physiological measurements will be made beyond what are typically gathered during standard clinical practice. All of these tests are noninvasive.

We do not anticipate any significant physical risk from participating in this study. Though unlikely, some subjects may experience itching or rashes from the adhesive hypoallergenic electrodes of the Medibyte or the SleepImage devices. The pulse oximeter may cause some minor irritation of the finger or finger nail. By wearing an OA, a subject may experience some discomfort and/or reduced function of the jaw joint (temporomandibular joint) and muscles of the jaw (masticatory muscles) and of the face during and after treatment. Subjects may also experience some reduction in sleep quality due to discomfort while getting used to wearing the OA (acclimation). Other minor risks include temporary irritation of the mouth and oral cavity due to contact with the OA, and excessive salivation or dry mouth from mouth breathing. Repositioning of the lower jaw and tooth movement may also occur, but are typically minor and reversible. Also highly unlikely, a subject could swallow or aspirate part of an OA should it break.

l. Potential benefits to subjects

1. Two customized oral appliances to keep upon completion of the study at no cost to the subject (value of $4600)
2. Effective devices that do not require electricity to operate, so can be used anywhere
3. Reduced apnea and snoring
4. Improved sleep quality and continuity

5. An effective treatment for obstructive sleep apnea that does not require wearing a face mask
6. No air pressure blowing through nose
7. Receiving information on sleep quality.
8. The researchers or study coordinator will discuss possible options that might be of benefit if a sleep issue is discovered.

Study Limitations

Hyperarousal response to the OA. Possible brief OA acclimation (4-weeks) and washout (1-week) period. No placebo device as a control condition. Interrater variability of HST polygraphy scoring. No controlled sleep environment which allows for variability in external conditions during sleep recordings. Absence of conventional sleep staging based on EEG activity.

- Adverse events and adverse device effects
    1. Definitions
        i. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational OAs. This includes events related to the investigational devices and this includes events related to the procedures involved (any procedures in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational OAs.

ii. Adverse Device Effect (ADE)

Adverse event related to the use of the OA. This includes any adverse event resulting from insufficiencies or inadequacies in the manufacturer's instructions for use, the deployment, the installation (customization procedure), or any malfunction of the investigational devices. This includes any event that is a result of a use error or intentional misuse.

iii. Serious Adverse Event (SAE)

A serious adverse event is considered when it:
a. Leads to death,
b. Leads to a serious deterioration in health that either resulted in a life-threatening illness or injury, or resulted in a permanent impairment of a body structure or a body function, or required in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

iv. Unanticipated Serious Adverse Device Effect

Unforeseeable serious adverse device events, are those having severity and occurrence not identified in the latest version of the report of the risk analysis. Consideration will be given to the:

- severity of the event
- corrective measures
- preventions from re-occurrence

The corrective measures are to be determined immediately and to be implemented. It is to be assessed whether the study can be continued.

The investigator(s) must determine whether the complication which may occur, was expected or unexpected. For this he or she must review the personal conditions and medical history of each study subject in question and determined, if the event was referenced in the protocol. An unexpected event is an event, which has not been mentioned in the study protocol.

v. Documentation and reporting of SAEs

Every adverse event that meets the criteria for an unanticipated problem must be reported to the IRB within 5 days.

vi. Protocol deviations

The Principal Investigator(s) is responsible for the conduct of the clinical trial. The PI will follow established procedures for the evaluation, approval and implementation of deviations to the study protocol and the reporting of protocol deviations as appropriate to the IRB.

vii. Early study termination

The study will be suspended immediately if unexpected high levels of complications occur and /or Adverse Device Effects occur which are unexpected in nature and/or severity as determined by the investigator(s) or IRB. The trial will not be resumed without IRB approval.

viii. Quality control

Study monitoring procedures ensure that the clinical trial is conducted in accordance with the study's protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable requirements.Trained and qualified members of the trial team will conduct investigational site visits throughout the study period in coordination with the Study Coordinator.

ix. OAs and sleep recording devices accountability

The physical location of all devices from shipment of devices to the clinical investigation site until return or removed from use due to malfunction will be documented by the Study Coordinator or Principle Investigator.The clinical investigation site also maintains controlled access to the investigational and recording devices and maintains that devices will only be used according to the study protocol.The investigation site must maintain records documenting the receipt, use, return and malfunction of the investigational device and sleep recorders with date of receipt, identification of device with serial or ID number, dates of use, subject identification, date on which investigational device was returned from subject, and date of unused or malfunctioning devices.

VIII.Ethical Considerations

The rights, safety, and well-being of the study's subjects are the most important considerations and will prevail over the interests of science and society. The available non-clinical and clinical information associated with the investigational OAs is adequate to support the proposed clinical trial. The clinical trial is scientifically sound and has been described in a clear, detailed protocol herein.
The trial will be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB) approval.
The care given to and decisions made on behalf of, subjects will be the responsibility of a qualified dentist and each individual involved in conducting the trial will be qualified by education, training, and experience to perform his or her respective task(s).
Freely given informed consent will be obtained from every subject prior to clinical trial participation.
All clinical trial information will be recorded, handled and stored in a way that allows its accurate reporting interpretation and verification.
The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

IX.Schedule

The study duration will be approximately nine months. Each subject from the time of initial OA use and sleep data recording will be involved in the study for approximately 9 weeks. (Figure 6)

a. Recruitment criteria & methods: Potential study participants will be recruited from the Texas A&M College of Dentistry (TAMCD), local A.W.A.K.E. group. Invitation to participate in the study will be by bulk email and posted flyers. The study will be registered with ClinicalTrials.gov. Data analyst and subjects will be blinded to treatment device type (i.e. sequence of use of the two OAs) and subject's identity will be coded.

b. After meeting the study's inclusion and exclusion criteria through telephone screening, study subjects will receive detailed information about the study from the Study Coordinator during their first appointment. The first appointment to the study center will include obtaining a copy of the patient's PSG/CPAP study reports and medical history, completion of the study's intake assessment, signing the informed consent form and obtaining impressions and protrusive bite. In the absence of a current PSG, subjects will be sent home with a HST to collect comparable baseline information. Both oral appliances will be constructed prior to the second appointment. The subjects will be randomized to an OA device at second appointment (this will allow any questions by the lab of the dentist to improve the device). During the second appointment, subjects will be examined and fitted by the dentist with both OAs. Subjects will be then scheduled within 4-weeks for the first HST with simultaneous SI recording for determination of the RDI and sleep quality criteria. Recordings will occur x1/subject at T_1 (first night in week-1 with first OA), T_2 (after four weeks using first OA), a washout period of 1 week using a mandible repositioner daily and CPAP nightly, T_3 (first night of week-6 with second OA) and T_4 (after four weeks using second OA). (Figure 1, below; Table 1)

c. **Table 5: Protocol for determining subject candidacy:**

EVALUATION	PURPOSE	PROCEDURE/RATIONALE
Recruitment / Orientation	Provide information about the study.	Provide the subject with information regarding the OA devices, the clinical study and an information brochure.
Medical Background Information	Gather information regarding the subject's medical background to determine candidacy, and recent sleep study evaluations.	Standard medical case history and physical with emphasis on OSA to include the Medical/Surgical History as part of the Case Report. Conducted individually by the team/Study Coordinator and discussed collectively to ensure that the subject has realistic expectations for the study.
Craniofacial & Oral Testing	Verify subject qualification with a craniofacial / oral exam.	Clinical assessment is performed to examine the upper airway and oropharynx to determine the subject qualification for using OA therapy.
Informed Consent	Obtain informed consent.	Informed consent will be obtained by providing information related to the time commitments of the trial, risks and contraindications.

d. Table 6: Protocol For Pre-OA Evaluations

EVALUATION	PURPOSE	PROCEDURE/RATIONALE
Pre-study AHI	Subject's own baseline AHI data for comparison to OA response	PSG or PG conducted within up to 1 year before study inclusion for baseline AHI/RDI
Pre-study questionnaire	Quality of life questionnaire for comparison to OA response	Complete the Epworth sleepiness scale and quality of life or functional outcomes sleep questionnaire. This data will be performed on the same day as sleep studies (T_{1-4}) .
Snore Index	Baseline snore index for comparison to OA response	Data collected as a part of PSG.
Number of Periodic Limb Movements (PLMS)	Baseline number of PLMS with arousals to determine study inclusion or exclusion	Data collected as a part of PSG. This is a study exclusion criteria.
Number of Central Sleep Apnea (CSA) events	Baseline number of CSA events to determine study inclusion or exclusion	Data collected as a part of PSG. This is a study exclusion criteria.

Table 4: Protocol for OA use and home sleep recordings

TASK	PURPOSE	PROCEDURE/RATIONALE
Oral Appliance, Home Sleep Test and SleepImage recorders orientation	To instruct subjects on how to apply, use, care for, remove and return the OAs, sleep recorders to obtain optimal recordings.	Explain and demonstrate OA use; provide instructions regarding the correct application and removal of HST electrodes and sensors. To provide instructions on care and return of study equipment for optimal data collection and timely return of equipment.

Completion of sleep diary and questionnaires	To instruct participants on how and when to complete the sleep diary and questionnaires.	The proper completion of the sleep diary and questionnaires facilitates assessment of the study' s secondary outcome measures.
Adverse Device Effects reporting	To instruct the study subject on the definition of an Adverse Event and how to report an event.	To ensure the study subject's safety and health, whether or not the changes are believed to be device related.

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{GO TO ATTACHED PROTOCOL FILE TO VIEW THE FOLLOWING CORRECTLY}

Figures 1 and 2

Figure 1. TAP 1 Oral Appliance (MT Style)

Figure 2. SomnoDent Flex Oral Appliance (BT Style)

Figure 3: Home Sleep Test device in recording position.
Figure 5: Sleepimage sleep device actual size.
Figure 4: Sleepimage sleep device in recording position.

Will audio recordings be collected?

○ Yes ◉ No

Will visual images be collected?

○ Yes ◉ No

If visual images will be collected, are they full, facial identifiable images?

○ Yes ◉ No

12.2 Locations

List locations or facilities where the research will be conducted (e.g. building name, physical address).

TAMU College of Dentistry Building at 3302 Gaston Avenue, Dallas TX 75246

Are any of the locations listed above non-Texas A&M facilities?

○ Yes ◉ No

What is the role of each location?

Is the PI of this IRB study application the lead investigator of a multicenter study (i.e. the study is taking place at multiple institutions that are obtaining their own IRB approval and you are coordinating and overseeing the research)?

○ Yes ◉ No

Has IRB approval been sought at another institution?

○ Yes ◉ No

Please submit the Site Authorization letter(s) with this application as a study document or indicate when site authorization will be obtained. Guidance is available at **http://rcb.tamu.edu/humansubjects/resources/site-authorization-letter**

12.3 Other Committee Approvals

Select all that apply.

☑ None
☐ Animal Use
☐ Biohazards

- [ ] Chemical
- [ ] Radiation
- [ ] Other

If any committee approvals apply, please provide the permit number and approval date.

13.0 Study Population

13.1 Number of Participants

Approximately how many subjects do you plan to enroll?

38

Provide the rationale for the number of subjects requested (for example, power analysis, sponsor requirements, etc.).

Approximately 38 subjects must complete the study to yield a power of 0.90 with alpha = .05 and an expected Effect Size of at least a 10 point difference in the post-treatment mean RDI scores between MT vs. BT devices. Recruitment will be extended to n=44 to accommodate a 10-20% drop-out rate. The projected numbers are based on Wilcoxon signed-rank test where the expected difference between-treatments (cross-over design) is expected to be at least a 10 point difference in RDI scores.
As many as 44 will be enrolled to account for attrition.

Will human subjects be used from the Qatar population?

- ○ Yes
- ◉ No

**** If Yes, then approval by an IRB in Qatar may also be required.***

Will human subjects be used from another international population?

- ○ Yes
- ◉ No

****If Yes, then approval by an international review board or government may also be required.***

Will human subjects be used from a Native American population?

- ○ Yes
- ◉ No

****If Yes, then approval by a tribal IRB(s) may also be required.***

If Yes for research in Qatar, in another country, or with Native Americans, provide justification for that research being conducted in that particular community.

13.2 Provide the age groups being enrolled into this study (Note the consent documents required for each age group listed in parentheses):

- [ ] 0-6 (parental consent only, Pediatric Assessment required for Clinical Trials)
- [ ] 7-11 (child's assent plus parental permission, Pediatric Assessment required for Clinical Trials)
- [ ] 12-17 (consent plus parental permission, Pediatric Assessment required for Clinical Trials)
- [x] 18+ (consent only)

Enter the specific age range for study population (if overlap or specific within a category):

13.3 Indicate the gender of participants being enrolled into this study:

- ☐ Male
- ☐ Female
- ☑ Both male and female

13.4 Inclusion/Exclusion Criteria

What are the inclusion and exclusion criteria for study participation?

Inclusion Criteria
OSA diagnosed adults, at least 18 years old, who have been recently diagnosed by polysomnography (PSG) or polygraphy home sleep test (HST) in the previous year and are currently being treated with continuous positive airway pressure (CPAP) having an AHI > 15 events/hour of sleep; two or more OSA symptoms (snoring, witnessed apnea or daytime hypersomnolence complaint); at least 8 teeth per arch to support either OA device; Mallampati score from I to III; Palatine tonsils – grade 0, 1, or 2; Central and mixed apnea index < 5 events/hour. Consent to study's timeline; willingness to wear home sleep test apparatus for at least 4 nights and to wear an oral appliance every night for 8 weeks; willingness to pick up and return home sleep test kits as needed.
Exclusion Criteria
Cardiac & pulmonary disease (e.g., congestive heart failure, severe arrhythmias, COPD); central sleep apnea; comorbidities of other sleep disorders other than OSA; no active TMD or jaw muscle pain, morphological airway abnormalities, BMI ≥35; pre-existing difficulty swallowing; throat or neck related health issues; endocrine dysfunction; severe psychiatric disorders; intellectually disabled; previous OA therapy; previous ENT surgery such as uvulopalatopharyngoplasty; restrictions in jaw opening; pregnant / breast feeding or intent to become pregnant during the study; inability to provide informed consent and apply the HST recorders.

Do the exclusion criteria exclude specific populations or individuals based on gender, culture, language, economics, race, or ethnicity?

○ Yes ◉ No

If Yes, then justify each exclusion:

13.5 Describe the setting where the informed consent process will take place (e.g. classroom, clinic, laboratory, office, park, personal computer, etc.).

If a waiver of documentation of informed consent is requested, then describe how participants will review the information sheet.

College of Dentistry clinic.

13.6 Experience of Subjects

Describe the experience of subjects while participating in this research. (Please describe what the participant will experience from the time of learning of the study through completion.)

After meeting the study's inclusion and exclusion criteria through direct or telephone screening, prospective participants will receive detailed information about the study from the study coordinator during their first appointments. They will have an opportunity to have all of their questions about the study answered to their satisfaction by the coordinator and investigators. Those individuals who give informed consent will be enrolled in the study. The first appointment to the study center will include obtaining a copy of the patient's polysomnogram/continuous positive air pressure (PSG/CPAP) study reports and medical history, completion of the study's intake assessment. In the absence of a current PSG, subjects will be sent home with a HST to collect comparable baseline information. During this approximately 2-hour first appointment, the prospective subject will be given an oral exam by one of the team dentists to insure that the dentition, periodontium, temporomandibular joints, muscles of

mastication are sufficiently healthy and stable for the safe participation in the study. If determined to be sufficient, the subject will then be fully enrolled in the study and have the study and tasks explained in greater detail. Dental impressions will then be obtained to prepare models for the fabrication of the custom oral appliances. Protrusive bite registrations will also be made at this time. Both oral appliances (OAs) will be constructed prior to the second appointment. During the second appointment, subjects will be examined and fitted by one of the study dentists with both OAs; if modifications are needed to improve fit, an OA may be sent back to the lab. The subjects will be assigned to one OA or the other at this second appointment according to predetermined randomization scheme. Neither the dentist nor the subject will know the assignment until the actual delivery. Subjects will be then scheduled within 4-weeks for the first home sleep study (HST, Medibyte system) with simultaneous SleepImage (SI) recording for determination of the Relative Disease Index (RDI) and sleep quality criteria. Recordings will occur x1 /subject at T_1 (first night in week-1 with first OA), T_2 (after four weeks using first OA), a washout period of 1 week using a mandible repositioner daily and CPAP nightly, T_3 (first night of week-6 with second OA) and T_4 (after four weeks using second OA) (Figure 1; Table 1).

Each participants involvement in the study while at home is as follows: On each of 4 nights over the course of 9 weeks the subject will put on the HST and SI prior to bedtime, and remove them upon awakening. The two systems include attaching sensors to various parts of the face, chest and abdomen. Adhesive pads and surgical tape are used to hold these devices and wires in place. Placement may take up to 20 minutes, and removal, about 5 minutes. The coordinator will demonstrate how to apply the sensor properly to insure valid recordings. Minor discomfort may be experienced when pulling off the tape. If a first night recording is faulty, a subject may be asked to do a second night recording; subjects will not be asked to record for more than 8 nights in total. Subjects will wear an OA every night for 4 weeks, no OA for the 1-week washout period, and an OA (the alternate device) for each night for another 4 weeks. They will put on the OAs prior to bed and remove them upon awakening. The OA will contain a computer chip that will also record the actual amount of time that the OA is worn each night. Subjects use their CPAP devices each night of the washout period as prescribed by their physicians.Some discomfort and/or tendeness in the temportomandibular joint (jaw joint or TMJ) and jaw muscles may be experienced during and after OA use. Also some minor tooth movement and discomfort may be experienced. In addition to their OAs, each subject will be given a mandibular repostioner, a small custom bite splint to be worn for two minutes after removing the OA upon awakening. Use of the mandibular repostioner will minimize or eliminate the aforementioned discomforts and tooth movement. All of this clinical care, potential discomforts and tooth movements will be carefully monitored and managed by the dentists on the research team.

How long will the participants be engaged in the research (length of time, e.g., 15 minutes, 45 minutes on Day 1, 60 minutes on Day 2, etc.)?

Visit 1: 120 minutes; Visit 2: 60 minutes; Visits 3-9: 15 minutes each. Total in office commitment: Approximately 5 hours. For the home sleep tests, approximately 30 minutes for at least 4 nights(but no more than 8 nights), for a total of at least 2 hours (but no more than 4 hours)

14.0 Privacy and Confidentiality

14.1 How will the identities of subjects be protected in all research records? The information collected /analyzed is:

Note: Data that are coded, where the key to the code is accessible to researchers, are considered confidential information and subject to privacy regulations.

- ☐ Anonymous: The identity of the participant cannot readily be determined by the investigator AND the identity of the participant is not connected to information gathered.
- ☑ Confidential: Research participants can be identified; however, information gathered will be protected.
- ☐ Neither: Research participants can be identified, and information gathered may be connected to the

participant.

Summarize procedures to protect the confidentiality and anonymity of participants (e.g., replies coded, etc.).

The identities of all subjects will be coded to insure confidentiality as well as the integrity of the data analysis. All data will be stored on encrypted computers of the research coordinator and investigators.

What are the plans for retention and/or destruction of linkages between study data and personal identifying information? (Specify when and how personal identifying information will be destroyed.)

Personally identifying data will be destroyed within 3 years of completion of the study, i.e the publication of all papers issuing from it.

If these linkages will not be destroyed, explain how you will maintain confidentiality of the personally identifying information.

If personally identifying information will not be kept confidential, then justify and explain the informed consent process for sharing this information.

Will a Certificate of Confidentiality (through DHHS or another Federal agency) be utilized?
https://humansubjects.nih.gov/coc/index

○ Yes ◉ No

15.0 Potentially Sensitive Subject Matter and Procedures

15.1 Will this type of information be collected?

○ Yes ○ No

15.2 Select all that describe the information.

- [x] No sensitive matters
- [ ] Abortion
- [ ] Alcohol
- [ ] Body composition
- [ ] Criminal activity
- [ ] Depression
- [ ] HIV/AIDS
- [ ] Learning disability
- [x] List of current medications
- [x] Medical/dental problems
- [x] Medical history
- [ ] Potential child abuse/neglect
- [ ] Psychology/psychiatry
- [ ] Sexual activity
- [ ] Suicide
- [ ] Unethical behavior
- [ ] Other

If other, please specify:

If Medical History or Mental Health History information will be collected, please describe:

15.3 Deception

Will deception be used as part of the study?

○ Yes ◉ No

If Yes, please describe the deception.

Please describe the debriefing procedures to be used.

Provide justification for the deception.

16.0 Risks and Benefits

16.1 Regulatory definition of minimal risk is that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(h)(i)).

Identify the types of risk associated with participation in the study:

- ☑ Physical
- ☑ Privacy
- ☑ Confidentiality
- ☐ Psychological/emotional
- ☐ Social
- ☐ Legal
- ☐ Other

If Other, please describe the risks:

Describe the potential risks or discomforts to participants. Include justification of the known risks, which were selected above.

The minor physical risk associated with the sleep-monitoring aspects of this study are no more than those involved with standards test of bodily (physiological) functions, for example wearing a heart monitor. The oral appliances are FDA cleared and are in wide use by dental patients throughout the US; they present no more risk than that involved in wearing a bite splint to prevent grinding (bruxing) at night, or a football player wearing a bite-guard. What makes this experience "research" rather than "routine clinical care" is that (1) the participants are randomly assigned to one OA or the other during the two active phases of the study, and (2) additional physiological measurements will be made beyond what are typically gathered during standard clinical practice. All of these tests are noninvasive.

We do not anticipate any significant physical risk from participating in this study. Though unlikely, some subjects may experience itching or rashes from the adhesive hypoallergenic electrodes of the Medibyte or the SleepImage devices. There may be minor discomfort upon removing the adhesive pads or surgical tape holding them in place, (e.g., pulling out hair with them). The pulse oximeter may cause some minor irrration of the finger or finger nail.
By wearing an OA, a subject may experience some discomfort and/or reduced function of the jaw joint (temporomandibular joint) and muscles of the jaw (masticatory muscles) and of the face during and after treatment. Subjects may also experience some reduction in sleep quality due to discomfort while getting used to wearing the OA (acclimation). Other minor risks include temporary irritation of the mouth and oral cavity due to contact with the OA, and excessive salivation or dry mouth from mouth breathing. Repositioning of the lower jaw and tooth movement may also occur, but are typically minor and reversible. Also highly unlikely, a subject could swallow part of an OA should it break.

Describe the approaches you will take to minimize these risks and/or to minimize their impact.

Participants will be carefully monitored for all of these risks (above) by one or more of the study dentists. The subjects will be able to contact a member of the research team 24/7 to address any concerns.

What alternatives are available to subjects outside the research (i.e., what is the standard of care, is the research intervention available without participating)?

No alternative treatment options are available as part of this study. If a prospective subject decides that either oral appliance therapy is not suitable, the alternative is to not enroll in the study and continue CPAP therapy as prescribed. Once enrolled in the study, if the subject decides that either oral appliance therapy is not suitable at any time, he/she may withdraw from the study and continue with CPAP therapy as prescribed.

16.2 What are the potential benefits of this study to individual participants? (This does not include payments, compensation, or incentives.)

The benefits of taking part in this study are:

1. Two customized oral appliances are yours to keep upon completion of the study at no cost to you
2. Effective devices that do not require electricity to operate, so can be used anywhere
3. Reduced apnea and snoring
4. Improved sleep quality and continuity
5. An effective treatment for obstructive sleep apnea that does not require wearing a face mask
6. No air pressure blowing through your nose
7. Receiving information on your sleep quality.

The researchers or study coordinator will discuss with you possible options that might be of benefit to you if a sleep issue is discovered.

16.3 What are the potential benefits of this study to the population or society?

The findings will provide objective evidence for consumers regarding the comparative effectiveness of oral appliance for treating snoring and sleep apnea. It will also establish baselineline data for future studies on the treatment of sleep disordered breathing in high risk populations such as (1) pregnant women, (2) academically underperforming school children, and (3) adults with atrial fibrillation. Additionally, it may lead to a widely usuable method of studying disordered sleep and its treatment that is both simple and cost-effective.

17.0 Personally Identifiable Information

17.1 Indicate which of the following personally identifiable information (PII) will be accessed or recorded in association with this study:

- [ ] None
- [x] Name
- [ ] Web addresses (URLs)
- [ ] Full Face Photographic Image
- [ ] Internet IP Address
- [ ] Health Plan Beneficiary Number
- [ ] Certificate/ License Number
- [ ] Any Other Unique Identifier or Combination
- [x] Geographic Information (including city and ZIP)
- [ ] Vehicle Identification Number and Serial Numbers Including License Plate Number
- [x] Telephone Number
- [x] Email address
- [ ] Fax number
- [ ] Social Security Number

- [x] Medical Record Number
- [ ] Account Number
- [x] Medical Device Identifiers
- [ ] Biometric Identifiers
- [x] Dates directly related to an individual (including birth, death, admission, discharge, date of procedure)
- [ ] Educational Records

Will any PII in your possession be coded?

(•) Yes ( ) No

Will you have the code in your possession?

(•) Yes ( ) No

Is this personally identifiable information considered Protected Health Information (PHI)? (PHI is any of the 18 identifiers listed above collected by or received by a covered entity, which includes a healthcare provider, healthcare clearing house, or as defined in the Univeristy SAP 16.99.99.M0.01.)

(•) Yes ( ) No

If Yes, additional requirements may be involved such as HIPAA authorization, Waiver of Authorization, or Data Use Agreement, or other agreements.

17.2 Explain why you need to obtain personally identifiable information (list all of the data fields to be collected):

Phone numbers, email addresses and physical addresses are needed to communicate with participants over the duration of the 9 week study. Diagnostic devices (home sleep test kits and their components such as batteries) will be sent back and forth between participants and study personnel as needed, such that addresses must be kept. Social security numbers may be needed to monetarily compensate subjects. Medical device numbers (sleep recorders) as well as the date/time of recordings will be recorded to insure the integrity of the sleep study data.
The identity of the subjects, as well as to which group they have been assigned will be coded to insure the integrity of the data analysis: the analysist will be "blinded" in this regard.

17.3 Does this study involve use of Protected Health Information (PHI) being received from a Covered Entity (e.g. healthcare provider, healthcare clearing house, health plan)?

(•) Yes ( ) No

Will the provider be a collaborator on this study who will maintain the code to the PHI in their possession?

( ) Yes (•) No

If yes, identify the covered entity and provide the data use agreement or business associate agreement.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

Covered Entity:

Does this study involve collection of PHI from participants or receipt of PHI from a covered entity?

(•) Yes ( ) No

Does this study involve distribution of PHI to a Covered Entity (e.g. healthcare provider, healthcare clearing house, health plan)?

( ) Yes (•) No

If Yes to any of these three previous questions, PHI authorization or a waiver of PHI authorization is required. Is a waiver of PHI authorization being requested? For more information, see the additional information online: **http://rcb.tamu.edu/humansubjects/resources/consentinfo**

○ Yes ◉ No

Please attach the HIPAA Authorization as needed to the application.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

17.4 Will the PHI used in this study be stored with encryption?

◉ Yes ○ No

How is PHI transmitted electronically being protected?

It will be sent in encrypted format. All computers used by the research team will have Bitlocker encryption on them.

How is PHI data protected?

The only PHI to be transmitted to the two companies reading the sleep studies are the dates, times, city and coded subject identities; these companies will be unable to link data to individuals.

Who has access to PHI?

Only the research team at the Texas A&M College of Dentistry.

18.0 Retrospective Details (Please note: This refers to the analysis of data, documents, records, or specimens that were existing as of the date of the IRB application.)

18.1 Will existing data or documents be used (e.g., patient records/charts, samples/specimens, public records, surveys, evaluation tools, etc.)?
NOTE: If you answer NO to this question, please skip the remaining questions in this section.

◉ Yes ○ No

If Yes, then:
Describe the data or documents that will be used.

Medical history including sleep apnea diagnosis, list of medications and polysomnogram/continuous positive air pressure (PSG/CPAP) study reports,

What is the date range of the original data collection?

No more than 3 years prior to enrollment and until the end of the proposed study.

How will the existing data be obtained? Additional information may be required to establish authority to use the data previously collected.

Patients will authorize the release of their medical history, polysomnogram/continuous positive air pressure (PSG/CPAP) study reports, and sleep apnea diagnoses from their physicians. This information will be obtained in paper forms or via encrypted electronic communication.

18.2 Will your research be limited to only existing data or specimens? NOTE: If data/specimens will be collected after submission of this application, then the answer here is "No". If you answered NO to this question and the main question above, please skip the remaining questions in this section.

◉ Yes ○ No

18.3 Will existing specimens be used (e.g., human blood, tissue, saliva, etc.)?

○ Yes ◉ No

If Yes, then describe the specimens that will be used and how they will be obtained.

Indicate the number of specimens.

How will the specimens be obtained?

Provide the documentation from the holder of the samples that gives you permission to use the samples for research purposes. If the samples were collected for research purposes, provide a copy of the approved informed consent document used to obtain the samples.

18.4 Retrospective Details – Publicly Available

Is the source of the data for your research accessible by the general public?

○ Yes ◉ No

Provide the link if applicable.

18.5 Retrospective Details – Identity

Will it be possible to determine a subject's identity directly or indirectly through a link (e.g., Medical Record Number (MRN), participant code, IP address, email)?

◉ Yes ○ No

18.6 Retrospective Details – Waiver of Informed Consent

Is it impractical to obtain informed consent from the subjects?

○ Yes ◉ No

If Yes, then please complete the Waiver of Informed Consent information in the next section.

18.7 Retrospective Details - Waiver of Document of Informed Consent

Is it possible to obtain informed consent, AND the only link between the data and the human subject would be the signed informed consent document?

○ Yes ◉ No

19.0 Data Management

19.1 General Information

STANDARD ADMINISTRATIVE PROCEDURE

15.99.03.M1.03 The Responsible Stewardship of Research Data

http://rules-saps.tamu.edu/PDFs/15.99.03.M1.03.pdf

Do you agree to adhere to the SAP with your data?

(•) Yes ( ) No

Where will the data be stored? Indicate building and room number on TAMU property.

Main College of Dentistry building at 3302 Gaston Avenue, Room 499.

How long will the data be stored? (Note: This time period should be a minimum of 3 years post completion of the research and perhaps longer, depending on sponsor requirements.)

For 3 years after completion.

If you are storing or transmitting collected data, is the storage and transmission of the data encrypted?

(•) Yes ( ) No

Please note that PHI must be stored and transmitted with encryption.

Who will have access to the data?

The research team.

19.2 Data Safety Monitoring Plan

(•) Yes ( ) No

If so, then:
How is it managed?

With what frequency is data reviewed for this project?
How often does the DSMB meet?
What is the frequency of reports from the DSMB?
Describe any planned interim analysis.
Provide names, affiliations, and qualifications of members.

It is managed through the Post Approval Managing Process.

20.0 Informed Consent

20.1 Select all that apply and attach to the application:

For templates and guidance regarding informed consent, see **http://rcb.tamu.edu/humansubjects/resources/consentinfo**

- [x] Informed Consent Document (signed consent, typically needed in Texas for research involving adults)
- [ ] Parent Informed Consent Document
- [ ] Parent Permission Form
- [ ] Assent Form (typically needed in Texas for research involving children under 18)
- [ ] Recruitment Script (verbal)
- [x] Recruitment Email
- [ ] Information Sheet (also select Waiver of Documentation of Informed Consent)

☐ Waiver of Informed Consent
☐ Waiver of Documentation of Informed Consent
☐ Other

If other, please specify:

Recruitment flyers posted at the College of Dentistry, Dallas A.W.A.K.E. office (support group for sleep apnea patients) and Dallas area sleep clinics. Online postings at clinicaltrials.gov and the College web site. Also post flyers at (1) regional hospitals and clinics, (2) city and county offices/stations (such as the Dallas Fire Department), (3) DART and other transportation offices and (4) Facebook, Twitter and similar site, (5) local newspapers and magazines, (6) local radio stations. The content of the advertisements on venues (5) and (6) will be the same as the approved flyers. Written permission will be sought from all sites at which flyers are to be posted.

20.2 Please provide the readability statistics for each informed consent document in terms of the Flesch-Kincaid Grade Level. In general, informed consent document for adults should be on an 8th grade level.

http://rcb.tamu.edu/humansubjects/resources/tipsconsentforms

This is currently at the 10.8 level.

20.3 Please describe the informed consent process. Include how participants will be adequately informed of what they will be asked to do in the study as well as how they will be protected. Include how the forms selected above will be used in the process including that the particpants will have sufficient time to review any information provided to them.

If a waiver of documentation of informed consent is requested, then the information sheet use must be described here.

Those interested in participating will discuss over the phone, via email or meet in person with the research coordinator (RC) at the College of Dentistry clinic. The Informed Consent Document (ICD) will be made available. The RC will determine eligibilty with regard to inclusion/exclusion criteria, as well as having a current sleep apnea diagnosis and polysomnogram. If eligible, The RC will then explain in detail the procedures, risks, benefits, compensation and time commitment involved in the study. The RC will ask the prospective subject (PS) to repeat his/her understanding of the study, their involvement, and especially risks and benefits. The PS will be given the opportunity to speak with the the principal investigator or other investigators on the team to futher discuss the study. The PS will also have the opportunity to take home the ICD and discuss it with family and friends. Once the PS indicates that all questions have been answered to his/her satisfaction, he/she may sign the informed consent document to enroll. The PS will be given a copy of the signed document.
The recruitment documents listed above will notify prospective subjects of the opportunity to participate and will contain the contact informtion for the RC. The bulk email will give a very brief overview of the study and provide a link to a detailed description.

20.4 Where will the informed consent process take place (e.g. building name, physical address)?

Where will the informed consent documents be physically stored?

In Room 499 at 3302 Gaston Avenue. In top drawer of horizontal file cabinet.

Who will have access to the Informed Consent documents?

The principal investigator and the research coordinator.

20.5 For studies involving research on children, will participants who reach age of majority be consented?

○ Yes ○ No

20.6 Have the PI, Co-I(s), and any persons interacting with study subjects completed CITI training?

◉ Yes ○ No

If No is selected, have the PI, Co-I(s), and any persons interacting with study subjects completed alternative human subjects training? If so, please provide a description and copy of the alternative training.

20.7 Please indicate the research personnel who will be obtaining informed consent from participants. (Use N/A to indicate that informed consent will not be collected.)

Emet D. Schneiderman
Steven D. Bender
Jason Hui
P. Duane Wilson
Clinical Research Coordinator : Zohre German
Preetam J. Schramm

20.8 What project-specific training/experience have individuals obtaining informed consent received (e.g. verbal instruction by the PI, practice with the PI)?

Verbal instruction and practice with the PI. Use of a script when explaining the two arms of the study to minimize bias and to maintain equipoise.

20.9 Will the subject have the opportunity to review the informed consent document or Information Sheet, ask questions, and understand the details of the study prior to participation?

◉ Yes ○ No

If Yes, then how much time will be provided?

As much time as needed.

20.10 How will cultural issues, including language, be addressed?

At this time participants must be fluent in English, both spoken and written. Should there be sufficient interest in participating by another language group, a bilingual staff member will be enlisted and translated versions of all of the forms and questionnaires will be added.

20.11 Will non-English speaking people be approached to participate in this study?

○ Yes ◉ No

Will a translation be available for non-English speaking subjects?

☐ Verbally (provide script)
☐ In writing (provide documents)
☐ Both

☑ Neither

20.12 If the study involves minors, then describe the informed consent process of parental permission and how the assent of the minor will be sought. Attach the documents to the application.

21.0 For Biomedical Research

21.1 Select all that apply to the study:

- ☐ Retrospective (data/specimens available at the time of this application)
- ☑ Prospective (data/specimens to be collected after IRB approval)
- ☑ Randomized
- ☐ Double-blind
- ☑ Single-blind
- ☐ Unblinded (open label)
- ☐ Placebo-controlled
- ☑ Therapy/Intervention/Prevention
- ☐ Pilot or Feasibility Study
- ☑ Diagnosis or Diagnostic Test
- ☐ Etiology/Harm/Risk Factors (incl Molecular Genetics)/Mechanism of Disease
- ☐ Prognosis
- ☐ Descriptive or Prevalence
- ☑ Device
- ☐ Drug
- ☐ Other

If other, please specify:

What is the disease or condition being studied?

Snoring and obstructive sleep apnea; unstable/poor sleep quality

Is your project evaluating an active intervention or treatment procedure (to determine whether an intervention/treatment is effective for the people undergoing it)?

◉ Yes ○ No

Please provide a justification for conducting this research in humans rather than animals.

This is a comparative effectiveness study on two widely used therapies for obstructive sleep apnea in humans. It is evaluating how they perform clinically, that is, in living humans, so that animal studies would be inappropriate. Also, this study must be done on humans because of the subjective aspects of (1) the human sleep experience, (2) the fit and comfort of the oral appliances; these cannot be evaluated in animals. All of the devices being evaluated in this study, both therapeutic and diagnositic have been designed for humans, and are cleared for human use. Comparative compliance will also be evaluated, which also is a strictly human behavior issue.

Does this study involve genomic data?

○ Yes ◉ No

If yes, will the genomic data be shared?

○ Yes ○ No

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No Document(s) have been attached to this form.						

If yes, please indentify the recipients and provide the Genomic Data Sharing Certification as required by NIH
(**http://gds.nih.gov/03policy2.html**).

22.0 Reporting

22.1 Clinical trials, both therapeutic and observational, may require reporting.

Please indicate where this study will be reported.

- [x] ClinicalTrials.gov
- [ ] National Cancer Institute (NCI)
- [ ] Other, please indicate below

23.0 Drugs, Biologics, Devices, and Dietary Supplements

23.1 Indicate if this project involves the study of any of the following:

- [ ] Drug
- [ ] Biologic
- [x] Device
- [ ] Dietary supplement (if the research is intended to evaluate the supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then select DRUG)
- [ ] Not applicable

24.0 Use of Study Drugs

24.1 Will drugs be used in this study?

○ Yes ◉ No

If yes, then is this study being conducted under an approved IND or drugs already approval and being used in accordance with the label?

○ Yes ○ No

If so, then who is the responsible physician? Include affiliation and contact information.

Include information concerning the intervention/treatment of participants and a description of the procedures being performed already for diagnostic or treatment purposes.

Attach the Investigator's Brochure to the application and indicate the version date.

24.2 Study Drug Details

Just below this line, add a row to begin the IRB Study Drug form. Complete one row per drug.

25.0 Medical Devices

25.1 Will medical devices be used in this study?

(•) Yes ( ) No

If using a device, then is this study being conducted under an approved IDE or HDE or already approved device used in accordance with the label?

( ) Yes (•) No

If so, then who is the responsible physician? Include affiliation and contact information.

Steven D. Bender, DDS

Include information concerning the intervention/treatment of participants and a description of the procedures being performed already for diagnostic or treatment purposes.

What measurements are to be conducted?

Braebon Medibyte: airflow, respiratory effort and blood oxygenation; apnea & hypopnea detection; respiratory effort using inductance plesthysmogrphy.
SleepImage M1: electrocardiogram (ECG), actigraphy, snoring, and body position; cardiopulmonary coupling.

Attach the device manual to the application and indicate the version date.

25.2 List the medical device(s) to be used:

Provide the following information:
Device name: Manufacturer/supplier of device: Where will the devices be stored? Will devices be supplied at no cost? Yes No Is this a HUD (HDE)? Yes No HDE number: FDA approved: A new device or a new used of approved device? Yes No IDE necessary? Yes No IDE number: Who holds the IDE? IDE details: Device level of risk: How will access be controlled? How will the device be used? How will the device be destroyed and disposed? Alternatives available to patients:

Home sleep test systems (HSTs; diagnostic)
Medibyte, Braebon Medical, Kanata, Ontario, Canada.
SleepImage home sleep test device, SleepImage, Broomfield Colorado, USA.

Oral appliances (OAs; therapeutic)
TAP 1, Airway Management, Inc., Dallas, Texas.
SomnoDent Flex, SomnoMed, Plano, TX

- Where will the devices be stored? *Room 499*
- Will devices be supplied at no cost? *Yes, however a refundable deposit will be required.*
- Is this a HUD (HDE)?*No*
- HDE number: *NA*
- FDA approved: *Yes, all are FDA cleared*
- A new device or a new used of approved device? *No*
- IDE necessary? *No*
- IDE number: *NA*
- Who holds the IDE? *NA*
- IDE details: *NA*
- Device level of risk: *No more than minimal*

- How will access be controlled? *The research coordinator will issue (check-out) and retrieve (check-in) the HST devices following outlined procedures the day before and after 1 night of sleep recording. The OAs will be issued in randomized order at the beginning of each 4-week testing period. Subjects are allowed to retain the OA indefinitely for their use after the study.*
- How will the device be used?*Each of the test custom-fitted OAs will be worn each night during sleep for a 4-week period with a 1-week washout period between test OAs. The subject is expected to wear their prescribed CPAP during the washout period. The HST recorders to evaluate sleep quality with OA use will be obtained by study subjects for each of the two OA testing periods on the first and last day of each 4-week period. A total of 4 sleep recordings/subject is expected over the 9-week study period.*
- How will the device be destroyed and disposed? *The HST recorders are reusable/non-disposable items, so they will not be destroyed.*
- Alternatives available to patients: *No alternative treatment options are directly part of this study. If a prospective subject decides that either oral appliance therapy is not suitable for him/her, the alternative is to continue to use his/her prescribed CPAP therapy.*

26.0 Before you Submit

26.1 Please note the following.

The following checklist is a guide for researchers regarding supporting documents that must be considered for and/or uploaded with this application for review and approval before use.

- Informed Consent Document
- Information Sheet
- Waiver of HIPAA Authorization
- Parental Permission Form/Minor Assent Form
- Recruitment materials (i.e. flyers, emails, advertisements, telephone scripts, social media posts)
- Site Authorization Letter (for study conduct and/or access to administrative records)
- Survey/Questionnaire/Data Collection/Abstraction Forms
- Grant Applications (cover to cover), required if funded or grant submitted
- Instructions
- Protocol Investigator's Brochure (for clinical trials only)
- Case report form (for clinical trials only)
- Device Manual (if using an approved or investigational device)
- Thesis/dissertation proposal
- Waiver of parental permission/minor assent form
- Letter of cultural evaluation for international research (link to SOP)
- IRB approvals from collaborating institutions
- Any other documents related to the research
- CVs for all investigators when proposed activities are more than minimal risk
- CITI training for all personnel

Investigators assume the following responsibilities:

1. **Continuing Review:** The study must be renewed by the expiration date in order to continue with the research. A Continuing Review application along with required documents must be submitted by the continuing review deadline. Failure to do so may result in processing delays, study expiration, and/or loss of funding.
2. **Completion Report:** Upon completion of the research study (including data collection and analysis), a Completion Report must be submitted to the IRB.
3. **Unanticipated Problems and Adverse Events:** Unanticipated problems and adverse events must be reported to the IRB immediately.
4. **Reports of Potential Non-compliance:** Potential non-compliance, including deviations from protocol and violations, must be reported to the IRB office immediately.
5. **Amendments:** Changes to the protocol and/or study documents must be requested by submitting an Amendment to the IRB for review. The Amendment must be approved by the IRB before being implemented.
6. **Consent Forms:** When using a consent form or information sheet, the IRB stamped approved version must be used. Please log into iRIS to download the stamped approved version of the

consenting instruments. If you are unable to locate the stamped version in iRIS, please contact the iRIS Support Team at 979.845.4969 or the IRB liaison assigned to your area. Human participants are to receive a copy of the consent document, if appropriate.

7. **Post Approval Monitoring:** Expedited and full board studies may be subject to post approval monitoring. During the life of the study, please review and document study progress using the PI self-assessment found on the RCB website as a method of preparation for the potential review. Investigators are responsible for maintaining complete and accurate study records and making them available for post approval monitoring. Investigators are encouraged to request a pre-initiation site visit with the Post Approval Monitor. These visits are designed to help ensure that all necessary documents are approved and in order prior to initiating the study and to help investigators maintain compliance.
8. **Recruitment**: All approved recruitment materials will be stamped electronically by the HRPP staff and available for download from iRIS. These IRB-stamped approved documents from iRIS must be used for recruitment. For materials that are distributed to potential participants electronically and for which you can only feasibly use the approved text rather than the stamped document, the study's IRB Study Number, approval date, and expiration dates must be included in the following format: TAMU IRB#20XX-XXXX Approved: XX/XX/XXXX Expiration Date: XX/XX/XXXX.
9. **FERPA and PPRA:** Investigators conducting research with students must have appropriate approvals from the FERPA administrator at the institution where the research will be conducted in accordance with the Family Education Rights and Privacy Act (FERPA). The Protection of Pupil Rights Amendment (PPRA) protects the rights of parents in students ensuring that written parental consent is required for participation in surveys, analysis, or evaluation that ask questions falling into categories of protected information.
10. **Food:** Any use of food in the conduct of human research must follow Texas A&M University Standard Administrative Procedure 24.01.01.M4.02.
11. **Payments:** Any use of payments to human research participants must follow Texas A&M University Standard Administrative Procedure 21.01.99.M0.03.
12. **Records Retention**: Federal Regulations require records be retained for at least 3 years after study closure. Records of a study that collects protected health information are required to be retained for at least 6 years after study closure. Some sponsors require extended records retention. Texas A&M University rule 15.99.03.M1.03 Responsible Stewardship of Research Data requires that research records be retained on Texas A&M property.

Post-approval monitoring requires that key study personnel have access to study materials.