# Document Coversheet

Study Title: Improvement in Nocturia With MAD and Changes in Polysomnographic Value

| | |
|---|---|
| Institution/Site: | University of Kentucky |
| Document (Approval/Update) Date: | 10/14/2022 |
| NCT Number: | NCT05562388 |
| IRB Number | 80084 |
| Coversheet created: | 7/8/2026 |

*Statistical Analysis*

Data analysis was conducted using SPSS Statistics Version 31 (IBM Corp., Armonk, NY). Given the pilot nature of this randomized controlled trial (N=17), the primary focus was on estimating effect sizes and assessing feasibility trends alongside hypothesis testing. However, given the small sample sizes and distributional characteristics of the data, emphasis was placed on examining associations among change scores. Changes in weight and muscle parameters from baseline to follow-up (3 and 6 months) were summarized as mean change ± standard deviation and analyzed using paired Wilcoxon signed-rank tests. Spearman's rank-order correlations were used to examine associations between biomarkers and anthropometric measures. Analyses were conducted across two frameworks: (1) cross-sectional correlations using all available measurements across participants over time and (2) longitudinal associations using change scores defined as follow-up (3-and 6- month) values minus baseline values. Pairwise complete-case deletion was applied for each correlation calculation. The sample sizes for each test are provided alongside the corresponding correlation coefficients and p-values. Demographic data are reported as mean ± SD or median (IQR). Significance was determined as $p < 0.05$.

IRB Approval
10/14/2022
IRB # 80084
IRB2

**PROTOCOL TYPE** (VERSION 4)

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
◉ Expedited (Must be risk level 1)
○ Full

**IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.**

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

***Which IRB***

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

**Note:** Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

***Which Protocol Process Type***

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

**The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.**

**EXPEDITED CERTIFICATION**

**0 unresolved comment(s)**

**To Be Completed Only If Protocol is to Receive Expedited Review**

**Applicability**

A. Research activities that (1) present no more than *minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

**"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. 45 CFR 46.102(i)*

Check the appropriate categories that apply to your research project:

☐ Study was originally approved by the full IRB at a convened meeting.

☑ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

A. Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
B. Research on medical devices for which (i) an investigational device exemption application is not required*; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.**

* Study must meet one of the IDE Exempt categories listed on the Device Form Attachment.
** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements.
NOTE: Select Category 1 for compassionate use medical device applications or individual patient expanded access investigational drug applications for which FDA has waived the requirement for full review.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

A. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
B. From other adults and children* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves "minimal risk".

*In Kentucky, "child/children" refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Informed Consent SOP for discussion of "Emancipated Individuals" under Kentucky state law.) Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., DHHS, FDA, and U.S. Department of Education). Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." If conducting research outside the state of Kentucky, you are responsible for complying with applicable state law.

☐ 3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

A. Hair and nail clippings in a nondisfiguring manner;
B. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
C. Permanent teeth if routine patient care indicates a need for extraction;
D. Excreta and external secretions (including sweat);
E. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
F. placenta removed at delivery;
G. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
H. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
I. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
J. Sputum collected after saline mist nebulization.

☐ 4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

A. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
B. Weighing or testing sensory acuity;
C. Magnetic resonance imaging;
D. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
E. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☑ 5) Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for non-research purposes (such as medical treatment or diagnosis) as well as research involving existing information or specimens that were previously collected for research purposes, provided they were not collected for the currently proposed research. (Note: Some research in this category may qualify for Exempt review. This listing refers only to research that is not exempt.)
(Note: If submission includes materials previously collected for either non-research or research purposes in a protocol for which IRB approval expired, you may check Category 5. However, a separate category must also be selected for prospective collection of data/specimens obtained solely for research purposes)

☐ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☑ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)

**PROJECT INFORMATION**

**0 unresolved comment(s)**

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Improvement in Nocturia with MAD and Changes in Polysomnographic Values

**Short Title Description**
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

MAD and changes in nocturia

Anticipated Ending Date of Research Project: 8/31/2024

Maximum number of human subjects (or records/specimens to be reviewed) 36

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? (•) Yes ( ) No

## PI CONTACT INFORMATION

**0 unresolved comment(s)**

**Principal Investigator (PI) role for E-IRB access**
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be listed as PI here.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

The Principal Investigator's (PI) contact information is filled in automatically based on who logged in to create the application.

**If you are not the Principal Investigator, do NOT add yourself as study personnel.**
To change the PI contact information on an application in Researcher edit status:

- click "Change Principal Investigator";
- search for the PI's name using the search feature;
- click "Select" by the name of the Principal Investigator, then "Save Contact Information".

  You will automatically be added as study personnel with editing permissions to continue editing the application.

**Change Principal Investigator:**

| | | | |
|---|---|---|---|
| First Name: | Fernanda | Room# & Bldg: | 800 Rose Street |
| Last Name: | Yanez Regonesi | Speed Sort#: | 40536 |
| Middle Name | | | |
| Department: | Dentistry Oral Health Science … | Dept Code: | 7A800 |
| PI's Employee/Student ID#: | 12364673 | Rank: | |
| PI's Telephone #: | 8593238491 | Degree: | DDS, MS |
| PI's e-mail address: | fernandayanez@uky.edu | PI's FAX Number: | |
| PI is R.N. ○ Yes ◉ No | | HSP Trained: | Yes |
| | | HSP Trained Date: | 10/13/2020 |
| | | RCR Trained: | Yes |

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

**RISK LEVEL**

**0 unresolved comment(s)**

Indicate which of the categories listed below accurately describes this protocol

- (●) (Risk Level 1) Not greater than minimal risk
- ( ) (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ( ) (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ( ) (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

*****For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).*****

Refer to UK's guidance document on assessing the research risk for additional information.

**SUBJECT DEMOGRAPHICS** **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 80

**Study Population:**

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

No specific population will be targeted in terms of sex/gender or racial/ethnic background. The age range considers patients over 18 until 80 y.o with a diagnosis of obstructive sleep apnea (OSA). Participants will be recruited from the consecutive patients referred to the Orofacial Pain Clinic for the management of OSA with a MAD.
Inclusion criteria will be:
- English speaker
- >18 years old
- Diagnosed by sleep physician with obstructive sleep apnea diagnosis with AHI=5.
- Equal or more than 2 voiding/night at baseline
- 8 or more teeth per arch upon clinical exam
- Range of mandibular protrusion (anteroposterior mandibular mobility) of 5 mm or more.
- Consent to participate in the study

The exclusion criteria will include:
- Central sleep apnea, concomitant sleep disorder (i.e. insomnia, narcolepsy, restless legs syndrome, rapid eye movement sleep behavior disorder).
- Prostate/kidney problems (urological disease: (eg overactive bladder, benign prostate hyperplasia)
- Pregnancy
- Heart failure
- Use of diuretics
- Diabetes
- Parkinson's disease
- Dementia
- Combination therapy for the management of OSA (CPAP + MAD)
- Upon clinical examination: periodontal disease (>4 mm on periodontal with bleeding on probing and visual signs of periodontal inflammation), tooth horizontal mobility >1 mm, vertical mobility, unfavorable crown to root ratio; open cavities, fractured restorations or ongoing dental treatment.
- Exaggerated gag reflex.
- Lack of coordination or dexterity.
- Previous history of MAD use.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
**(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):**

**Participant Demographics**

| | Cisgender Man | Cisgender Woman | TGNB/TGE | Unknown/Not Reported |
|---|---|---|---|---|
| American Indian/Alaskan Native: | | | | |
| Asian: | 1 | 1 | | |
| Black/African American: | 2 | 2 | | |
| Latinx: | 1 | 1 | | |
| Native Hawaiian/Pacific Islander: | | | | |
| White: | 14 | 14 | | |
| American Arab/Middle Eastern/North African: | | | | |

| | | | | |
|---|---|---|---|---|
| Indigenous People Around the World: | | | | |
| More than One Race: | | | | |
| Unknown or Not Reported: | | | | |

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

***ADDITIONAL INFORMATION:***

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

**Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):**

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

**Examples of such conditions include:**

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

**INFORMED CONSENT/ASSENT PROCESS/WAIVER**

**1 unresolved comment(s)**

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

**Consent/Assent Tips:**

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

## How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

| Attach Type | File Name |
|---|---|
| Informed Consent/HIPAA Combined Form | 80084_Informed ConsentHIPAA Combined Form_clean version Oct 2022.pdf |
| InformedConsent-Highlighted/Tracked_Changes | 80084_Informed ConsentHIPAA Combined Form_highlighted track changes Oct 2022.pdf |

**Informed Consent Process:**

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)
- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

We will recruit participants from the consecutive patients referred to the Orofacial Pain Clinic (OFPC) for the management of obstructive sleep apnea (OSA) with a mandibular advancement device (MAD) who also have nocturia. As part of the standard clinical protocols, these patients are initially evaluated for eligibility to start OSA therapy with a mandibular advancement device by the residents under supervision of an attending provider of the Orofacial Pain Division (College of Dentistry – University of Kentucky) at the OFPC. After the evaluation, if the patient is eligible to start MAD therapy, the study will be offered as an option for their treatment or they can continue with the standard of care provided at the clinic. If the patient expresses interest in participating in the study, they will be evaluated for eligibility by having an initial assessment done by Dr. Fernanda Yanez Regonesi or by Dr. Isabel Moreno Hay. If the patient is eligible and agrees verbally to participate, they will be given the consent form to read.
Consent form will be signed by the patient and copy of it will be provided to them. The hand-signed consent will remain in the OFP clinic in the locked office of the PI (room E236).
Patients concerns and complaints in regard to this study will be made by contacting the Orofacial Pain Center office or by calling the PI (Fernanda Yanez Regonesi DDS,MS). This information will remain confidential and the PI will provide the best information possible to the patient. The participants will keep a copy of the informed consent form which contains the contact information of the PI and the University of Kentucky's Office of Research Integrity.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

**SECTION 1.**

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

**SECTION 2.**

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

**Option 1**

**Describe how your study meets these criteria:**

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

**Option 2**

**Describe how your study meets these criteria:**

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

**Option 3**

**Describe how your study meets these criteria:**

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

**STUDY PERSONNEL** **0 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
**After selecting 'Yes' or 'No' you must click the 'Save Study Personnel Information' button.**

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

**NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Getting Started page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (HSPTrainingSupport@uky.edu) for credit.**

**Study personnel assisting in research project:**

| Last Name | First Name | Responsibility In Project | Role | AC | Contact | Degree | StatusFlag | (HSP) | (HSP)Date | (RCR) | Removed? | Last Updated | SFI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Boggero | Ian | Co-Investigator | SP | N | N | Pdh | P | Y | 07/14/2020 | Y | N | 07/28/2022 | N |
| Dawson | Dawn | Project Assistance/Support | DP | N | Y | RDH CCRC | P | Y | 01/18/2022 | Y | N | 07/28/2022 | N |
| Moreno Hay | Isabel | Co-Investigator | SP | Y | N | DDS Phd | P | Y | 08/02/2022 | Y | N | 07/28/2022 | N |
| Pasha | Sara | Co-Investigator | SP | N | N | MD | P | Y | 10/13/2020 | Y | N | 07/28/2022 | N |

**RESEARCH DESCRIPTION**

**0 unresolved comment(s)**

**You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.**

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

**Workaround(s):**

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

## Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Nocturia is defined by the International Continence Society as "waking up at least two times for voiding", while polyuria refers to the production of an abnormally large volume of urine at night (1). Ten percent of the general population over 20 years old suffers from nocturia (2), with increasing prevalence with aging (2-4). The nocturnal awakenings are frequently associated with sleep loss, daytime fatigue, and mood disturbance (5-7) Studies have demonstrated a significant negative impact in patient's quality of life (QoL) and well-being, with a significant dose-dependent relationship (8). Potential causes associated with nocturia are bladder storage problems, use of diuretics, diabetes, and other medical conditions, such as Parkinson's disease, dementia, heart failure and sleep disorders (9).

Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway during sleep resulting intermittent hypoxia and hypercapnia (10). A recent systematic review indicated that the prevalence varies between 9-38% in the general population (11). Studies in the literature report a relationship between OSA and nocturia in adults (12, 13). Indeed, studies have found that the rate of nocturia is significantly greater in patients with OSA than in healthy controls. A recent systematic review and meta-analysis reinforced the significant association between OSA and the risk of nocturia (RR = 1.41, 95% CI 1.26–1.59) (14). The prevalence of nocturia in OSA patients varies between 45-70% and is reported to increase with the severity of the OSA (12-15). However, there is still a gap in the understanding of the relationship between urine production and OSA. The relation between OSA and nocturia might be explained by the greater fractional urinary flow and the lower percentage of filtered sodium reabsorption in OSA patients. Other studies proposed that obstructive events along with sustained ventilatory effort generated a negative intrathoracic pressure, thus conducting a false signal of volume overload to the heart. This in turn induces an increase in atrial natriuretic peptide (16) and B-type natriuretic peptide (BNP) secretion, thereby augmenting urinary production by stimulating water and sodium excretion, and inhibiting antidiuretic hormone (ADH) and renin-angiotensin-aldosterone system (2). Another possible explanation is that hypoxia following obstructive events causes oxidative stress, leading to detrusor instability, spontaneous contractions, and reduction in ANP recreation at night (17), thus inducing nocturia. According to Finamore et al. (18), nocturia seems to be significantly associated to intermittent desaturation rather than to severity and length of hypoxia, although sporadic night arousals have also been advocated as responsible for nocturia (19)

Continuous positive airway pressure (CPAP) is the gold standard for the management of OSA. A systematic review and meta-analysis indicated that CPAP therapy results in a statistically significant decrease both in the frequency of nocturia and in the volume of urine associated with it, likely due to a normalization in oxygen desaturation (17). Margel et al. evaluated 97 patients after CPAP treatment and noted a significant improvement in nocturia in all OSA severities, especially in severe cases. Surprisingly, a reduction was already noted after only one night of treatment (20). Another study confirmed the reduction in nocturia and improvement in QoL even after 1 year of treatment with CPAP (21). A recent study compared the effects of CPAP and surgical treatment of OSA on nocturia. Regardless of treatment modality, the mean numbers of voiding per night improved significantly in both group with no difference between groups. This suggests that correcting the OSA might be important for the improvement in nocturia (22)
To the best of our knowledge, to the date no studies have specifically evaluated the management of nocturia with the use of mandibular advancement devices (MAD) in OSA patients. Attali et al. studied the predictors of long-term adherence to MAD, and they noted a significant short-term reduction in nocturia, from 48% to 13% in 3-6 months; however, the treatment was less efficient in the long-term (23). The main limitation of this study was that the results were obtained through telephone survey.

Archieval data from sleep patients at our orofacial pain clinic, revealed that 50% (23/46) of patients presented with nocturia at baseline and demonstrated a significant decrease in the number of voiding per night up even until the last follow up 1.4±0.4 years later. A limitation is the lack of second sleep study to assess if these changes were associated with improvement in apnea hypopnea index (AHI) (IRB#46643) . In fact, no literature is available regarding the correlation between changes in nocturia and AHI with MAD use.

References
1) Weiss JP, Monaghan TF, Epstein MR, Lazar JM. Future Considerations in Nocturia and Nocturnal Polyuria. Urology. 2019;133S:34-42
2) Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep. 2004;27(1):139-44.
3) Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol. 2010;184(2):440-6.
4) Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. J Urol. 2006;175(2):596-600.
5) Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int. 2003; 92:948–54.
6) Ohayon MM. Nocturnal awakenings and comorbid disorders in the American general population. J Psychiatr Res. 2008; 43:48–54.
7) Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT, Lose G. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population. BJU Int 2006 Sept, 98(3):599-604.
8) Tikkinen KA, Johnson TM, 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol. 2010;57(3):488-96.
9) Aydur E. DR. Medical Conditions Associated with Nocturia. In: Weiss M, FACS, J, editor. Nocturia: Springer, New York; 2012.
10) Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. 2020;323(14):1389-400.
11) Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017;34:70-81.
12) Saldias Penafiel F, Salinas Rossel G, Cortes Meza J, Farias Nesvadba D, Penaloza Tapia A, Aguirre Mardones C, et al. [Gender differences in clinical features and performance of sleep questionnaires in adults with obstructive sleep apnea syndrome]. Rev Med Chil. 2019;147(10):1291-302.
13) Basoglu OK, Tasbakan MS. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. Sleep Breath. 2018;22(1):241-9.
14) Zhou J, Xia S, Li T, Liu R. Association between obstructive sleep apnea syndrome and nocturia: a meta-analysis. Sleep Breath. 2020;24(4):1293-8.
15) Krieger J, Petiau C, Sforza E, Delanoe C, Hecht MT, Chamouard V. Nocturnal poliuria is a symptom of obstructive sleep apnea. Urol Int 1993;50:93-7.
16) Sillanpaa M PP, Kero P. . Prevalence of headache at preschool age in an unselected child population. . Cephalalgia. 1991;11:239-42.
17) Wang T, Huang W, Zong H, Zhang Y. The Efficacy of Continuous Positive Airway Pressure Therapy on Nocturia in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. Int Neurourol J. 2015;19(3):178-84.
18) Finamore P, Scarlata S, Laudisio A, Galdi F, Pipita ME, Chiarella I, et al. Occurrence of nocturia is not mediated by nocturnal hypoxia length and severity in patients with sleep-disordered breathing. Sleep Med. 2018;45:69-73.
19) Witthaus MW, Nipa F, Yang J et al., Bladder oxidate stress in sleep apnea contributes to detrusor instability and nocturia. J Urol 2015; 193:1692-9
20) Margel D, Shochat T, Getzler O, Livne PM, Pillar G. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. Urology. 2006;67(5):974-7.
21) Vrooman OPJ, van Balken MR, van Koeveringe GA, van Kerrebroeck PVA, Driessen L, Schouten LJ, et al. The effect of continuous positive airway pressure on nocturia in patients with obstructive sleep apnea syndrome. Neurourol Urodyn. 2020;39(4):1124-8.
22) Deger M, Ozgur S, Kuleci S et al., Comparison of the Effect of Continuous Positive Airway Pressure and Surgical Treatment of Obstructive Sleep Apnea Syndrome on Nocturia, Journal of Urological Surgery, 2021, 8(2), 106-110.
23) Attali V, Chaumereuil C, Arnulf I, Golmard JL, Tordjman F, Morin L, et al. Predictors of long-term effectiveness to mandibular repositioning device treatment in obstructive sleep apnea patients after 1000 days. Sleep Med. 2016;27-28:107-14.

## Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

Aim 1: test if using a MAD is associated with reductions in nocturia
Aim 2. to investigate if response to therapy in terms of nocturia is associated with improvement in AHI. We hypothesize that using a MAD will improve nocturia and that improvement in nocturia will result in an improvement in AHI.
An exploratory 3rd Aim is to evaluate the changes in quality of life, fatigue, and insomnia symptomatology after MAD treatment and see how changes in these variables correlate with changes in nocturia

## Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.

- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

Uncontrolled open label clinical trial.
Data gathered from recruitment date until appliance delivery will be used allowing each participant to be their own control, as wait-list design type of study.

Attachments

### Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

We will recruit participants from the consecutive patients referred to the Orofacial Pain Clinic (OFPC) for the management of obstructive sleep apnea (OSA) with a mandibular advancement device (MAD) who also have nocturia. As part of the standard clinical protocols, these patients are initially evaluated for eligibility to start OSA therapy with a mandibular advancement device by the residents under supervision of an attending (provider) of the Orofacial Pain Division (College of Dentistry – University of Kentucky) at the OFPC. The PI, Dr. Fernanda Yanez-Regonesi is one of the attendings. After this evaluation, if the patient is eligible to start MAD therapy, they will be offered the opportunity to continue with the standard of care at the clinic or to be evaluated to participate in this study. If the patient decides to proceed and be evaluated for eligibility for this study, the initial assessment will be done by Dr. Fernanda Yanez Regonesi or by Dr. Isabel Moreno Hay. If the patient is eligible and agrees to participate, verbal consent will be obtained and all forms will be completed. After consent, the follow-up study visits will be performed at the OFPC (UK Kentucky Clinic).
None

Attachments

Back to Top

### Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

The research procedures include:

following the consent process, the participants will complete a battery of baseline screening questionnaires along with psychological questionnaires. A pdf of the questionnaires is included below in data collection attachments (baseline package). Participants will undergo a baseline home sleep study (Alice One Night) to collect the following baseline sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2.

After the delivery of the appliance (SOC), the participants will be scheduled for follow-up visits every 2 weeks during the titration period (SOC).
From baseline until second sleep study, participants will complete a daily dairy of nocturnal voiding frequency, fluid intake before bedtime, hours of sleep and hours of MAD use. Diary will be sent to the participants via automated server (RedCap) every morning.
Typically, once patient complete the titration (SOC) of their appliance, they are referred for a second sleep study. As part of the research procedure, second home sleep study (Alice One Night) will be performed at no cost to the patient. Home sleep study results will be provided to the patients, written and verbal instructions of use will be provided to the participants, and they will complete a final outcome assessment battery (available below in data collection package).
Sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2 will be extracted from initial and second home sleep study (HST). Scoring will be performed by trained sleep physician (Dr. Sara Pasha).

The improvement in nocturia with the management of OSA with mandibular advancement appliance with be evaluated. For that, each participant will be their own control on a “wait-list” design type of study. Daily diaries with nocturnal voiding obtained from baseline until delivery of the appliance will be used as control.
Participants will be classified as responders in terms of nocturia when the average voiding per night is less than 2 as recorded by the daily diaries over the preceding 2-week period. The percentage of responders in terms of nocturia will be quantified at which follow up.
Efficacy of MAD will be assessed by comparing the AHI values pre- and post-sleep study with MAD. Patients will be classified as responders if they have 50% improvement in AHI.
Other polysomnographic values like time spent under 90% SpO2 and minimum SpO2 will also be compared and used as predictors of response.
Changes in fatigue, quality of life, and insomnia severity index will be assessed.
The participation in this research will last between six to fifteen weeks depending on the time for each patient's individual improvement. The initial visit will last 45-60 minutes, and the follow-up visits will take about 30-45 minutes. After participation in the study is completed, the participants will be allowed to keep the MAD and TAP® AM aligner.

All other procedures are standard of care, table 1 shows all the procedure. In red at highlighted the research procedure. Black is SOC. Same for clinical procedure table, red shows research procedure, black SOC.

Attachments

| Attach Type | File Name |
|---|---|
| ResearchProcedures | Table 1.JPG |
| ResearchProcedures | clinical procedures.JPG |
| ResearchProcedures | clinical procedures updated.pdf |
| ResearchProcedures | table 1 updated.pdf |

### Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts,

survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Data will be obtained using paper questionnaires and Redcap survey.
- Demographic information regarding age, race, gender and comorbidities will be extracted from the initial questionnaire and general medical history (Screening package) -SOC
- The self-reported use of MAD will be assessed at each follow-up visit via questionnaire on a five-point checklist (number hours per night and nights per week) (Follow up package). - SOC
- Daytime sleepiness will be evaluated at baseline and each follow up: Epworth sleepiness scale (ESS) (Screening and follow up package) - SOC
- Snoring, observed apneic events, morning headache, daytime sleepiness and daytime fatigue, will be assessed via questionnaire using a numerical rating scale (NRS) (to be extracted from screening and follow up package). - SOC
- Sleep parameters including: AHI, RDI, minimum and average oxygen saturation will be extracted from the initial and final HST provided. - research procedure
- The presence of signs and/or symptoms of TMD will be assessed following the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Symptom Questionnaire and Examination Form (follow up package). - SOC
- Sleep quality (will be assessed at baseline and when performing the home sleep apnea test, using the Pittsburgh Sleep Quality Index (PSQI) questionnaire). (baseline and outcome package) - research procedure
- Patients subjective perception of improvement will be assessed at each follow up visit using visual analog scale (follow up package). - SOC
- Incidence of side effects will be assessed at each follow-up visit, including subjective increase/decrease salivation (measure via questionnaire using numeric rating scale), increase/decrease teeth mobility, changes in occlusal contacts (measured in habitual occlusion using 0.01 mm occlusal registration strips (ARTUS corporation®) (follow up package). - SOC
- Severity of urinary symptoms will be evaluated at baseline with the American urological association symptom index (baseline package) - research procedure
- Fatigue will be evaluated at baseline with fatigue assessment scale. (baseline package)- research procedure
- Insomnia will be evaluated at baseline and at second sleep study with insomnia severity index. (baseline and outcome package)-research procedure
- Stress will be evaluated at baseline with perceived stress scale. (baseline package)-research procedure
- Anxiety will be evaluated at baseline with general anxiety disorder 7 scale. (baseline package)-research procedure
- Health related quality of life will be evaluated at baseline and at second sleep study with quality of life scale. (baseline and outcome package)-research procedure

Between follow up visits, participants will receive a daily dairy to complete via Redcap automated server to evaluate for: (in between package)-research procedure
- Hours of sleep
- Compliance with MAD use (hours of use).
- Frequency of nocturnal voiding
- Intake of fluids before bedtime.

Attachments

| Attach Type | File Name |
|---|---|
| DataCollection | Baseline Package.pdf |
| DataCollection | Outcome package.pdf |
| DataCollection | Inbetweenqx.pdf |
| DataCollection | Screening package.pdf |
| DataCollection | Follow-up package.pdf |

## Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

a) Staff and personnel:
- Dr. Fernanda Yanez Regonesi (PI): participation in the recruitment of patients, clinical procedures and data collection.
- Dr. Isabel Moreno Hay DDS PhD (Co-Investigator): participation in the recruitment of patients, clinical procedures and data collection.
- Dawn Dawson, RDH, CCRC: Project Assistance/Support - Manage OnCore and enrollment spreadsheet
- Dr. Ian Boggero PhD: Co investigator, and biostatistician.
- Dr. Sara Pasha MD: co investigator, evaluation of sleep studies.
b) Facilities:

- Primary center: Orofacial Pain clinic (UK Kentucky Clinic. 740 S. Limestone, Second Floor, Wing C, Room E214, Lexington, KY 40536)

c) Resources:
- Desk computer at the Orofacial Pain Clinic (Kentucky Clinic room E234; UK Healthcare system; N037632): This computer will be used for data entry, collection and analysis. It is accessible only by Dr. Fernanda Yanez Regonesi (protected with password). Files (Microsoft Word and Excel) will also be protected with a password.
- Excel file will be shared via UKHC secured folder with other investigators and it will be password protected.
- UKHC share folder. IT will be contacted to create a UK healthcare HIPAA complaint shared folder to share de-identified information with Dr. Sara Pasha. The raw data from the sleep studies will be uploaded here for her to perform analysis from her office.
- Land line phone (at the OFPC): will be the primary way of communication with participants. 859-323-8491, alternatively 859-323-5500.
- Email of Dr. Fernanda Yanez Regonesi (PI) (fya232@uky.edu) may be used as an alternative to the land line phone if it is needed to communicate with the participants.
- Digital scanner and computer: 3Shape TRIOS® 3 (at the OFPC). The scans will be obtained and sent to the lab from the computer that is associated with the scanner.
- Home sleep apnea test (HSAT): Alice NightOne, Phillips Respironics©.
- EPIC

## Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Side effects related to the participation in the study are not greater than standard of care.
When explaining the consent form, the patient will be informed regarding the potential side effects associated to the oral appliance therapy for OSA, and will be instructed to contact us (via phone call or email) if they have any question or if they notice any side effects. The incidence of side effects will be assessed at each follow-up visit, including subjective increase/decrease salivation (measured via questionnaire using numeric rating scale), increase/decrease teeth mobility, changes in occlusal contacts (measured in habitual occlusion using 0.01 mm occlusal registration strips (ARTUS corporation®). Problems related to the appliance will be measured at each follow up visit, considering appliance breaks, cracks, deformation, retention changes, wear, discoloration changes and calculus accumulation.
The use of the home sleep apnea test machine does not represent significant risks for the subjects. The nasal canula and tape to be used are one-time use, and each patient will be provided with a new one. The machine will be disinfected once it is returned, and will stay at least one day without use between different patients. The potential risk to participating in an at home sleep study is disrupted sleep and possible cheek irritation if they decide to use medical tape to secure the nasal tubing to keep it in place overnight. Participants might find it challenging to sleep with the additional equipment, so sleep disturbances might occur.
In 1995 the American Academy of Sleep Medicine (AASM) approved the use of oral appliances for the management of OSA. Since then, the use of oral appliances has significantly increased and today MADs are widely recognized as the main alternative treatment to CPAP therapy (1-2).
This study will be the first to formally test if the use of MAD can improve nocturia – a finding which has already been demonstrated with CPAP therapy. Further, despite the promising results of MADs, in clinical practice it is still difficult to know when to stop titrating/ adjusting the appliance because self-reporting of changes in symptoms is not a reliable method of determining success with treatment (3). This study will test if changes in nocturia could be used as a specific and sensitive criteria for determining how to titrate sleep appliances. The clinical application of this study would help in the determination of clinical guidelines for the titration of MAD. Additionally, it would provide another treatment outcome for MAD equivalent to CPAP therapy. Our study is innovative because it will utilize longitudinal daily diary methodology to define an existing gap in the literature linking MAD and nocturia, and it will do so with a multidimensional team with a wide array of clinical and research experience.

There is a risk that someone could get access to the stored information. In spite of the security measures and safeguards we will use, we cannot guarantee that your identity will never become known.

RISKS: Oral appliance therapy is associated with short and long-term side effects. In relation to the short-term adverse effects, usually mild and transient, it has been reported hypersalivation, dry mouth, dental pain, gingival irritation, and temporomandibular disorders. Regarding the long-term side effects, we can expect: temporomandibular disorders, occlusal changes including: a reduction in overjet, overbite, and development of posterior open bite among others.
BENEFITS vs. RISKS: This therapeutic option can be associated with minimal and non life-threatening risks, and the risks to subjects are reasonable in relation to the anticipated benefits. The mandibular advancement devices are considered as a standard of care option for the management of OSA.

1) J. Durán-Cantolla, R. Crovetto-Martínez, M. Alkhraisat et al., “Efficacy of mandibular advancement device in the treatment of obstructive sleep apnea syndrome: a randomized controlled crossover clinical trial,” Medicina Oral Patología Oral Y Cirugia Bucal, vol. 20, no. 5, pp. e605–e615, 2015.
2) S. Serra-Torres, C. Bellot-Arcís, J. M. Montiel-Company, J. Marco-Algarra, and J. M. Almerich-Silla, “Effectiveness of mandibular advancement appliances in treating obstructive sleep apnea syndrome: a systematic review,” The Laryngoscope, vol. 126, no. 2, pp. 507–514, 2016.
3) Almeida FR, Parker JA, Hodges JS, Lowe AA, Ferguson KA. Effect of a titration polysomnogram on treatment success with a mandibular repositioning appliance. Journal of Clinical Sleep Medicine. 2009; 5(3): p. 198-204.

### Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

Continuous positive air pressure (CPAP) is the main therapeutic option in patients with OSA.
The patients referred to the Orofacial Pain Clinic for MAD therapy will be recruited for this study,. These patients have not been able to tolerate previous therapeutic options.

Back to Top

### Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Information will be obtained via questionnaires and RedCad survey.
Sleep study results will be obtained from HST provided to patients.
All the information will be collected via paper questionnaires and forms and Redcap survey, and then transferred to an Excel spreadsheet (password protected) that will be stored in a desktop computer (UK Kentucky Clinic room E234; UK Healthcare system;N037632 ), to which initially only Dr. Fernanda Yanez Regonesi will have access. In the spreadsheet, the patients will be identified with consecutive numbers (MAD1-MAD36) along with their dates of birth. After the recruitment period, the statistician (Dr. Ian Boggero) and Dr. Isabel Moreno Hay will have access to the de-identified spreadsheet. All the paper questionnaires and forms will be stored (for back up and data verification if needed) in a keyed locker only accessible to Dr. Fernanda Yanez Regonesi and Dr. Isabel Moreno Hay. Data will be retained for 6 years after study closure and deleted using UK Policy(s) A13-050 and A05-055.
- UKHC share folder. IT will be contacted to create a UK healthcare HIPAA complaint shared folder to share de-identified information with Dr. Sara Pasha. The raw data from the sleep studies will be uploaded here for her to perform analysis from her office.
Special protection:
- Desk computer at the Orofacial Pain Clinic (UK Kentucky Clinic room E234; UK Healthcare system; N037632): This computer will

be used for data entry, collection and analysis. Accessible only by Dr. Fernanda Yanez Regonesi (protected with password). Files (Microsoft Word and Excel) will be protected with a password.
- Digital scanner and computer: 3Shape TRIOS® 3 (at the OFPC). The scans will be obtained and sent to the lab from the computer that is associated to the scanner. Access is password protected.
The side effects associated with the oral appliance therapy for the management of obstructive sleep apnea are minimum and not associated with life-threatening events. The patient will be informed regarding the potential side effects associated with the oral appliance therapy for OSA, and will be instructed to contact us (via phone call or email) if they have any question or if they notice any side effects. The incidence of side effects will be assessed at each follow-up visit.
Active contact with the participants for recruitment, scheduling and clinical visits, will be carried out by Dr. Fernanda Yanez Regonesi and/or Dr. Isabel Moreno Hay. All the information will be collected via paper questionnaires and forms, and then transferred to an Excel spreadsheet (password protected) that will be stored in a desktop computer (Kentucky Clinic room E234; UK Healthcare system; N037632), to which initially only Dr. Fernanda Yanez Regonesi will have access. In the spreadsheet, the patients will be identified with consecutive numbers (MAD1-MAD36) along with their dates of birth. After the recruitment period, the statistician (Dr. Ian Boggero) and
Dr. Isabel Moreno Hay will have access to the de-identified spreadsheet. All the paper questionnaires and forms will be stored (for back up and data verification if needed) in a key locked locker (at Orofacial Pain Clinic, UK Kentucky Clinic, Room E234). Data will be retained for 6 years after study closure and deleted using UK Policy(s) A13-050 and A05-055, under the responsibility of the primary investigator (Dr. Fernanda Yanez Regonesi).

**UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?**

◉ Yes ○ No

Back to Top

### Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

There will be no reward or payment for participation in the study. However, patients will be encouraged to complete the daily questionnaires by offering a raffle ticket for entry into a drawing for a one hundred dollar gift card. The more diaries completed the more raffle tickets they will accumulate. At the end of the study, one raffle ticket will be drawn to determine which participant receives the $100 gift card. The raffle will be divided among the 36 participants. If each participant completes at least 1 entry, there will be 1/36 chances of receiving the gift card. Chances depend on amount of questionnaires completed among participants. We will calculate a percentage of the completed studies, 100% completed studies will translate into 35 entries, that will be the maximum entries anyone can receive. If someone participates 15 weeks the % will be calculated based on a maximum of 35 entries.
The device and sleep study will be provided at no cost to the participants.

### Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is “standard” – and thus not covered by the sponsor/study – unless you tell them.

The device and the home sleep study will be provided at no cost for the participants. The participant will be responsible for the expenses for commuting to the research location (parking costs, gas, transportation, etc).

### Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

This study is considered not greater than minimal risk (Risk Level 1), so should not require a data and safety monitoring board. The DSM Plan will consist in that the PI will be responsible for the study to review safety, progress, compliance, quality, and data integrity on an ongoing basis.
The clinical component of this research will be carried out by Dr. Fernanda Yanez Regonesi. At each study visit, the patient will be

asked via questionnaire about the occurrence of any side effect or problems related to the appliance (see previous description in protocol). Additionally, the patient will be instructed to contact us if any harm has occurred (contact information will be provided). If the occurrence of any of the expected minor side effects previously described is reported by the patient, or detected by Dr. Fernanda Yanez Regonesi during the examination, the patient will be notified, and asked if they want to continue in the study. No other measures will be taken. If any injury, or potential injury, is detected, the PI will be informed immediately in order to establish the most beneficial management for the patient. Additionally, the IRB will be notified. If required, the participation of the subject in the study will end, and it will be recommended that the patient continue with standard of care treatments. Additionally, the research team will meet every six months, to discuss study progress, or sooner if any concerns arise prior to a scheduled meeting. This is an independent study and there is no conflict of interest nor economic profit for any of the members of the research team.

### Future Use and Sharing of Research Data

If the results of this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

Can use the stored information to learn more about the management of obstructive sleep apnea with mandibular advancement devices or research additional scientific questions.
All of the study information collected via paper questionnaires and forms will be transferred to an Excel spreadsheet that will be stored on a password protected desktop computer at the Orofacial Pain Clinic. Dr. Fernanda Yanez Regonesi will maintain the Excel spreadsheet and will assign a study number (ie, MAD1- MAD36).
All the paper questionnaires and forms will be stored for back up and data verification, if needed, in a keyed locker. This locker is only accessible to Dr. Fernanda Yanez Regonesi and Dr. Isabel Moreno Hay.
We will take careful steps to keep information confidential. Researchers will store identifiable information, in password-protected database. For data analysis, we will remove name or other direct identifiers from your information. We will label the information with a code and will store the key separately from the master code list. Only select staff will have access to the list that links the code to you. All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or samples collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent. Once you give your permission to have your de-identified information or samples stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

**Recruitment and Consent:**

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

**Cultural and Language Consultants:**

The PI is required to identify someone to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who will act as the cultural consultant for your study.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

**Local Requirements:**

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the “Additional Information/Materials” section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

**HIV/AIDS Research:** There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

**PI-Sponsored FDA-Regulated Research**

Is this an investigator-initiated study that:

Back to Top

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

**HIPAA**

**0 unresolved comment(s)**

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form
☐ HIPAA Waiver of Authorization

Attachments

**STUDY DRUG INFORMATION**

**0 unresolved comment(s)**

**The term drug may include:**

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

**Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?**

○ Yes ◉ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ○ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

| | | | |
|---|---|---|---|
| Sponsor: ☐ | | Held By: | |
| Investigator: ☐ | | Held By: | |
| Other: ☐ | | Held By: | |

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

**Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.**

Attachments

**STUDY DEVICE INFORMATION**

**0 unresolved comment(s)**

**A DEVICE may be a:**

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

**Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?**

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

**LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW**

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

**Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.**

Attachments

**RESEARCH SITES**

**0 unresolved comment(s)**

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☐ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK

sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Attachments

B) Is this a multi-site study for which **you are the lead investigator or UK is the lead site**? ○ Yes ◉ No

If YES, describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

C) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

**RESEARCH ATTRIBUTES**

**0 unresolved comment(s)**

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

| | For additional requirements and information: |
|---|---|
| ☐ Academic Degree/Required Research | • Cancer Research (MCC PRMC)<br>• Certificate of Confidentiality (look up "Confidentiality/Privacy...")<br>• CCTS (Center for Clinical and Translational Science) |
| ☐ Alcohol/Drug/Substance Abuse Research | • Clinical Research (look up "What is the definition of....) |
| ☐ Biological Specimen Bank Creation (for sharing) | • Clinical Trial |
| ☐ Cancer Research | • Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...") |
| ☐ CCTS-Center for Clinical & Translational Science | • Collection of Biological Specimens (look up "Specimen/Tissue Collection...") |
| ☐ Certificate of Confidentiality | • Community-Based Participatory Research (look up "Community-Engaged...") |
| ☑ Clinical Research | • Data & Safety Monitoring Board (DSMB)<br>*For Medical IRB: Service Request Form for CCTS DSMB |
| ☐ Clinical Trial - Phase 1 | |
| ☑ Clinical Trial | • Data & Safety Monitoring Plan<br>• Deception*<br>*For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process" |
| ☐ Collection of Biological Specimens for internal banking and use (not sharing) | |
| ☐ Community-Based Participatory Research | |
| ☐ Deception | |
| ☐ Educational/Student Records (e.g., GPA, test scores) | |
| ☐ Emergency Use (Single Patient) | • Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)<br>• Genetic Research (look up "Specimen/Tissue Collection...")<br>• Gene Transfer<br>• HIV/AIDS Research (look up "Reportable Diseases/Conditions")<br>• Screening for Reportable Diseases [E2.0000] (PDF)<br>• International Research (look up "International & Non-English Speaking")<br>• NIH Genomic Data Sharing (GDS) Policy (PDF)<br>• Planned Emergency Research Involving Waiver of Informed Consent*<br>*For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process" |
| ☐ Gene Transfer | |
| ☐ Genetic Research | |
| ☐ GWAS (Genome-Wide Association Study) or NIH Genomic Data Sharing (GDS) | |
| ☐ Human Cells, Tissues, and Cellular and Tissue Based Products | |
| ☐ Individual Expanded Access or Compassionate Use | |
| ☐ International Research | |
| ☐ Planned Emergency Research Involving Exception from Informed Consent | |
| ☐ Recombinant DNA | |
| ☐ Registry or data repository creation | |
| ☐ Stem Cell Research | |
| ☐ Suicide Ideation or Behavior Research | |
| ☐ Survey Research | |
| ☐ Transplants | |
| ☐ Use, storage and disposal of radioactive material and radiation producing devices | • Use, storage and disposal of radioactive material and radiation producing devices |
| ☐ Vaccine Trials | |

**FUNDING/SUPPORT**

**0 unresolved comment(s)**

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☑ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

American Academy of Dental Sleep Medicine

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

American Academy of Dental Sleep Medicine

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

## OTHER REVIEW COMMITTEES

**0 unresolved comment(s)**

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

**Additional Information**

- ☐ Institutional Biosafety Committee
- ☐ Radiation Safety Committee
- ☐ Radioactive Drug Research Committee
- ☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
- ☐ Graduate Medical Education Committee (GME)
- ☐ Office of Medical Education (OME)

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

**ADDITIONAL INFORMATION/MATERIALS**

**0 unresolved comment(s)**

Do you want specific information inserted into your approval letter? ○ Yes ◉ No

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

- ☐ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☐ Other Documents

Protocol/Other Attachments

NOTE: Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

**If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.**

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

**SIGNATURES (ASSURANCES)**

**0 unresolved comment(s)**

All IRB applications require additional assurances by a Department Chairperson or equivalent (DA), and when applicable, a Faculty Advisor or equivalent (FA). This signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. The person assigned as DA *should not* also be listed in the Study Personnel section, and the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, refer to "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

## Required Signatures:

| First Name | Last Name | Role | Department | Date Signed | |
|---|---|---|---|---|---|
| Melvyn | Yeoh | Department Authorization | Dentistry Oral Health Science | 08/22/2022 02:26 PM | View/Sign |
| Fernanda | Yanez Regonesi | Principal Investigator | Dentistry Oral Health Science | 08/17/2022 04:44 PM | View/Sign |

**Department Authorization**

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

**SUBMISSION INFORMATION**

**0 unresolved comment(s)**

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed. Otherwise your submission for IRB review and approval cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and you will receive a message to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Your protocol has been submitted.

| | Document Type | File Loaded | Document Description | File Size | Modified By | Mod Date |
|---|---|---|---|---|---|---|
| | ApprovalLetter | ApprovalLetter.pdf | | 0.079 | jchine2 | 10/17/2022 2:51:43 PM |
| | Stamped Consent Form | 80084_Informed ConsentHIPAA Combined Form_clean version Oct 2022.pdf | | 0.344 | jchine2 | 10/17/2022 2:51:43 PM |
| | Informed ConsentHIPAA Combined Form | 80084_Informed ConsentHIPAA Combined Form_clean version Oct 2022.pdf | Informed Consent/HIPAA-clean form | 0.298 | fya232 | 10/12/2022 2:52:27 PM |
| | InformedConsent_HighlightedChanges | 80084_Informed ConsentHIPAA Combined Form_highlighted track changes Oct 2022.pdf | informed consent highlighted changes | 0.641 | fya232 | 10/12/2022 2:51:58 PM |
| | ResearchProcedures | table 1 updated.pdf | table 1 updated | 0.124 | fya232 | 10/12/2022 2:11:31 PM |
| | ResearchProcedures | clinical procedures updated.pdf | Updated clinical procedures | 0.152 | fya232 | 10/12/2022 2:10:27 PM |
| | ResearchProcedures | clinical procedures.JPG | Clinical procedures/timeline | 0.125 | fya232 | 8/9/2022 11:34:31 AM |
| | ResearchProcedures | Table 1.JPG | Table 1 | 0.186 | fya232 | 8/9/2022 11:33:28 AM |
| | DataCollection | Follow-up package.pdf | Follow up package | 0.315 | fya232 | 8/9/2022 11:30:43 AM |
| | DataCollection | Screening package.pdf | Screening package | 0.240 | fya232 | 8/9/2022 11:21:40 AM |
| | DataCollection | Inbetweenqx.pdf | In between questionnaire | 0.038 | fya232 | 8/9/2022 11:21:27 AM |
| | DataCollection | Outcome package.pdf | Outcome package | 0.138 | fya232 | 8/9/2022 11:21:06 AM |
| | DataCollection | Baseline Package.pdf | Baseline package | 0.373 | fya232 | 8/9/2022 11:20:43 AM |

# Protocol Changes



**FutureUseAndSharing** changed by fya232 on 10/12/2022 2:31:53 PM

Can use the stored information to learn more about the management of obstructive sleep apnea with mandibular advancement devices or research additional scientific questions. ¶
All of the study information collected via paper questionnaires and forms will be transferred to an Excel spreadsheet that will be stored on a password protected desktop computer at the Orofacial Pain Clinic. Dr. Fernanda Yanez Regonesi will maintain the Excel spreadsheet and will assign a study number (ie, MAD1- MAD36). ¶
All the paper questionnaires and forms will be stored for back up and data verification, if needed, in a keyed locker. This locker is only accessible to Dr. Fernanda Yanez Regonesi and Dr. Isabel Moreno Hay. ~~Data will be retained for 6 years after study closure, then properly destroyed according to the University of Kentucky guidelines.~~ ¶
We will take careful steps to keep information confidential. Researchers will store identifiable information, in password-protected database. For data analysis, we will remove name or other direct identifiers from your information. We will label the information with a code and will store the key separately from the master code list. Only select staff will have access to the list that links the code to you. ¶
All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or samples collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent. Once you give your permission to have your de-identified information or samples stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

**StudyPopulation** changed by fya232 on 9/19/2022 9:12:02 AM

No specific population will be targeted in terms of sex/gender or racial/ethnic background. The age range considers patients over 18 until 80 y.o~~-~~ with a diagnosis of obstructive sleep apnea (OSA). Participants will be recruited from the consecutive patients referred to the Orofacial Pain Clinic for the management of OSA with a MAD. ¶
Inclusion criteria will be: ¶
- English speaker ¶
- >18 years old ¶
- Diagnosed by sleep physician with obstructive sleep apnea diagnosis with AHI=5. ¶
- Equal or more than 2 voiding/night at baseline ¶
- 8 or more teeth per arch upon clinical exam ¶
- Range of mandibular protrusion (anteroposterior mandibular mobility) of 5 mm or more. ¶
- Consent to participate in the study ¶
¶
The exclusion criteria will include: ¶
- Central sleep apnea, concomitant sleep disorder (i.e. insomnia, narcolepsy, restless legs syndrome, rapid eye movement sleep behavior disorder). ¶
- Prostate/kidney problems (urological disease: (eg overactive bladder, benign prostate hyperplasia) ¶
- Pregnancy ¶
- Heart failure ¶
- Use of diuretics ¶
- Diabetes ¶
- Parkinson's disease ¶
- Dementia ¶
- Combination therapy for the management of OSA (CPAP + MAD) ¶
- Upon clinical examination: periodontal disease (>4 mm on periodontal with bleeding on probing and visual signs of periodontal inflammation), tooth horizontal mobility >1 mm, vertical mobility, unfavorable crown to root ratio; open cavities, fractured restorations or ongoing dental treatment. ¶
- Exaggerated gag reflex. ¶
- Lack of coordination or dexterity. ¶
- Previous history of MAD use.

**Expedited Categories XPCategory5** changed by fya232 on 10/11/2022 11:30:43 AM

~~N~~Y

**Expedited Categories XPCategory7** changed by fya232 on 10/11/2022 11:30:43 AM

~~N~~Y

**Funding/Support PrivateFoundAssociation** changed by fya232 on 9/19/2022 2:53:43 PM

Y

**PI Contact Information Degree** changed by fya232 on 9/19/2022 9:09:14 AM

DDS, MS

**Project Information IsSubEnrollDataSpecimen** changed by fya232 on 9/19/2022 9:10:43 AM

~~N~~Y

**Research Description Background** changed by fya232 on 9/19/2022 2:11:22 PM

Nocturia is defined by the International Continence Society as “waking up at least two times for voiding”, while polyuria refers to the production of an abnormally large volume of urine at night (1). Ten percent of the general population over 20 years old suffers from nocturia (2), with increasing prevalence with aging (2-4). The nocturnal awakenings are frequently associated with sleep loss, daytime fatigue, and mood disturbance (5-7) Studies have demonstrated a significant negative impact in patient’s quality of life (QoL) and well-being, with a significant dose-dependent relationship (8). Potential causes associated with nocturia are bladder storage problems, use of diuretics, diabetes, and other medical conditions, such as Parkinson’s disease, dementia, heart failure and sleep disorders (9). ¶
¶
Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway during sleep resulting intermittent hypoxia and hypercapnia (10). A recent systematic review indicated that the prevalence varies between 9-38% in the general population (11). Studies in the literature report a relationship between OSA and nocturia in adults (12, 13). Indeed, studies have found that the rate of nocturia is significantly greater in patients with OSA than in healthy controls. A recent systematic review and meta-analysis reinforced the significant association between OSA and the risk of nocturia (RR = 1.41, 95% CI 1.26–1.59) (14). The prevalence of nocturia in OSA patients varies between 45-70% and is reported to increase with the severity of the OSA (12-15). However, there is still a gap in the understanding of the relationship between urine production and OSA. The relation between OSA and nocturia might be explained by the greater fractional urinary flow and the lower percentage of filtered sodium reabsorption in OSA patients. Other studies proposed that obstructive events along with sustained ventilatory effort generated a negative intrathoracic pressure, thus conducting a false signal of volume overload to the heart. This in turn induces an increase in atrial natriuretic peptide (16) and B-type natriuretic peptide (BNP) secretion, thereby augmenting urinary production by stimulating water and sodium excretion, and inhibiting antidiuretic hormone (ADH) and renin-angiotensin-aldosterone system (2). Another possible explanation is that hypoxia following obstructive events causes oxidative stress, leading to detrusor instability, spontaneous contractions, and reduction in ANP recreation at night (17), thus inducing nocturia. According to Finamore et al. (18), nocturia seems to be significantly associated to intermittent desaturation rather than to severity and length of hypoxia, although sporadic night arousals have also been advocated as responsible for nocturia (19) ¶
¶
Continuous positive airway pressure (CPAP) is the gold standard for the management of OSA. A systematic review and meta-analysis indicated that CPAP therapy results in a statistically significant decrease both in the frequency of nocturia and in the volume of urine associated with it, likely due to a normalization in oxygen desaturation (17). Margel et al. evaluated 97 patients after CPAP treatment and noted a significant improvement in nocturia in all OSA severities, especially in severe cases. Surprisingly, a reduction was already noted after only one night of treatment (20). Another study confirmed the reduction in nocturia and improvement in QoL even after 1 year of treatment with CPAP (21). A recent study compared the effects of CPAP and surgical treatment of OSA on nocturia. Regardless of treatment modality, the mean numbers of voiding per night improved significantly in both group with no difference between groups. This suggests that correcting the OSA might be important for the improvement in nocturia (22) ¶
To the best of our knowledge, to the date no studies have specifically evaluated the management of nocturia with the use of mandibular advancement devices (MAD) in OSA patients. Attali et al. studied the predictors of long-term adherence to MAD, and they noted a significant short-term reduction in nocturia, from 48% to 13% in 3-6 months; however, the treatment was less efficient in the long-term (23). The main limitation of this study was that the results were obtained through telephone survey. ¶
¶
~~Unpublished preliminary data from our research group, which consisted of a retrospective pilot study~~Archieval data from sleep patients at our orofacial pain clinic, revealed that 50% (23/46) of patients presented with nocturia at baseline and demonstrated a significant

decrease in the number of voiding per night up even until the last follow up 1.4±0.4 years later. A limitation ~~of the study wa~~is the lack of second sleep study to assess if these changes were associated with improvement in apnea hypopnea index (AHI) (IRB#46643) . In fact, no literature is available regarding the correlation between changes in nocturia and AHI with MAD use. ¶
¶
References ¶
1) Weiss JP, Monaghan TF, Epstein MR, Lazar JM. Future Considerations in Nocturia and Nocturnal Polyuria. Urology. 2019;133S:34-42 ¶
2) Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep. 2004;27(1):139-44. ¶
3) Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol. 2010;184(2):440-6. ¶
4) Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. J Urol. 2006;175(2):596-600. ¶
5) Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int. 2003; 92:948–54. ¶
6) Ohayon MM. Nocturnal awakenings and comorbid disorders in the American general population. J Psychiatr Res. 2008; 43:48–54. ¶
7) Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT, Lose G. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population. BJU Int 2006 Sept, 98(3):599-604. ¶
8) Tikkinen KA, Johnson TM, 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol. 2010;57(3):488-96. ¶
9) Aydur E. DR. Medical Conditions Associated with Nocturia. In: Weiss M, FACS, J, editor. Nocturia: Springer, New York; 2012. ¶
10) Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. 2020;323(14):1389-400. ¶
11) Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017;34:70-81. ¶
12) Saldias Penafiel F, Salinas Rossel G, Cortes Meza J, Farias Nesvadba D, Penaloza Tapia A, Aguirre Mardones C, et al. [Gender differences in clinical features and performance of sleep questionnaires in adults with obstructive sleep apnea syndrome]. Rev Med Chil. 2019;147(10):1291-302. ¶
13) Basoglu OK, Tasbakan MS. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. Sleep Breath. 2018;22(1):241-9. ¶
14) Zhou J, Xia S, Li T, Liu R. Association between obstructive sleep apnea syndrome and nocturia: a meta-analysis. Sleep Breath. 2020;24(4):1293-8. ¶
15) Krieger J, Petiau C, Sforza E, Delanoe C, Hecht MT, Chamouard V. Nocturnal poliuria is a symptom of obstructive sleep apnea. Urol Int 1993;50:93-7. ¶
16) Sillanpaa M PP, Kero P. . Prevalence of headache at preschool age in an unselected child population. . Cephalalgia. 1991;11:239-42. ¶
17) Wang T, Huang W, Zong H, Zhang Y. The Efficacy of Continuous Positive Airway Pressure Therapy on Nocturia in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. Int Neurourol J. 2015;19(3):178-84. ¶
18) Finamore P, Scarlata S, Laudisio A, Galdi F, Pipita ME, Chiarella I, et al. Occurrence of nocturia is not mediated by nocturnal hypoxia length and severity in patients with sleep-disordered breathing. Sleep Med. 2018;45:69-73. ¶
19) Witthaus MW, Nipa F, Yang J et al., Bladder oxidate stress in sleep apnea contributes to detrusor instability and nocturia. J Urol 2015; 193:1692-9 ¶
20) Margel D, Shochat T, Getzler O, Livne PM, Pillar G. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. Urology. 2006;67(5):974-7. ¶
21) Vrooman OPJ, van Balken MR, van Koeveringe GA, van Kerrebroeck PVA, Driessen L, Schouten LJ, et al. The effect of continuous positive airway pressure on nocturia in patients with obstructive sleep apnea syndrome. Neurourol Urodyn. 2020;39(4):1124-8. ¶
22) Deger M, Ozgur S, Kuleci S et al., Comparison of the Effect of Continuous Positive Airway Pressure and Surgical Treatment of Obstructive Sleep Apnea Syndrome on Nocturia, Journal of Urological Surgery, 2021, 8(2), 106-110. ¶
23) Attali V, Chaumereuil C, Arnulf I, Golmard JL, Tordjman F, Morin L, et al. Predictors of long-term effectiveness to mandibular repositioning device treatment in obstructive sleep apnea patients after 1000 days. Sleep Med. 2016;27-28:107-14.

**Research Description DataCollection** changed by fya232 on 10/12/2022 2:15:17 PM

Data will be obtained using paper questionnaires and Redcap survey. ¶
- Demographic information regarding age, race, gender and comorbidities will be extracted from the initial questionnaire and general medical history (Screening package) -SOC ¶
- The self-reported use of MAD will be assessed at each follow-up visit via questionnaire on a five-point checklist (number hours per night and nights per week) (Follow up package). - SOC ¶
- Daytime sleepiness will be evaluated at baseline and each follow up: Epworth sleepiness scale (ESS) (Screening and follow up package) - SOC ¶
- Snoring, observed apneic events, morning headache, daytime sleepiness and daytime fatigue, will be assessed via questionnaire

using a numerical rating scale (NRS) (to be extracted from screening and follow up package). - SOC ¶
- Sleep parameters including: AHI, RDI, minimum and average oxygen saturation will be extracted from the initial and final HST provided. - research procedure ¶
- The presence of signs and/or symptoms of TMD will be assessed following the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Symptom Questionnaire and Examination Form (follow up package). - SOC ¶
- Sleep quality (will be assessed at baseline and when performing the home sleep apnea test, using the Pittsburgh Sleep Quality Index (PSQI) questionnaire). (baseline and outcome package) - research procedure ¶
- Patients subjective perception of improvement will be assessed at each follow up visit using visual analog scale (follow up package). - SOC ¶
- Incidence of side effects will be assessed at each follow-up visit, including subjective increase/decrease salivation (measure via questionnaire using numeric rating scale), increase/decrease teeth mobility, changes in occlusal contacts (measured in habitual occlusion using 0.01 mm occlusal registration strips (ARTUS corporation®) (follow up package). - SOC ¶
- Severity of urinary symptoms will be evaluated at baseline with the American urological association symptom index (baseline package) - research procedure ¶
- Fatigue will be evaluated at baseline with fatigue assessment scale. (baseline package)- research procedure ¶
- Insomnia will be evaluated at baseline and at second sleep study with insomnia severity index. (baseline and outcome package)- research procedure ¶
- Stress will be evaluated at baseline with perceived stress scale. (baseline package)-research procedure ¶
- Anxiety will be evaluated at baseline with general anxiety disorder 7 scale. (baseline package)-research procedure ¶
- Health related quality of life will be evaluated at baseline and at second sleep study with quality of life scale. (baseline and outcome package)-research procedure ¶
¶
Between follow up visits, participants will receive a daily dairy to complete via Redcap automated server to evaluate for: (in between package)-research procedure ¶
- Hours of sleep ¶
- Compliance with MAD use (hours of use). ¶
- Frequency of nocturnal voiding ¶
- Intake of fluids before bedtime.

**Research Description Payment** changed by fya232 on 10/12/2022 2:15:17 PM

There will be no reward or payment for participation in the study. However, patients will be encouraged to complete the daily questionnaires by offering a raffle ticket for entry into a drawing for a one hundred dollar gift card. The more diaries completed the more raffle tickets they will accumulate. At the end of the study, one raffle ticket will be drawn to determine which participant receives the $100 gift card. The raffle will be divided among the 36 participants. If each participant completes at least 1 entry, there will be 1/36 chances of receiving the gift card. Chances depend on amount of questionnaires completed among participants. We will calculate a percentage of the completed studies, 100% completed studies will translate into 35 entries, that will be the maximum entries anyone can receive. If someone participates 15 weeks the % will be calculated based on a maximum of 35 entries. ¶
The device and sleep study will be provided at no cost to the participants.

**Research Description Payment** changed by fya232 on 9/19/2022 2:52:18 PM

There will be no reward or payment for participation in the study. However, patients will be encouraged to complete the daily questionnaires by offering a raffle ticket for entry into a drawing for a one hundred dollar gift card. The more diaries completed the more raffle tickets they will accumulate. At the end of the study, one raffle ticket will be drawn to determine which participant receives the $100 gift card. The raffle will be divided among the 36 participants. If each participant completes at least 1 entry, there will be 1/36 chances of receiving the gift card. Chances depend on amount of questionnaires completed among participants. ¶
The device and sleep study will be provided at no cost to the participants.

**Research Description PotentialRisks** changed by fya232 on 9/19/2022 2:11:22 PM

Side effects related to the participation in the study are not greater than standard of care. ¶
When explaining the consent form, the patient will be informed regarding the potential side effects associated to the oral appliance therapy for OSA, and will be instructed to contact us (via phone call or email) if they have any question or if they notice any side effects. The incidence of side effects will be assessed at each follow-up visit, including subjective increase/decrease salivation (measured via questionnaire using numeric rating scale), increase/decrease teeth mobility, changes in occlusal contacts (measured in habitual occlusion using 0.01 mm occlusal registration strips (ARTUS corporation®). Problems related to the appliance will be measured at each follow up visit, considering appliance breaks, cracks, deformation, retention changes, wear, discoloration changes and calculus

accumulation. ¶
The use of the home sleep apnea test machine does not represent significant risks for the subjects. The nasal canula and tape to be used are one-time use, and each patient will be provided with a new one. The machine will be disinfected once it is returned, and will stay at least one day without use between different patients. The potential risk to participating in an at home sleep study is disrupted sleep and possible cheek irritation if they decide to use medical tape to secure the nasal tubing to keep it in place overnight. Participants might find it challenging to sleep with the additional equipment, so sleep disturbances might occur. ¶
In 1995 the American Academy of Sleep Medicine (AASM) approved the use of oral appliances for the management of OSA. Since then, the use of oral appliances has significantly increased and today MADs are widely recognized as the main alternative treatment to CPAP therapy (1-2). ¶
This study will be the first to formally test if the use of MAD can improve nocturia – a finding which has already been demonstrated with CPAP therapy. Further, despite the promising results of MADs, in clinical practice it is still difficult to know when to stop titrating/ adjusting the appliance because self-reporting of changes in symptoms is not a reliable method of determining success with treatment (3). This study will test if changes in nocturia could be used as a specific and sensitive criteria for determining how to titrate sleep appliances. The clinical application of this study would help in the determination of clinical guidelines for the titration of MAD. Additionally, it would provide another treatment outcome for MAD equivalent to CPAP therapy. Our study is innovative because it will utilize longitudinal daily diary methodology to define an existing gap in the literature linking MAD and nocturia, and it will do so with a multidimensional team with a wide array of clinical and research experience. ¶
¶
There is a risk that someone could get access to the stored information. In spite of the security measures and safeguards we will use, we cannot guarantee that your identity will never become known. ¶
¶
RISKS: Oral appliance therapy is associated with short and long-term side effects. In relation to the short-term adverse effects, usually mild and transient, it has been reported hypersalivation, dry mouth, dental pain, gingival irritation, and temporomandibular disorders. Regarding the long-term side effects, we can expect: temporomandibular disorders, occlusal changes including: a reduction in overjet, overbite, and development of posterior open bite among others. ¶
BENEFITS vs. RISKS: This therapeutic option can be associated with minimal and non life-threatening risks, and the risks to subjects are reasonable in relation to the anticipated benefits. The mandibular advancement devices are considered as a standard of care option for the management of OSA. ¶
¶
1) J. Durán-Cantolla, R. Crovetto-Martínez, M. Alkhraisat et al., “Efficacy of mandibular advancement device in the treatment of obstructive sleep apnea syndrome: a randomized controlled crossover clinical trial,” Medicina Oral Patología Oral Y Cirugia Bucal, vol. 20, no. 5, pp. e605–e615, 2015. ¶
2) S. Serra-Torres, C. Bellot-Arcís, J. M. Montiel-Company, J. Marco-Algarra, and J. M. Almerich-Silla, “Effectiveness of mandibular advancement appliances in treating obstructive sleep apnea syndrome: a systematic review,” The Laryngoscope, vol. 126, no. 2, pp. 507–514, 2016. ¶
3) Almeida FR, Parker JA, Hodges JS, Lowe AA, Ferguson KA. Effect of a titration polysomnogram on treatment success with a mandibular repositioning appliance. Journal of Clinical Sleep Medicine. 2009; 5(3): p. 198-204.

**Research Description ResearchMaterialsRecordsPrivacy** changed by fya232 on 9/19/2022 2:52:18 PM

Information will be obtained via questionnaires and RedCad survey. ¶
Sleep study results will be obtained from HST provided to patients. ¶
All the information will be collected via paper questionnaires and forms and Redcap survey, and then transferred to an Excel spreadsheet (password protected) that will be stored in a desktop computer (UK Kentucky Clinic room E234; UK Healthcare system;N037632 ), to which initially only Dr. Fernanda Yanez Regonesi will have access. In the spreadsheet, the patients will be identified with consecutive numbers (MAD1-MAD36) along with their dates of birth. After the recruitment period, the statistician (Dr. Ian Boggero) and Dr. Isabel Moreno Hay will have access to the de-identified spreadsheet. All the paper questionnaires and forms will be stored (for back up and data verification if needed) in a keyed locker only accessible to Dr. Fernanda Yanez Regonesi and Dr. Isabel Moreno Hay. Data will be retained for 6 years after study closure and deleted using UK Policy(s) A13-050 and A05-055. ¶
- UKHC share folder. IT will be contacted to create a UK healthcare HIPAA complaint shared folder to share de-identified information with Dr. Sara Pasha. The raw data from the sleep studies will be uploaded here for her to perform analysis from her office. ¶
Special protection: ¶
- Desk computer at the Orofacial Pain Clinic (UK Kentucky Clinic room E234; UK Healthcare system; N037632): This computer will be used for data entry, collection and analysis. Accessible only by Dr. Fernanda Yanez Regonesi (protected with password). Files (Microsoft Word and Excel) will be protected with a password. ¶
- Digital scanner and computer: 3Shape TRIOS® 3 (at the OFPC). The scans will be obtained and sent to the lab from the computer that is associated to the scanner. Access is password protected. ¶
The side effects associated with the oral appliance therapy for the management of obstructive sleep apnea are minimum and not associated with life-threatening events. The patient will be informed regarding the potential side effects associated with the oral

appliance therapy for OSA, and will be instructed to contact us (via phone call or email) if they have any question or if they notice any side effects. The incidence of side effects will be assessed at each follow-up visit. ¶
Active contact with the participants for recruitment, scheduling and clinical visits, will be carried out by Dr. Fernanda Yanez Regonesi and/or Dr. Isabel Moreno Hay. All the information will be collected via paper questionnaires and forms, and then transferred to an Excel spreadsheet (password protected) that will be stored in a desktop computer (Kentucky Clinic room E234; UK Healthcare system; N037632), to which initially only Dr. Fernanda Yanez Regonesi will have access. In the spreadsheet, the patients will be identified with consecutive numbers (MAD1-MAD36) along with their dates of birth. After the recruitment period, the statistician (Dr. Ian Boggero) and ¶ Dr. Isabel Moreno Hay will have access to the de-identified spreadsheet. All the paper questionnaires and forms will be stored (for back up and data verification if needed) in a key locked locker (at Orofacial Pain Clinic, UK Kentucky Clinic, Room E234). Data will be retained for 6 years after study closure and deleted using UK Policy(s) A13-050 and A05-055, under the responsibility of the primary investigator (Dr. Fernanda Yanez Regonesi).

**Research Description ResearchProcedures** changed by fya232 on 10/12/2022 2:12:19 PM

The research procedures include: ¶
¶
following the consent process, the participants will complete a battery of baseline screening questionnaires along with psychological questionnaires. A pdf of the questionnaires is included below in data collection attachments (baseline package). Participants will undergo a baseline home sleep study (Alice One Night) to collect the following baseline sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2. ¶
¶
After the delivery of the appliance (SOC), the participants will be scheduled for follow-up visits every 2 weeks during the titration period (SOC). ¶
From baseline until second sleep study, participants will complete a daily dairy of nocturnal voiding frequency, fluid intake before bedtime, hours of sleep and hours of MAD use. Diary will be sent to the participants via automated server (RedCap) every morning. ¶
Typically, once patient complete the titration (SOC) of their appliance, they are referred for a second sleep study. As part of the research procedure, second home sleep study (Alice One Night) will be performed at no cost to the patient. Home sleep study results will be provided to the patients, written and verbal instructions of use will be provided to the participants, and they will complete a final outcome assessment battery (available below in data collection package). ¶
Sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2 will be extracted from initial and second home sleep study (HST). Scoring will be performed by trained sleep physician (Dr. Sara Pasha). ¶
¶
The improvement in nocturia with the management of OSA with mandibular advancement appliance with be evaluated. For that, each participant will be their own control on a “wait-list” design type of study. Daily diaries with nocturnal voiding obtained from baseline until delivery of the appliance will be used as control. ¶
Participants will be classified as responders in terms of nocturia when the average voiding per night is less than 2 as recorded by the daily diaries over the preceding 2-week period. The percentage of responders in terms of nocturia will be quantified at which follow up. ¶
Efficacy of MAD will be assessed by comparing the AHI values pre- and post-sleep study with MAD. Patients will be classified as responders if they have 50% improvement in AHI. ¶
Other polysomnographic values like time spent under 90% SpO2 and minimum SpO2 will also be compared and used as predictors of response. ¶
Changes in fatigue, quality of life, and insomnia severity index will be assessed. ¶
The participation in this research will last between six to fifteen weeks depending on the time for each patient's individual improvement. The initial visit will last 45-60 minutes, and the follow-up visits will take about 30-45 minutes. After participation in the study is completed, the participants will be allowed to keep the MAD and TAP® AM aligner. ¶
¶
All other procedures are standard of care, table 1 shows all the procedure. In red at highlighted the research procedure. Black is SOC. Same for clinical procedure table, red shows research procedure, black SOC.

**Research Description ResearchProcedures** changed by fya232 on 10/12/2022 2:00:15 PM

~~At their initial visit, participants will be asked to complete the following~~The research procedures include: ¶
¶
following the consent process, the participants will complete a battery of baseline screening questionnaires along with psychological questionnaires ~~(see table 1). ¶~~
. A pdf of the questionnaires is included below (baseline package). Participants will undergo a baseline home sleep study (Alice One Night) to collect the following baseline sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2. ~~The participants will be scheduled for digital impression (3Shape TRIOS®) of upper and lower arches, and protrusive registration at 50% of the maximal anatomical protrusion. ¶~~

~~All patients will be fitted with an FDA approved MAD Somnodent Classic (Somnomed ®). ¶~~
~~At the device delivery appointment, we will fabricate an aligner for the patient to wear for 10 minutes each morning after waking and removing the Somnodent Classic (Somnomed ®). oral appliance. The morning aligner (TAP® AM Aligner) is a record of the patient's habitual bite (the way the teeth come together normally) that will reposition their mandible back into its normal position. It is part of the standard of care for patients undergoing mandibular advancement (MAD) therapy. The aligner is constructed from a thermoplastic material that, when heated, can be molded by hand onto the upper or lower teeth. Once the thermoplastic material is molded around the teeth, they will be instructed to bite down while it is still soft. This will create indentations for the opposing teeth and allow them to be set at their 'normal' and proper biting position. After the molded thermoplastic material has hardened at normal temperature, it is removed from the mouth and trimmed, if needed. ¶~~
~~After the delivery of the appliance, the participants will be scheduled for follow-up visits every 2 weeks during the titration period. As part of standard/routine clinical care at their follow-up visits, intra and extra-oral physical examination will be performed, along with evaluation of the appliance, follow-up battery questionnaire (see table1) and titration of the appliance as needed. From baseline until second sleep study, participants will complete a daily dairy of nocturnal voiding frequency, fluid intake before bedtime, hours of sleep and hours of MAD use. Diary will be sent to the participants via automated server (RedCap) every morning. Titration will be completed once they are classified as responders in terms of nocturia or maximum anatomical protrusive movement is reached. Titration is performed following manufacturers intructions, with the calibration screw system, advancing 1mm per side each visit. At this time, a ¶~~
¶
After the delivery of the appliance (SOC), the participants will be scheduled for follow-up visits every 2 weeks during the titration period (SOC). ¶
From baseline until second sleep study, participants will complete a daily dairy of nocturnal voiding frequency, fluid intake before bedtime, hours of sleep and hours of MAD use. Diary will be sent to the participants via automated server (RedCap) every morning. ¶
Typically, once patient complete the titration (SOC) of their appliance, they are referred for a second sleep study. As part of the research procedure, second home sleep study (Alice One Night) will be performed~~. HST~~ at no cost to the patient. Home sleep study results will be provided to the patients, written and verbal instructions of use will be provided to the participants, and they will complete a final outcome assessment battery (~~table 1~~available below). ¶
Sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2 will be extracted from initial and second home sleep study (HST). Scoring will be performed by trained sleep physician (Dr. Sara Pasha). ¶
¶
The improvement in nocturia with the management of OSA with mandibular advancement appliance with be evaluated. For that, each participant will be their own control on a "wait-list" design type of study. Daily diaries with nocturnal voiding obtained from baseline until delivery of the appliance will be used as control. ¶
Participants will be classified as responders in terms of nocturia when the average voiding per night is less than 2 as recorded by the daily diaries over the preceding 2-week period. The percentage of responders in terms of nocturia will be quantified at which follow up. ¶
Efficacy of MAD will be assessed by comparing the AHI values pre- and post-sleep study with MAD. Patients will be classified as responders if they have 50% improvement in AHI. ¶
Other polysomnographic values like time spent under 90% SpO2 and minimum SpO2 will also be compared and used as predictors of response. ¶
Changes in fatigue, quality of life, and insomnia severity index will be assessed. ¶
¶
The participation in this research will last between six to fifteen weeks depending on the time for each patient's individual improvement. The initial visit will last 45-60 minutes, and the follow-up visits will take about 30-45 minutes. After participation in the study is completed, the participants will be allowed to keep the MAD and TAP® AM aligner.~~ Visits after second sleep study will be part of standard of care.~~

**Research Description ResearchProcedures** changed by fya232 on 9/19/2022 2:11:22 PM

At their initial visit, participants will be asked to complete the following baseline screening questionnaires along with psychological questionnaires (see table 1). ¶
Participants will undergo a baseline home sleep study (Alice One Night) to collect the following baseline sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2. The participants will be scheduled for digital impression (3Shape TRIOS®) of upper and lower arches, and protrusive registration at 50% of the maximal anatomical protrusion. ¶
All patients will be fitted with an FDA approved MAD Somnodent Classic (Somnomed ®). ¶
At the device delivery appointment, we will fabricate an aligner for the patient to wear for 10 minutes each morning after waking and removing the Somnodent Classic (Somnomed ®). oral appliance. The morning aligner (TAP® AM Aligner) is a record of the patient's habitual bite (the way the teeth come together normally) that will reposition their mandible back into its normal position. It is part of the standard of care for patients undergoing mandibular advancement (MAD) therapy. The aligner is constructed from a thermoplastic material that, when heated, can be molded by hand onto the upper or lower teeth. Once the thermoplastic material is molded around the teeth, they will be instructed to bite down while it is still soft. This will create indentations for the opposing teeth and allow them to be set at their 'normal' and proper biting position. After the molded thermoplastic material has hardened at normal temperature, it is removed from the mouth and trimmed, if needed. ¶

After the delivery of the appliance, the participants will be scheduled for follow-up visits every 2 weeks during the titration period. As part of standard/routine clinical care at their follow-up visits, intra and extra-oral physical examination will be performed, along with evaluation of the appliance, follow-up battery questionnaire (see table1) and titration of the appliance as needed. From baseline until second sleep study, participants will complete a daily dairy of nocturnal voiding frequency, fluid intake before bedtime, hours of sleep and hours of MAD use. Diary will be sent to the participants via automated server (RedCap) every morning. Titration will be completed once they are classified as responders in terms of nocturia or maximum anatomical protrusive movement is reached. Titration is performed following manufacturers intructions, with the calibration screw system, advancing 1mm per side each visit. At this time, a second home sleep study (Alice One Night) will be performed. HST results will be provided to the patients, written and verbal instructions of use will be provided to the participants, and they will complete a final outcome assessment battery (table 1). ¶
Sleep parameters: AHI, minimum SpO2, time spent under 90% SpO2 will be extracted from initial and second home sleep study (HST). Scoring will be performed by trained sleep physician (Dr. Sara Pasha). ¶
¶
The improvement in nocturia with the management of OSA with mandibular advancement appliance with be evaluated. For that, each participant will be their own control on a “wait-list” design type of study. Daily diaries with nocturnal voiding obtained from baseline until delivery of the appliance will be used as control. ¶
Participants will be classified as responders in terms of nocturia when the average voiding per night is less than 2 as recorded by the daily diaries over the preceding 2-week period. The percentage of responders in terms of nocturia will be quantified at which follow up. ¶
Efficacy of MAD will be assessed by comparing the AHI values pre- and post-sleep study with MAD. Patients will be classified as responders if they have 50% improvement in AHI. ¶
Other polysomnographic values like time spent under 90% SpO2 and minimum SpO2 will also be compared and used as predictors of response. ¶
Changes in fatigue, quality of life, and insomnia severity index will be assessed. ¶
¶
The participation in this research will last between six to fifteen weeks depending on the time for each patient's individual improvement. The initial visit will last 45-60 minutes, and the follow-up visits will take about 30-45 minutes. After participation in the study is completed, the participants will be allowed to keep the MAD and TAP® AM aligner. Visits after second sleep study will be part of standard of care.

**Research Description Resources** changed by fya232 on 9/19/2022 2:11:22 PM

a) Staff and personnel: ¶
- Dr. Fernanda Yanez Regonesi (PI): participation in the recruitment of patients, clinical procedures and data collection. ¶
- Dr. Isabel Moreno Hay DDS PhD (Co-Investigator): participation in the recruitment of patients, clinical procedures and data collection. ¶
- Dawn Dawson, RDH, CCRC: Project Assistance/Support - Manage OnCore and enrollment spreadsheet ¶
- Dr. Ian Boggero PhD: Co investigator, and biostatistician. ¶
- Dr. Sara Pasha MD: co investigator, evaluation of sleep studies. ¶
b) Facilities: ¶
- Primary center: Orofacial Pain clinic (UK Kentucky Clinic. 740 S. Limestone, Second Floor, Wing C, Room E214, Lexington, KY ¶ 40536) ¶
¶
c) Resources: ¶
- Desk computer at the Orofacial Pain Clinic (Kentucky Clinic room E234; UK Healthcare system; N037632): This computer will be used for data entry, collection and analysis. It is accessible only by Dr. Fernanda Yanez Regonesi (protected with password). Files (Microsoft Word and Excel) will also be protected with a password. ¶
- Excel file will be shared via UKHC secured folder with other investigators and it will be password protected. ¶
- UKHC share folder. IT will be contacted to create a UK healthcare HIPAA complaint shared folder to share de-identified information with Dr. Sara Pasha. The raw data from the sleep studies will be uploaded here for her to perform analysis from her office. ¶
- Land line phone (at the OFPC): will be the primary way of communication with participants. 859-323-8491, alternatively 859-323-5500. ¶
- Email of Dr. Fernanda Yanez Regonesi (PI) (fya232@uky.edu) may be used as an alternative to the land line phone if it is needed to communicate with the participants. ¶
- Digital scanner and computer: 3Shape TRIOS® 3 (at the OFPC). The scans will be obtained and sent to the lab from the computer that is associated with the scanner. ¶
- Home sleep apnea test (HSAT): Alice NightOne, Phillips Respironics©. ¶
- EPIC

## Study Personnel Changes:

No Changes

There are no recorded changes to study personnel.

**Protocol Type** Comment by Joanne Hines - ORI to IRB/PI on 10/3/2022 11:34:17 AM

Minor Revisions

IF CHANGES TO THE DOCUMENT(S) HAVE BEEN REQUESTED, PLEASE NOTE: Revisions submitted without being highlighted will not be forwarded for review but returned to the PI. Also, submit one clean copy of the form(s), i.e., do not highlight or underline this copy. If approved, the consent form(s) will be returned to you with a valid "IRB Approval" stamp.

1. Standard of care/SOC needs to be better understood in research procedures, consent has numerous corrections needed and additional expedited categories added based on your answers. Any additional revisions will depend on the PIs answers to the questions on research procedures and SOC. It isn't clear, the IRB doesn't think the titration is part of the research, but the consent reads like it is. Efficacy of the MAD is not being researched rather the effects of its utilization on nocturia? If titration schedule is same for MAD regardless of your study, then that information is SOC and not part of the research study. If it's not the same, then you are using the device differently and additional information needs to be included.

2. Expedited Categories – which categories are used is dependent on PIs responses to these revisions/questions. It appears categories 1, 5, and 7 should be marked.

3. Informed Consent – revise using the 9/19 consent form – please remove oldest version (as it has already been modified once).

Page 1
-add "FDA" language here about devices (FDA listed under authorization section).

Page 2
-Not Qualify -add over 80 years? What about lack of coordination or dexterity? Not mentioned in research description/RD.
-end of page - looks like may be missing something after evaluating - "Those symptoms will be evaluated using questionnaires, and we will perform a clinical exam, evaluating that is part of SOC"?

Page 3
-Risk/Discomforts - first sentence true (SOC)? What "nasal tubing"? Add "breach of confidentiality".

Page 4
-remove empty space.

Page 5
-bullets - not "testing" or "asking" any of these kinds questions are you? Add below "To ensure the study is conducted properly, officials from the University of Kentucky (FDA?) may look at or copy pertinent portions of records that may identify you".

Page 6
-Rewards - questionnaires? Diaries? PI also needs to include odds of winning (it appears the math is off if daily between 5-15 "weeks" of daily entries).
-Remove "Incidental findings" - none noted in RD.
-include Clinical Trials template language.
-Future use - should match what subjects are told in the consent form. (e.g. - if PI will let other researchers have access to the data for "other projects").

Page 8
-Authorization - it appears PI will be accessing medical records after obtaining informed consent? Use and share - FDA? Expedited category 5 would then appear to apply.

4. Please confirm PI has a relationship with the subjects – if this is incorrect, a HIPAA Waiver of Authorization may be needed to identify patients.

5. Research Description/RD –

a. Recruitment-how will you make sure patients are not unduly influenced. Can they receive MAD treatment regardless of your study?

b. Procedures / Data Collection & Research Materials - not clear which questionnaires are considered SOC. Please indicate which are

for actual research study in table 1 and clinical procedures table. Maybe make bold to differentiate? It's the IRBs understanding these patients will receive the MAD treatment regardless of your study. You are conducting surveys during their normally scheduled office visits (or at least normal cadence) and (they would normally come in for adjustments every 2 weeks as SOC?) so the IRB thinks the "research" is the surveys and review of medical/dental records. Everything else is SOC?

c. Available Alternative Opportunities/Treatments - will they receive MAD therapy if they are not included in your study?

d. Future Use and Sharing of Research Data - will data be made available to secondary researchers? If so how? How are data withdrawn from repository?

**Protocol Type** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:54:06 PM

Comments are added in sections, thanks

**Protocol Type** Comment by Joanne Hines - ORI to PI on 8/26/2022 12:27:55 PM

ORI screening comments/recommendations – the IRB has not yet seen the application.

-Expedited Categories – for category 1B research (see instructions/Study Device Information) section and provide the "Study Device Form" for IRB review – if the device section doesn't apply – attach form under "Additional Information/Materials" section instead. It also appears expedited category 7 also applies (questionnaires, etc.).

- PI Contact Information – add your rank/degrees.

-Project Information – change "No" to "Yes" for "After approval, will the study be open to enrollment of new subjects or new data/specimen collection?" question - the study has not yet begun.

-Subject Demographics – ages 18-80?
-Study Population – ages 18 and older? Please note your "cut off" age will be the number listed in boxes at top of section (18-80).

-Informed Consent Process – not about recruiting here, but consent process – how is eligibility determined – by record review (or are these the PIs patients)? Generally, subjects sign informed consent before screening for inclusion/exclusion criteria, but this is not clear.

-Informed Consent –

Page 1
-use lay language/explanations throughout (polysomnographic, titrate, nocturia should be explained in first paragraph for example). Spell out acronyms before each one (or example - MAD is not explained until key reasons to participate, CPAP).
-depending on responses - FDA language may need to be added IN addition to Clinical Trail language.
-remove "Dr." before you name (on first page) - afterwards can leave as Dr.

Page 2
-not qualify - recruitment is not clear - will some inclusion/exclusion criteria be determined prior to screening participants in person? These should only list those not "pre-determined".
-amount of time - according to 1 data collection tool - it takes 45 mins. In addition, please add the following (see template) - The total amount of time... is __x__ over 5-15 weeks (including daily diary entries).
-asked to do - explain what "registration" of their bite means. What "clinical exam"? Standard of care OR for research purposes only (if for research purposes, expedited category 4 may also apply)?

Page 3
-mid first paragraph - "final" set of questionnaires? Not clear who their "sleep physician" is - primary care? Stated differently throughout.
-not greater than SOC? Not clear what is SOC (vs research activities). Several questionnaires appear to be intake forms for the clinic?
-risks in research description should be added here - risk of the research (breach of confidentiality for example) not what is done as SOC.
-benefit - add "personal" before benefit in first sentence.
-cost - add "2" or "both" before the sleep studies (plural isn't it)?

Page 4

-who will see-top of page - third sentence - identifying information should be protected "before completion of study visits". See attached guidance for creating a crosswalk - believe you are using, but identifiable data should be protected during data collection until link/code is removed. This section also appears to conflict with other sections - data destroyed but option 3 for future use? Remove extra bullets - 3 only, not 6. FDA regulated? See device comments - the IRB will determine if the study meets minimal risk/expedited review. REDCap template language is missing.

Page 5
-rewards - perhaps reword "questionnaires" or add "daily REDCap questionnaires" instead? The odds of winning should be given to participants.
-Future use - conflicts - should be option 1 or 2 - destroying (and must also be addressed in research description if saving/sharing).

Page 6
-future use option 3 should be removed.

Page 7
-add zip code under revocation section.

Page 8
-removed "or, if applicable, *research subject's legal representative" - legally authorized representative were not included - all subjects must consent for themselves.

-Research Description –

-Background – what is the IRB protocol number for the pilot study – the IRB may ask.
-Objectives – how will Aim 3 data be collected? Are you asking these questions from participants?
-Subject Recruitment Methods & Privacy – so patients have OSA with MAD to be included? Isn't use of the MAD the "research"? If these are your patients – how will you minimize undue influence?
-Procedures – testing the "efficacy" of the MAD? Are the Alice One Night, 3Shape TRIOS and TAP AM Aligner all FDA approved and being used in their approved manner? How is the MAD "titrated"? This may need to be added to device form.
-Data Collection & Research Materials - differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. It would appear several of these questionnaires are standard of care for incoming OSA patients? Which are specifically for research purposes? If that is correct, expedited category 5 may also apply (medical/dental record review). Believe you mean "diary" not "dairy" here.
-Resources –Pasha and all other are listed as study personnel so would have access to any/all data (reason added as SP) - why would only PI have access to data? Computers encrypted?
-Potential Risks & Benefits – testing the device – "This study will be the first to formally test if the use of MAD can improve nocturia…"? Add breach of confidentiality.
-Records, Privacy, and Confidentiality – again only PI has access?
-Payment – please clarify the "odds" of winning (also add to informed consent).
-Data & Safety Monitoring – add "DSMP" to attribute section. The IRB will determine if the plan is adequate.
-PI – Sponsored FDA-regulated – unknown

-Study Device Information – unknown

-Attributes – add "DSMP".

-Funding / Support – check "Private Foundation/Association"?

**Expedited Categories** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 9:08:33 AM

-Expedited Categories – for category 1B research (see instructions/Study Device Information) section and provide the "Study Device Form" for IRB review – if the device section doesn't apply – attach form under "Additional Information/Materials" section instead. It also appears expedited category 7 also applies (questionnaires, etc.).

I am not sure I follow the comment, the medical device is cleared and approved by the FDA and is being used in according with its cleared approved labeling for the management of obstrucitve sleep apnea. Please clarifiy what you want me to add here and I am happy to do so.

**Project Information** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 9:10:42 AM

Solved the comment, changed no for yes in last question

**PI Contact Information** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 9:09:12 AM

Resolved PI contact information

**Subject Demographics** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 9:12:12 AM

clarify the age

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:11:19 PM

and how the others will have access

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:11:04 PM

Records, Privacy, and Confidentiality – again only PI has access?
It says that after recruitment period the statistician Ian Boggero will have acess to the de-identified information

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:08:10 PM

-Potential Risks & Benefits – testing the device – “This study will be the first to formally test if the use of MAD can improve nocturia…”? Add breach of confidentiality.

Was added

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:06:28 PM

-Resources –Pasha and all other are listed as study personnel so would have access to any/all data (reason added as SP) - why would only PI have access to data? Computers encrypted?

Sara Pasha will be evaluating the sleep studies and is explained for the raw data of the sleep studies will be shared to her.
Data in desk computer will only be accessible for PI since if password protected and yes encrypted with UK security.

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:04:01 PM

Data Collection & Research Materials - differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. It would appear several of these questionnaires are standard of care for incoming OSA patients? Which are specifically for research purposes? If that is correct, expedited category 5 may also apply (medical/dental record review).
I can certainly do this, many of the questionnaires and clinical examination are part of the standard of care. We added just a couple for completeness of the study, let me know how do you want me to introduce this information.

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:00:47 PM

Procedures – testing the “efficacy” of the MAD?  Are the Alice One Night, 3Shape TRIOS and TAP AM Aligner all FDA approved and being used in their approved manner? How is the MAD “titrated”? This may need to be added to device form.

Yes they are all FDA approved and used in the approved menas.

MAD is titrated 1 mm per side every visit using the calibration screws.

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 1:53:06 PM

Subject Recruitment Methods & Privacy – so patients have OSA with MAD to be included? Isn't use of the MAD the "research"? If these are your patients – how will you minimize undue influence?

I think is not clear. Patient to be managed with mandibular advacement device, the previous us of MAD was exclusion criteria

**Research Description** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 1:24:56 PM

In regards to question for Aim 3 and how will it be collected, yes, those questions will be asked to the participants

**Informed Consent** Comment by Joanne Hines - ORI to IRB/PI on 10/17/2022 2:50:10 PM

ORI removed previous "outdated" ICFs (from 8/22 and 9/22) - FYI only

**Informed Consent** Comment by Fernanda Yanez Regonesi - PI to PI on 10/12/2022 2:54:55 PM

please find all the answer to each question under question

1. Standard of care/SOC needs to be better understood in research procedures, consent has numerous corrections needed and additional expedited categories added based on your answers. Any additional revisions will depend on the PIs answers to the questions on research procedures and SOC. It isn't clear, the IRB doesn't think the titration is part of the research, but the consent reads like it is. Efficacy of the MAD is not being researched rather the effects of its utilization on nocturia? If titration schedule is same for MAD regardless of your study, then that information is SOC and not part of the research study. If it's not the same, then you are using the device differently and additional information needs to be included.
Research procedure section was updated to better understand what is research procedure. You will now see explained. Also updated data collection and research material to make it clear what is SOC and what is a research material. Table 1 and clinical procedure was updated, showing in red research procedure. Did not delete previous attachment to have clean copy all in black if its needed.

2. Expedited Categories – which categories are used is dependent on PIs responses to these revisions/questions. It appears categories 1, 5, and 7 should be marked.
Categories added as recommended.

3. Informed Consent – revise using the 9/19 consent form – please remove oldest version (as it has already been modified once).
Added highlighted-tracked changes version as well as cleaned version.
Page 1
-add "FDA" language here about devices (FDA listed under authorization section).
It is not and FDA device study. We are not gathering information regarding safety and effectiveness of the device. This is all SCO.
Please see updated list of research procedure,
Page 2
-Not Qualify -add over 80 years? What about lack of coordination or dexterity? Not mentioned in research description/RD.
It was listed under study population.
-end of page - looks like may be missing something after evaluating - "Those symptoms will be evaluated using questionnaires, and we will perform a clinical exam, evaluating that is part of SOC"?
Was corrected. It was as typo. Evaluation not evaluating.
Page 3
-Risk/Discomforts - first sentence true (SOC)? What "nasal tubing"? Add "breach of confidentiality".
First sentence is true. Most of the side effects come from MAD use which is SOC. Nasal tubing refers to the tube canula use during sleep study, Breach of confidentiality was already added, I have highlighted for your convenience.
Page 4
-remove empty space.
Thanks, something is going on with my word document, creating weird space.
Page 5
-bullets - not "testing" or "asking" any of these kinds questions are you? Add below "To ensure the study is conducted properly, officials

from the University of Kentucky (FDA?) may look at or copy pertinent portions of records that may identify you".
Added the sentence, however FDA is not part of the study as stated before. It is not and FDA device study. We are not gathering information regarding safety and effectiveness of the device. This is all SCO. Please see updated list of research procedure and data collection section.
Page 6
-Rewards - questionnaires? Diaries? PI also needs to include odds of winning (it appears the math is off if daily between 5-15 "weeks" of daily entries).
Added. We will calculate a percentage of the completed studies, 100% completed studies will translate into 35 entries, that will be the maximum entries anyone can receive. If someone participates 15 weeks the % will be calculated based on a maximum of 35 entries.
-Remove "Incidental findings" - none noted in RD.
Removed.
-include Clinical Trials template language.
Is already there, I have highlighted for your convenience.
-Future use - should match what subjects are told in the consent form. (e.g. - if PI will let other researchers have access to the data for "other projects").
Updated

Page 8
-Authorization - it appears PI will be accessing medical records after obtaining informed consent? Use and share - FDA? Expedited category 5 would then appear to apply.
Category 5 was added. As stated before FDA is not applicable.
4. Please confirm PI has a relationship with the subjects – if this is incorrect, a HIPAA Waiver of Authorization may be needed to identify patients.
Patients are referred to the orofacial pain clinic, they will only be eligible after initial screening exam.
5. Research Description/RD –

a. Recruitment-how will you make sure patients are not unduly influenced. Can they receive MAD treatment regardless of your study?
Mad is standard of care, after study criteria eligibility is evaluated, it will be offered as an option for qualifying patient. Compensation or no cost treatment will only be offered after explaining study and obtaining verbal consent.
b. Procedures / Data Collection & Research Materials - not clear which questionnaires are considered SOC. Please indicate which are for actual research study in table 1 and clinical procedures table. Maybe make bold to differentiate? It's the IRBs understanding these patients will receive the MAD treatment regardless of your study. You are conducting surveys during their normally scheduled office visits (or at least normal cadence) and (they would normally come in for adjustments every 2 weeks as SOC?) so the IRB thinks the "research" is the surveys and review of medical/dental records. Everything else is SOC?
Have separated and clarify what is research procedure and data collection section.
c. Available Alternative Opportunities/Treatments - will they receive MAD therapy if they are not included in your study?
Yes, MAD therapy is still SOC. Study will be offered as an option.
d. Future Use and Sharing of Research Data - will data be made available to secondary researchers? If so how? How are data withdrawn from repository?
Updated according to template option 2. Will not keep identifiers.

**Informed Consent** Comment by Joanne Hines - ORI to IRB/PI on 9/22/2022 9:38:52 AM

Please disregard the first consent attached on 8/17 - PI had updated at ORIs recommendations - use the last version attached 9/19. PI asked for it sent back to her again to attach/remove but she didn't remove older version.

**Informed Consent** Comment by Joanne Hines - ORI to PI on 9/19/2022 3:15:51 PM

PI emailed me - returning to PI - she will remove old ICF and attach newest version (for the IRB).

**Research Attributes** Comment by Joanne Hines - ORI to IRB/PI on 9/22/2022 8:43:44 AM

E-IRB V4 updates - DSMP/B no longer in this section as "Attribute" - fyi only

**Research Attributes** Comment by Fernanda Yanez Regonesi - PI to PI on 9/19/2022 2:53:32 PM

how do I add DSMP here?

**KEY INFORMATION FOR**

# Improvement in Nocturia with MAD and Changes in Polysomnographic Values:

We are asking you to choose whether or not to volunteer for a research study about the effectiveness of oral appliance therapy for nocturia in obstructive sleep apnea patients. We will be evaluating 1) if mandibular advancement devices (MAD) are associated with a reduction in nocturia (waking up to go to the bathroom at night) and 2) if this response to therapy is associated with improvement in obstructive sleep apnea. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

## WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn if oral appliance therapy can improve nocturia in patients with obstructive sleep apnea, a finding which has already been demonstrated with continuous positive airway pressure (CPAP) therapy. Your participation in this research will last between five (5) to fifteen (15) weeks.

## WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

The use of mandibular advancement devices (MAD) is a therapeutic option for the management of obstructive sleep apnea (OSA). This study will test if changes in nocturia could be used as a specific and sensitive criterion for determining how to reach a therapeutic level of advancement (titrate) of the sleep appliances. The clinical application of this study would help in the determination of clinical guidelines for the titration of MAD. Additionally, it would provide another treatment option that would be equivalent to CPAP therapy. For a complete description of benefits, refer to the Detailed Consent

## WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

Oral appliance therapy using a mandibular advancement device may be associated with short and long-term side effects. The possible short-term adverse effects include hyper-salivation, dry mouth, dental pain, gingival irritation, and temporomandibular disorders. The long-term side effect can include temporomandibular disorders and occlusal changes (the way your teeth come together) among others. For a complete description of risks, refer to the Detailed Consent.

## DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

## WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Fernanda Yanez Regonesi DDS, MS of the University of Kentucky, Department Orofacial Pain at 859-323-5500.

If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

## DETAILED CONSENT:

**ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?**

- Under the age of 18 or over the age of 80.

- Have other diagnosed sleep disorder (i.e. central sleep apnea, insomnia, narcolepsy, restless legs syndrome, rapid eye movement sleep behavior disorder).

- Have medical conditions such as: prostate/kidney problems (urological disease: (i.e. overactive bladder, benign prostate hyperplasia), heart failure, diabetes, dementia, Parkinson's disease.

- Are pregnant.

- Use diuretics.

- Currently using another device or combination therapy for the management of OSA (i.e. positive air pressure (PAP) therapy or positional therapy).

- Have periodontal disease ("gum disease") or other oral condition that may not be compatible with this therapy.

- Have an exaggerated gag reflex.

- Have lack of coordination or dexterity.

**WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?**

The research procedures will be conducted at the Orofacial Pain Clinic (UK Kentucky Clinic). You will need to come between three (3) and eight (8) times during the study. Each of those visits will take about thirty (30) to forty- five (45) minutes. Additionally, you will have to complete a daily morning dairy that will take less than 1 minute. The total amount of time is approximately 4 and half hours over 5-15 weeks (including daily dairy entries).

**WHAT WILL YOU BE ASKED TO DO?**

Initially, you will be asked to complete a screening questionnaire that asks about the severity of your urinary symptoms, fatigue, insomnia, stress, anxiety, your sleep quality and how the nocturia is impacting your quality of life. The estimated completion time is 20 minutes.

You will be provided with a home sleep study device to do at home to obtain baseline sleep parameters.
We will then obtain digital scans of your upper and lower teeth (no x-ray/radiation involved), and a bite registration (of your upper and lower teeth). Those records will be sent to the laboratory for the fabrication of your oral appliance. Once we receive the appliance, we will contact you to schedule an appointment for the delivery.

At the delivery appointment, we will fabricate a morning aligner. The morning aligner (TAP® AM Aligner) is a record of your habitual bite (the way your teeth come together normally) that you will use for around ten (10) minutes in the morning after you wake up and remove the Somnomed® Somnodent Classic oral appliance. The morning aligner will reposition your mandible back into its normal position. It is part of the standard of care for patients undergoing mandibular advancement (MAD) therapy. The aligner is constructed from a thermoplastic material that, when heated, can be molded by hand onto the upper or lower teeth. Once the thermoplastic material is molded around your teeth, you will be instructed to bite down while it is still soft. This will create indentations for the opposing teeth and allow them to be set at their 'normal' and proper position. After the molded thermoplastic material has hardened at normal temperature, it is removed from the mouth and trimmed, if needed.

Your follow-up appointments will be scheduled every two (2) weeks to evaluate improvement of the symptoms of your sleep apnea; such as: daytime tiredness, snoring, apneic events, and others. We will also evaluate you for any possible side effects. Those symptoms will be evaluated using questionnaires, and we will perform a clinical exam, evaluation that is part of standard of care.

In between follow up visits, we will ask you to complete a morning diary that should take 1 minute to complete. It will ask how many hours you slept, how many hours did you use your appliance, how many times you woke up to urinate and any intake of fluids before bedtime. This diary will be of importance since once we notice improvement in your nocturia over the preceding 2-week period, we will ask you to complete a one-night at-home sleep apnea test. We will provide you with instructions on how to operate the machine, and provide a printed copy of the manufacturer's protocol. Additionally, we will provide our contact number in case you have any questions or concerns. An appointment will be scheduled in the following 2-3 days to return the machine, at that time your participation in the study will be completed and you will be asked to complete a final set of questionnaires to evaluate your sleep quality, insomnia and quality of life (10 minutes completion time). After your participation in the study you will have the option of keeping the Somnomed® Somnodent Classic oral appliance. If maximum benefits are not achieved during the study period you will continue to receive care but as part of standard of care. If you do not reach successful management of your obstructive sleep apnea at 100% of advancement or if you are unable to tolerate the advancements, you will be referred back to your sleep physician to consider other treatment options.

**WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**

Side effects related to the participation in the study are not greater than standard of care.

Possible side effects of MAD include: Increased salivation, dry mouth, sore teeth, sore jaws, jaw joint pain, gum or cheek irritation, loosening of teeth, movement of teeth, bite changes, aspiration or swallowing of a tooth, a dental instrument, or dental material, dislodgement of ill-fitting dental crowns or restorations, and other possible problems that your dentist cannot predict. Tooth movement or bite changes may or may not be fully reversible should they occur.

The use of the home sleep apnea test machine does not represent significant risk. The potential risk to participate in a home sleep study is disrupted sleep and possible cheek irritation if you need to use medical tape on the nasal tubing to keep it in place overnight. Participants might find it challenging to sleep with the additional equipment, so sleep disturbances might occur.

There is a risk that someone could get access to the stored information. In spite of the security measures and safeguards we will use, we cannot guarantee that your identity will never become known.

There is always a chance that any medical treatment can harm you. The research treatments/procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect.

**WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?**

You might or might not receive any personal benefit from taking part in this study. However, some people have experienced improvement regarding the symptoms of obstructive sleep apnea when treated with mandibular advancement devices. If you take part in this study, information learned may help others with your condition.

**IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?**

If you do not want to take part in the study, we strongly recommend you to discuss other therapeutic options for the management of your obstructive sleep apnea, with your sleep physician, that may be beneficial for you.

**WHAT WILL IT COST YOU TO PARTICIPATE?**

You and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you would normally receive for any conditions you may have. These are costs that are considered medically necessary and will be part of the care you receive even if you do not take part in this study.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.

The Somnomed® Somnodent Classic oral appliance, TAP® AM morning Aligner, both at-home sleep study and follow up visits will be provided at no cost to you. You will be responsible for transportation and parking costs for study visits.

**WHO WILL SEE THE INFORMATION THAT YOU GIVE?**

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. Your information will be accessed only by authorized members of this study team. Before completion of your study visits, your identifying information will be replaced with a random code. After the study ends, your records will be kept for six years then destroyed using an acceptable system provided by the healthcare system of the University of Kentucky.

Additionally, at the end of your participation in our study we will offer to send a report to your sleep physician, including progress notes and results of the sleep study performed as part of this study.
You should know that in some cases we may have to show your information to other people. For example, the law may require or permit us to share your information with:

- a court or agencies, if you have a reportable disease/condition;
- authorities, such as child or adult protective services, if you report information about a child or elder being
- abused;
- authorities or a mental health professional if you pose a danger to yourself or someone else (e.g. suicidal thoughts).

To ensure the study Is conducted properly, officials of the University of Kentucky may look at or copy pertinent portions of records that identify you.

**CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?**

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.
If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.
The investigators conducting the study may need to remove you from the study. You may be removed from the study if:

- you are not able to follow the directions,
- we find that your participation in the study is more risk than benefit to you, or
- the agency paying for the study chooses to stop the study early for a number of scientific reasons.

**ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?**

You may take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should discuss this with the investigator/your doctor before you agree to participate in another research study while you are in this study.

**WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?**

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Dr. Fernanda Yanez Regonesi DDS, MS at 859-323-5500 immediately.
Dr. Fernanda Yanez Regonesi DDS, MS will determine what type of treatment, if any, is best for you at that time. It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.
Medical costs related to your care and treatment because of study-related harm

- may be paid by your insurer if you are insured by a health insurance company (you should ask your insurer if you have any questions regarding your insurer's willingness to pay under these circumstances);
- may be paid by Medicare or Medicaid if you are covered by Medicare or Medicaid (If you have any questions regarding Medicare/Medicaid coverage you should contact Medicare by calling 1-800-Medicare (1-800-633-4227) or Medicaid 1-800-635-2570.).

A co-payment/deductible may be needed by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be costly.

You do not give up your legal rights by signing this form.

**WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?**

You will receive 1 raffle ticket for each daily RedCap questionnaires you complete between your follow up visits. All raffle tickets will be entered into a drawing for a one hundred- dollar (100$) gift card. The more questionnaires you complete, the more raffle chances you will receive, you and other 35 participants will be entered into the raffle. You will not receive any other reward or payment for taking part in the study. Percentage (%) of the completed questionnaires will be calculated, and the maximum of entries will be 35. EG: 15 weeks participants will be adjusted based on completion rate, 100% equals 35 entries.

**WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?**

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

**WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?**

Do you give permission for us to contact you about research results that are determined to be important to you/your family's health?

☐ Yes ☐ No Initials_____

You may also withdraw your consent to be contacted with information about research results or incidental findings by sending a written request to Fernanda Yanez Regonesi, DDS, MS, at Kentucky Clinic, E214, 740 South Limestone. Lexington, KY (phone number: 859-323-5500).

**WILL WE CONTACT YOU WITH INFORMATION ABOUT PARTICIPATING IN FUTURE STUDIES?**

The research staff would like to contact you in the future with information about participating in additional studies. If so, it will be limited to three (3) times per year.

Do you give your permission to be contacted in the future by Dr. Fernanda Yanez Regonesi or Dr. Isabel Moreno Hay regarding your willingness to participate in future research studies?

☐ **Yes** ☐ **No** **Initials**_____

**WHAT ELSE DO YOU NEED TO KNOW?**

If you volunteer to take part in this study, you will be one (1) of about thirty six (36) participants at the University of Kentucky.
The American Academy of Dental Sleep Medicine is providing a research grant for this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**STORING AND SHARING YOUR INFORMATION FOR FUTURE USE:**

All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or samples collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent. Once you give your permission to have your de-identified information or samples stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

**AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION**

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

**Your health information that may be accessed, used and/or released includes:**

- Demographic information (gender, age, comorbidities).
- Medical history related to study.
- Clinical records.
- Sleep study results.

**The Researchers may use and share your health information with:**

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies when required by law;
- University of Kentucky representatives;
- Health systems outside of UK for which you have a patient relationship;
- Your primary physician will be contacted if the researcher, in the course of the project, learns of a medical condition that needs immediate attention.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information may still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

**After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:**

- Send a written letter to Dr. Fernanda Yanez Regonesi (Kentucky Clinic, E214, 740 South Limestone. Lexington, KY, 40536-0284). to inform her of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

You will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you may have the right to access the information.
The use and sharing of your information has no time limit.

**If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the ORI/IRB between business hours of 8 am and 5 pm EST, Monday- Friday at 859- 257-9428 or toll free at 1-866-400-9428**

## INFORMED CONSENT SIGNATURES

**This consent includes the following:**

- **Key Information Page**
- **Detailed Consent**

**You will receive a copy of this consent form after it has been signed.**

_____ _____

**Signature of research subject** **Date**

_____

**Printed name of research subject**

_____ _____ _____

Printed name of [authorized] person obtaining informed consent and HIPAA authorization Date

Statistical Analysis

We have run an interim analysis of our data and 100% of our recruited participants had resolution of their nocturia at the first follow up, given the results we have decided you changes our proposed Anova repeated measure across one group and 3 observation point to a pre-post analysis.

Given those changes, a new sample size calculation was performed, with an alpha of .05, and 70% power we need to recruit 10 patients to have a significant treatment effect.

To test the first aim that using an MAD will improve nocturia, we will compute the average nocturia ratings for the month prior to the delivery of the MAD and the first follow up following the delivery of the MAD for each person. A paired sample t-test was conducted.

To test the second aim that nocturia can predict efficacy to MAD in terms of AHI improvement, we conducted a pearson correlation analysis. We compared the change in AHI with the change in nocturia.