

Precision Approach to PPI Therapy in Gastroesophageal reflux disease.

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**UCSD Human Research Protections Program**  
**New Biomedical Application**  
**RESEARCH PLAN**

Instructions for completing the Research Plan are available on the [HRPP website](#).

The headings on this set of instructions correspond to the headings of the Research Plan.

General Instructions: Enter a response for all topic headings.

Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2019

**1. PROJECT TITLE**

Precision Approach to PPI Therapy in Gastroesophageal reflux disease.

**2. PRINCIPAL INVESTIGATOR**

Dr. Rena Yadlapati, Associate Professor of Clinical Medicine, Department of Medicine, Division of Gastroenterology & Hepatology

**3. FACILITIES**

University of California San Diego

**4. ESTIMATED DURATION OF THE STUDY**

5 years.

**5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)**

The clinical and financial burden of patients with suspected reflux associated laryngeal symptoms (RALS) is substantial. RALS is the process where gastro-esophago-pharyngeal reflux contributes to chronic laryngeal symptoms such as sore throat and dysphonia. The objectives of this proposal are to understand the performance of standard of care diagnostic tools and treatment options among suspected RALS.

**6. SPECIFIC AIMS**

**Aim 1:** To determine the ability of novel diagnostic tools to predict symptom-based treatment response in suspected RALS.

Hypothesis: Salivary pepsin will have high sensitivity for response to proton pump inhibitor (PPI); pH-impedance (Z2pH) and esophageal manometry (HRIM) will have high specificity for response to Upper esophageal sphincter assist device (UESAD) in adjunct to PPI.

**Aim 2:** To examine the therapeutic efficacy of UES augmentation in suspected RALS.

Hypothesis: UESAD in adjunct to PPI will result in greater symptom response versus PPI alone.

Approach: We will perform an 8 week clinical trial. Patients with suspected RALS will undergo baseline standard of care diagnostic tests (esophageal manometry (HRIM), pH-impedance (Z2pH)) and research diagnostic test (salivary pepsin) followed by two standard of care therapies (PPI x 4 weeks followed by UESAD in adjunct to PPI x 4 weeks).

**7. BACKGROUND AND SIGNIFICANCE**

Reflux associated laryngeal symptoms (RALS), coined "laryngopharyngeal reflux", occurs when gastro-esophago-pharyngeal reflux contributes to chronic laryngeal symptoms such as throat clearing, sore throat and dysphonia.<sup>1, 2, 23</sup> Over the past 25 years, RALS has been increasingly, and often incorrectly, diagnosed and has emerged as a point of controversy and confusion.

**Critical Healthcare Burden RALS is prevalent, costly, and impairs quality of life** Fifty percent of

patients with laryngeal symptoms are considered to have RALS, although 60% of cases are likely misdiagnosed.<sup>5, 12, 18</sup> The evaluation of suspected RALS entails an average of 10 specialist office visits and 6 diagnostic tests, often without clarity or improved health-related quality of life.<sup>12, 24-26</sup> This redundant and ineffective clinical paradigm contributes to health care costs of \$5,438 per patient, equating to over \$50 billion annually.<sup>12</sup> Thus, there is a critical need for cost-effective and patient-centered approaches to suspected RALS.

### **Clinical Barrier Treatment strategies for suspected RALS are inappropriately generalized**

Patients presenting with laryngeal complaints are heterogeneous in terms of symptom presentation, underlying physiology, and response to treatment. For instance, non-reflux mechanisms commonly generate laryngeal irritation; in these cases acid suppression and anti-reflux therapy is unwarranted.<sup>27</sup> Nonetheless, the majority of patients with suspected RALS are trialed on empiric PPIs over long and oftentimes indefinite intervals. However, fewer than 50% of patients will derive symptom relief with PPI therapy.<sup>13, 14</sup> The low response to PPI therapy relates to the dilutional effect of patients incorrectly considered to have RALS.<sup>28</sup> Furthermore, anti-reflux surgery is often considered, even though anti-reflux surgery is invasive, morbid and costly, and not shown to improve outcomes.<sup>15-17</sup> Thus, effective, safe, and personalized treatment options are needed.

### **Diagnostic Challenges Current diagnostic tools are unable to reliably identify RALS**

A major barrier to identifying true RALS is that traditional diagnostic tools assess anatomic or physiologic properties in isolation, resulting in poor specificity, sensitivity, and prognostic ability

#### **8. PROGRESS REPORT**

Start Date: July 1, 2018 (University of Colorado)

Total enrolled: 17.

Total completed phase 1 (PPI trial): 15

Total completed phase 1 and 2 (PPI trial & UESAD): 8

Currently enrolled: 2

Dropped out or lost to follow-up: 1

#### **9. RESEARCH DESIGN AND METHODS**

**Study Design:** This is a prospective multicenter single-arm non-randomized non-controlled clinical trial registered with clinicaltrials.gov. This study will be performed at the UCSD Medical Campus and the University of Colorado (CU) Medical Campus. With regards to IRB the plan is that University of Colorado will have IRB oversight of the study activities at University of Colorado and UCSD will have IRB oversight of study activities at UCSD. The study has already been active and IRB approved at University of Colorado. (IRB Approval letter from University of Colorado included)

**Setting at UCSD:** Patients will be enrolled from clinics of study investigators that are also the treating provider for the patient. Therefore, the patients are known to the investigator and have a treatment relationship. Inclusion and exclusion criteria are below. The clinics are clinics of Dr. Yadlapati, Dr. Mittal, Dr. Kunkel, Dr. Weissbrod, Dr. Vahabzadeh.

#### **Study Protocol:**

**Screening:** Upcoming clinics staffed by study investigators will be screened by Research Assistant (RA) to identify potential participants. The PI/RA will notify the study investigator MD of patient's eligibility. Once investigator approves, the RA will contact the potential research participant by phone to provide information about the study, determine eligibility, and answer any questions.

**Standard of care Clinic Visit (Visit 1):** At the already scheduled standard of care clinic visit the treating physician will provide the potential participant with information regarding the study. If the patient is interested in participating in the study, the RA will review the study in detail and obtain informed consent. At this time requests for procedures, office visits, and PPI therapy will be placed to the insurance company during this standard of care visit so that the participant understands expense coverage at the onset of study participation.

**Table 1.**

	<b>Standard of Care</b>	<b>Coverage</b>	<b>Visit Time (mins)</b>	<b>Costs to Manage Side Effects</b>
<b>Esophageal manometry</b>	Yes	*Insurance	45	Not anticipated, but would be covered as standard of care by Insurance
<b>pH impedance</b>	Yes	*Insurance	45	Not anticipated, but would be covered as standard of care by Insurance
<b>Questionnaires</b>	Yes	No coverage needed	10	None
<b>Salivary peptest</b>	No	Research costs	2	None
<b>4 week PPI therapy</b>	Yes	*Insurance	Not applicable	Covered as standard of care by Insurance
<b>UES Assist Device</b>	Yes	Typically self-pay; In this study will be a research cost	30 min visit to receive device	Not anticipated, but would be covered as standard of care by insurance

**Standard of Care Diagnostic Evaluation (Visit 2):** Participants will present for standard of care (SOC) diagnostic evaluation.

- Esophageal manometry (will not be repeated if performed within 3 months of study)
- 24 hour pH impedance monitoring (will not be repeated if performed within 3 months of study)
- Patient reported outcome questionnaires: the Gerd questionnaire (GerdQ) and the Reflux Symptom Index. These are validated patient reported outcome instruments, available in English and Spanish.
- Saliva sample collection. Participants will self-induce (non-invasive) 2cc of saliva. Saliva will be collected in a testtube and immediately processed using the Peptest technique to measure pepsin concentration in the saliva. Saliva will not be stored.

Per national guidelines and recommendations, it is SOC to evaluate patients with suspected RALS with esophageal manometry and pH impedance in the motility laboratory. This practice is SOC at UCSD. Therefore, esophageal manometry and pH impedance procedures are expenses that insurance typically covers. Patient reported outcome questionnaires are SOC nationwide and are SOC at our motility lab at UCSD. The time for these SOC procedures combined is 90 minutes. \* in the table indicates that the costs for these SOC procedures are expected to be covered by insurance however there is always a risk that for a certain subject insurance may cover the costs. Therefore, orders for tests will be placed at the first SOC clinic visit and potential costs not covered by insurance will be disclosed to the patient.

Saliva samples will be collected non-invasively via the method described below and analyzed for pepsin concentration. Saliva sample collection will be performed in the motility lab and will add two minutes to the visit time. Salivary peptest is FDA approved though not a SOC procedure at UCSD and therefore the supplies will be covered through research costs and analyses will be performed by the research team. There are no expected costs to manage side effects.

**Standard of Care Drop off of Ph Impedance Catheter (Visit 3):** Participants will return the pH impedance catheter to the motility lab as per SOC. There are no costs associated with this visit.

**PPI Therapy (Weeks 0 to 4):** Following the diagnostic evaluation (visit 2 & 3) the participants will start their 4 week course of PPI therapy. PPI therapy is an FDA approved standard treatment per national guidelines and recommendations, and is the SOC practice at UCSD covered by insurance. The 4 week course of PPI therapy is not an intervention. Per SOC the PPI will be Omeprazole 40mg BID or equivalent; 4 weeks is chosen given reports of esophagitis healing within 2 weeks of PPI.<sup>52</sup> The PPI will be obtained through the participant's pharmacy. The RA will call the participant at week 2 and week 3 of PPI therapy per phone script attached to review appropriate PPI use, adherence, and remind the participant of the mid-treatment visit.

**Mid-Treatment Visit (Visit 4):** After 4 weeks of PPI therapy, the participant will present to a clinic room at Clinical Trial Research Institute for a mid-treatment visit. During this visit the PI/RA will collect a saliva sample non-invasively via the method described below and analyzed for pepsin concentration (2 minutes). The participant will complete a SOC questionnaire to assess clinical outcomes following the PPI therapy. The participant will be given an UES assist device. The PI/RA will fit the UES assist device during this visit and educate the participant on use of the UES assist device. The UES assist device is an FDA approved non-invasive device that is available over the counter for this proposed participant population, and is not considered a research intervention. For this study the research team will provide the UES assist device free of cost to the participant. Therefore, the participant will not incur any costs related to the UES assist device. The visit duration will be 30 minutes.

**UES Assist Device & PPI Therapy (Weeks 5 to 8):** The participant will use the UES assist device and continue their PPI therapy for 4 weeks. The RA will call the participant at week 5 and 7 therapy per phone script attached to review appropriate use, adherence, and remind the participant of the mid-treatment visit.

**Post-Treatment Clinic Visit (Visit 5):** Participants will return to the treating MD's clinic at the end of the 8 week treatment to review test results, symptom response, and discuss next steps as per standard of care. For patients without signs of esophagopharyngeal reflux or GERD, MD will recommend further evaluation by either laryngology, asthma, allergy, and/or behavioral psychology as indicated by standard practice. During this visit, the PI/RA will collect a saliva sample non-invasively via the method described below and analyzed for pepsin concentration (2 minutes). The participant will complete a SOC questionnaire to assess clinical outcomes following the PPI + UES assist device therapy. Participants are permitted to keep the UES assist device if they intend to continue to use it, free of cost.

**Phone Call:** The PI/RA will call the participant at week 20 with basic questions about their progress after the completion of the trial, whether they have continued using the reflux band, and their current

medications to understand long-term outcomes and adherence.

Typically, patients with suspected RALS will see 10 consultants, undergo 6 diagnostic tests, and receive treatment with PPI therapy and a trial of the UES assist device. In this research protocol, patients will present for 2 clinic visits, have diagnostic testing expedited and scheduled all within one setting, and undergo a streamlined therapeutic flow of PPI therapy, and UES assist device within 2 months. This study protocol was specifically designed to entail minimal perturbation to participants, including time and cost, and provide a streamlined and efficient evaluation.

## SPECIFIC AIMS & DATA ANALYSIS

**Aim 1:** To determine the ability of novel diagnostic tools to predict symptom-based treatment response in suspected RALS.

### ***Data Analysis for Aim 1***

Aim 1 analysis will employ a series of receiver operating characteristic (ROC) curves to assess and compare baseline diagnostic tool ability to predict patient-reported symptom response to treatment (positive or negative) at time points B (post-PPI) and C (post-UESAD+PPI). The areas under the ROC curves (AUCs) will be

***Sample Size & Power Calculation:*** At UCSD we plan to enroll 100 participants with an expected <15% dropout, with an overall analytic sample size of  $\geq 80$ . Assuming a minimal response rate of 50% to PPI and 67% to UESAD+PPI, a sample size of 80 and alpha level of 0.05 allows for 90% power to detect an AUC  $\geq 0.70$ . The UESAD+PPI response rate is an extrapolated combined estimate of UESAD alone and PPI alone from our prior data.

**Aim 2:** To examine the therapeutic efficacy of UES augmentation in suspected RALS.

### ***Data Analysis for Aim 2***

Aim 2 analysis will employ a longitudinal mixed model to assess the association between intervention (PPI or UESAD+PPI) and outcome (patient reported symptom response). Longitudinal data will be clustered by participant measured in per month units, and analyzed at 3 study time points: A (baseline), B (post-PPI), and C (post-UESAD+PPI) to specifically compare change from A to B and B to C. Salivary pepsin at time points B and C will also serve as an objectively measured response variable.

***Sample Size & Power Calculation:*** The participants in Aim 1 will be included in Aim 2. With 80 participants, if we conservatively assume that the correlations among the repeated measures is  $\geq 0.5$ , we have 90% power to detect an effect of 0.37SD as measured by the change from A to B and B to C (the effects measured in pilot data exceeds 0.1SD). It is likely that we would also want to estimate change from B to C in the subset of PPI responder and non-responders; we have 90% power to detect a change of 0.37SD (30 participants) or 0.53SD (40 participants).

***Inclusion of Women & Minorities:*** Approximately 25% of women and minorities have RALS. We anticipate that approximately 60% of participants will be women and at least 10% will be minorities.

**UCSD as Prime Grant Holder:** UCSD will be the prime grant holder and University of Colorado will be a second site for participant enrollment and data collection. Data will be collected in REDCap database developed by UCSD REDCap. University of Colorado will be able to enter de-identified data into the REDCap database.

## 10. HUMAN PARTICIPANTS

**Total number of participants to be enrolled at:** UCSD (100), University of Colorado Aurora CO (100). The study has already been active at CU since 2018 and actively enrolling as described in the progress report.

**A. Inclusion:** Age 18-89 years male and female, >8 weeks of symptoms of sore throat, throat clearing, and/or voice hoarseness, naïve to PPI or able to stop for 8 weeks, any ethnic background

**B. Exclusion criteria:** Laryngeal mass lesion on laryngoscopy (if performed); Pregnant; Breastfeeding; Unable to consent in English or Spanish as questionnaires are only validated in English and Spanish; Imprisoned; PPI intolerance; Contraindication to UESAD use per manufacturer guidelines which include:

- Patients with implants or implant parts that reside in the area where UESAD is applied.
- Patients with an implanted pacemaker, implanted cardioverter defibrillator (ICD), vagus nerve stimulator, or other such similar devices implanted in the neck.
- Patients diagnosed with glaucoma.
- Patients who had a malignancy of the neck, including neck surgery.
- Patients that may have an altered mental status including due to the use of sedative drugs or narcotics.
- Patients with carotid artery disease, thyroid disease, a history of cerebrovascular disease, or any disorder of connective tissues (e.g., Marfan's Syndrome or Ehlers-Danlos Syndrome).
- Patients who use nocturnal NIV machines such as CPAP or BiPAP.

## 11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

**How will participants be identified for recruitment?** The research assistant (RA)/PI will screen eligible patients coming in for evaluation in the clinic, endoscopy unit and motility lab that are patients of study investigators. The RA/PI will notify study investigators/treating MDs if eligible participant meeting inclusion criteria is identified. RA will keep a password protected screening list stored in a secure server separate from research data. This will protect identifiers from improper use and disclosure. A partial HIPAA waiver will be used for the minimal risk record review because identifying and contacting thousands of potential subjects would not be feasible for a medical record review where results would not change care the individuals already would have received, and waiver will not adversely affect the rights of welfare of the subjects.

- 1. What PHI will be accessed to identify participants?** Participants name, DOB, MRN, current medications, disease diagnosis, and relevant medical records (gastroenterology and laryngology records) will be accessed to identify if a patient meets inclusion criteria. No PHI will be stored in the screening log if the patient does not meet the inclusion criteria. This will protect identifiers from improper use and disclosure.
- 2. When will participants be approached for recruitment?** If treating MD/study investigator approves, the RA will call the potential research participant using the pre-screening phone script to notify the participant about the study, review eligibility and answer any questions and/or will contact the potential research participant in person in clinic. They will be given the consent form

and sufficient time to read it and ask any questions they may have. They will be given the opportunity to speak to the PI about any questions they have that cannot be answered by the RA.

- 3. Who can refer patients to the study?** Patients may be referred to the study by study investigators, and are participant to the same screening process to determine if they are eligible. Patients will not be obtained from any recruitment database.
- 4. Who will not be considered for recruitment?** Participant must be able to consent to the study. This protocol involves minimal risk, and/or targets only populations wherein impaired decision-making capacity is unlikely. Based upon past experience, we expect that the population of patients we will be including in this protocol will be competent to give informed consent. If there is any concern by an investigator that a potential research participant has a condition or circumstance that is associated with a possible decrease in decision making capacity, that participant will not be included in the study.

At risk populations including but not limited to prisoners, pregnant women, breastfeeding women, the mentally disabled, cognitively impaired, those requiring legal adult representation, and individuals under the age of 18 will not be approached. Pregnant women are excluded from our protocols, to make that distinction clear, we will ask if the potential research participant is pregnant at when determining eligibility. Breastfeeding women are excluded from our protocols. To make that distinction clear, the we will ask about breastfeeding when determining eligibility.

If potential research participants are not interested in participating in the study then their identifying information in the screening log will be destroyed at the earliest opportunity consistent with conduct of research.

## **12. INFORMED CONSENT**

This study has a consent process. The RA/PI will obtain informed consent. Participants will be screened prior to consent by reviewing medical records. Only patients under a treating relationship by one of the study investigators will be screened and consented. No research procedures will be done prior to obtaining consent (including fasting). Participants will not provide information about other identifiable persons, such as relatives or friends (secondary participants) that will be used for data analysis. Participants will receive a signed and dated copy of the consent form to be kept in their electronic medical record, and can ask for a paper copy in clinic. There is no deception involved in this study.

- 1. How will consent be obtained?** Consent will be obtained face-to-face and/or via email. The consent will be obtained by the RA/PI. If consent is obtained face-to-face it will take place in a private clinic setting. The participant will be given time to read the consent and ask questions before they decide to participate. Comprehension and autonomy will be assessed by asking questions about the study and assessing their responses. Only the participant may provide consent or permission.
- 2. Who will obtain consent?** The RA/PI will obtain consent for all participants. The PI will be responsible for ensuring the RA is completely trained on the study and the consent process.
- 3. Who will be excluded from the study and why?** Participants unable to consent and complete questionnaires in English or Spanish will be excluded. This study requires participant's patients to answer their own questionnaires. The questionnaires used in this study are verified in English and Spanish. Participants who are blind, illiterate or have similar reading limitations will be excluded. A

self-reporting questionnaire will be used in this study. It may alter the answers if the questionnaire is read to them. If English is not the participant's primary language then an official health translator will be used. A Spanish version of the informed consent form will also be developed after the current informed consent version is approved by the IRB.

**4. How will consent be documented?** A copy of the signed informed consent and HIPAA authorization will be placed in the participant's medical record. The patient will also receive a signed and dated copy of the consent form electronically, and may request a paper copy in clinic if this is not accessible to them. The original consent form and HIPAA authorization will be kept in a secure office until completion of the study.

### **13. ALTERNATIVES TO STUDY PARTICIPATION**

Patients may elect to not participate in the study and continue with a standard course of treatment for their GERD and RALS as discussed with their physician.

### **14. POTENTIAL RISKS**

**Completion of questionnaire (Standard of Care):** There exists a small risk of emotional upset when filling out questionnaires. Participants may experience some anxiety as they are asked to answer personal questions or are reminded of unpleasant thoughts or experiences during the questionnaire process. The participant, as always, has the right to refuse to answer any question they are asked. However the study team shall determine if the extent of refusal may warrant the removal of the participant from the research study so as to ensure complete and accurate data collection.

**Pepsin analysis (Research):** The Peptest requires non-invasive (participant induced) collection of saliva. There is no diagnostic or therapeutic procedure performed. There may be a small amount of discomfort when the participant is bringing up saliva for collection. There is also a risk that the Peptest result will be incorrect (false negative or false positive). However, no decisions regarding management of a patient's disease will be made based on the results of this test.

#### **Esophageal Manometry (HRIM) (Standard of Care)**

The manometry test measures the strength of the esophagus muscle and the direction of movement of the muscular contractions. Impedance can also detect the direction and speed of fluid and airflow through the esophagus. This procedure takes approximately 45 minutes. It involves passing a recording tube (less than 1/4 inch across) through the nose into the esophagus. The tube is designed to measure pressures in the pharynx, esophagus and stomach. A lubricant will be put on the end of the tube to make the placement more comfortable. An anesthetic (numbing) jelly (Lidocaine®) is also available if you choose. Once the manometry tube is in place, the participant will be asked to swallow 5 ml (1 teaspoon) of water or a salt solution several times throughout the measurement.

#### **pH impedance (Standard of Care) (Z2pH):**

A pH-impedance catheter will then be placed in a similar manner through the nose and into the esophagus. This catheter measures how acidic the environment in your esophagus is. Impedance can also detect the direction and speed of fluid and airflow through the esophagus. These measurements allow the physician to determine if gastro-esophageal reflux is contributing to your symptoms. This procedure takes approximately 45 minutes.

The catheter will be attached to a portable receiver that you will wear for 24 hours. You will be given instructions as to how to note meals, sleep, and symptoms throughout the 24 hour period.

**The risks of manometry (HRIM) and pH impedance (Z2pH):** Placement of the manometry and pH-Impedance catheters through the nose can cause gagging or mild pain in the nose and throat, skin irritation. Nosebleeds can also rarely occur. These tests are standard of care and care will be taken to reduce these risks as much as possible. All procedures will be performed by experienced personnel who specialize in these procedures.

**Upper esophageal sphincter assist device (Standard of Care):**

The upper esophageal sphincter assist device (UESAD) is a band that is worn externally around the neck, and provide increased pressure at the upper esophageal sphincter. It is recommended to be worn at nighttime.

The safety of the UESAD (Reflux Band) has been assessed in previous studies. Adverse events that were reported during these studies were generally mild, short in duration, and the majority of these events were not related to the device. Those events that were related to the device were also generally mild and short in duration. Potential risks include discomfort, difficulty sleeping, skin irritation, risk of over compression, misuse, incorrect fitting, and malfunctions.

Device-related adverse events did not result in reduced outcomes in relation to the change of the RSI score from baseline to the score measured after 4 weeks of use. There were no deaths in these studies and there were no unexpected adverse events, and none of the participants withdrew from the studies due to an adverse event. These studies also showed that there was no effect on heart rate, blood pressure, cardiac rhythm, or intraocular pressure when the UESAD was worn as intended as well as when it was intentionally displaced laterally, as compared to the baseline. This device has been approved for sale and marketing by the FDA for the proposed participant population, and is available as an over the counter device.

**Proton pump inhibitor (PPI) Therapy:** Short-term use of PPI therapy may be associated with the following side effects: headache, diarrhea, constipation, abdominal pain, flatulence, nausea, vomiting, and rash. Short-term PPI use may increase the risk of *Clostridium difficile* infection of the colon. The FDA has determined that short-term use of PPI therapy has an unlikely risk of fracture.

**Potential loss of confidentiality:** Finally, there is a risk that confidentiality of participant information will be breached. However, all participant data will be kept confidential, following HIPAA regulations. Participant data will be stored on encrypted files.

**Data safety and compliance monitoring:** Compliance to UESAD use will be monitored via patient-reported outcomes during telephone follow-up by the research assistant. In addition, research assistant will assess for adverse events to the UESAD during telephone follow-up. A designated physician in gastroenterology team will serve as the safety monitor will to assess adverse events and safety concerns.

## 15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

**Questionnaires-** The participant, as always, has the right to refuse to answer any question they are asked. However the study team shall determine if the extent of refusal may warrant the removal of the participant from the research study so as to ensure complete and accurate data collection.

**Manometry & pH impedance –**

-Gagging or mild pain in the nose and throat. In this event, the nurse/technician will stop catheter advancement and will use a light to inspect the oral cavity and nares. If the catheter is in an appropriate configuration, the patient will be asked to take deep breaths and promote relaxation. Once the patient is comfortable the patient will be advised to drink sips of water as catheter advancement is attempted. If symptoms do not improve catheter placement will be aborted and the ordering provider notified.

-Skin irritation. The catheter is transnasally placed and the proximal end of the catheter will sit gently across the patient's cheek and loop around the ear lobe. To ensure adequate placement of the pH impedance catheter over the 24 hour period, a non-abrasive anti-slip tape will be used to secure the catheter to the cheek. There is risk of skin irritation. The motility nurse/technician and gastroenterology team are on call 24 hours a day, and in the event of skin irritation the patient will be advised by the team to remove the adhesive and permit a finger width space between the catheter and the cheek. The skin will be evaluated the following day when the patient drops the catheter off by the nurse. However, if the skin remains irritated the patient will be educated on catheter removal over the phone.

-Nosebleeds can also rarely occur. In this rare event, pressure will be applied by the nurse. An epistaxis kit is also available to nurses in the motility lab inclusive of gauze and decongestant nose drops.

**Reflux band Band (UESAD)-** the device, and how it works will be fully explained to the participant, any questions they have will be answered. If the device is worn the correct way, there have been no risks found. Participants will have the phone number of the PI and research assistant, and will be advised to contact the research team if they experience symptoms related to the device or any issues. The PI will evaluate the symptoms over the phone or in person without added cost to the participant, and will discuss how they will move forward which may include re-education about device use, re-fitting of the device, or stopping device use.

**Peptest-** very little risk to begin with, other than the participant being slightly uncomfortable during saliva production. The procedure will be explained to the participant so they know what to expect. If there is false negative or false positive result, no decisions regarding management of a patient's disease will be made based on the results of this test.

To protect confidentiality, all participant data will be kept confidential, following HIPAA regulations. Participant data will be stored on encrypted files on a password protected data base that only the study team will have access to.

RALS participants will be called every 2 weeks by the coordinator. This will assess their symptoms and if they are having any issues with the device or treatment.

**16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT**

Data will be stored in REDCap and accessible only by authorized research personnel who have undergone appropriate training. All research data will be stored in REDCap. When the study closes the data will be stored in REDCap for 7 years until destruction per REDCap policies. As for paper document, all records will be retained for 7 years after study closes before being destroyed. The records will be retained 1 year in the GI record storage room and transported to Iron Mountain for 7

year storage. We will store the pre-screening list on the GI Division secure server. The excel list will be password protected. In the event that confidentiality is lost, this event will be reported to the UCSD IRB HRPP within 10 days.

#### **17. POTENTIAL BENEFITS**

Benefits of this study include assisting doctors in having a better diagnostic and therapeutic plan for RALS to be more accurate and efficient, and offering an improved diagnostic and therapeutic plan to society.

#### **18. RISK/BENEFIT RATIO**

The risks in this research study are minimal. UESAD has very little found side-effects, and has been proven to help symptoms. This device is non-medication and non-surgical. It is not invasive.

The pepsin test also has minimal risk, but it could help the doctor better diagnose and assess the participant to find the best course of treatment. The pepsin test is much less invasive than all the other diagnostic tests that are being used for RALS, hopefully this will be a much easier way to diagnose RALS and more comfortable for the participant.

The benefits to this study could entail much more affordable and more effective treatments for the patient suffering from RALS, which outweighs the minimal risks listed.

The ineffective and circuitous care for suspected RALS contributes to an estimated \$50 billion in health care costs.

This study will allow for not only a more efficient way to diagnose RALS, but also to decrease the symptoms. This can minimize the cost that all the current procedures and misdiagnoses regarding

#### **19. EXPENSE TO PARTICIPANT**

The study protocol is designed so that participants will not incur any expenses outside of standard of care, and so that participants will receive compensation for participation.

The following procedures are standard of care for this patient population at UCSD and the procedure and related side effects will be covered by insurance: esophageal manometry, pH impedance, and PPI therapy.

Questionnaires are standard of care for this patient population at UCSD and there are no costs related to questionnaires.

Salivary peptest is not standard of care, and the costs (equipment and processing) will be covered by the PI as a research expense.

The UES assist device is standard of care, and typically obtained over the counter (\$199) by the patient. In this study the UES assist device will be covered by the PI as a research expense and provided to the participant free of cost.

	<b>Standard of Care</b>	<b>Coverage</b>	<b>Visit Time (mins)</b>	<b>Costs to Manage Side Effects</b>
<b>Esophageal manometry</b>	Yes	Insurance	45	Not anticipated, but would be covered as standard of care by Insurance
<b>pH impedance</b>	Yes	Insurance	45	Not anticipated, but would be covered as standard of care by Insurance
<b>Questionnaires</b>	Yes	No coverage needed	10	None
<b>Salivary peptest</b>	No	Research costs	2	None
<b>4 week PPI therapy</b>	Yes	Insurance	Not applicable	Covered as standard of care by Insurance
<b>UES Assist Device</b>	Yes	Typically self-pay; In this study will be a research cost	30 min visit to receive device	Not anticipated, but would be covered as standard of care by insurance

## 20. COMPENSATION FOR PARTICIPATION

Participants will receive \$100 pro-rated for their time: \$25 for completing visit 3, \$25 for completing visit 4, and \$50 for completing visit 5. Participants will also receive the Reflux band (commercial cost \$199.00) free of cost.

## 21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Rena Yadlapati MD, MSHS is a licensed gastroenterologist at UCSD with expertise in esophageal reflux. David Kunkel MD is a licensed gastroenterologist at UCSD with expertise in esophageal reflux. Ravi Mittal MD is a licensed gastroenterologist at UCSD with expertise in esophageal reflux. Andrew Vahabzadeh MD is a licensed otolaryngologist at UCSD with expertise in laryngeal symptoms. Philip Weissbrod MD is a licensed otolaryngologist at UCSD with expertise in laryngeal symptoms. Madeline Greytak is the research assistant to this protocol.

**Table 2.**

Role	Name	Responsibilities								
		Administer Consent	Screen participants	Obtain medical history	Determine eligibility	Assess adverse events	Complete source documents	Complete study forms	Make follow-up phone calls	
Principal Investigator	Rena Yadlapati	x	x	X	x	x	x	x	x	
Research Assistant	Madeline Greytak	x	X				X	X		x
Co-Investigator	David Kunkel			X						
Co-Investigator	Ravi Mittal			X						

Co-Investigator	Andrew Vahabzadeh			X					
Co-Investigator	Philip Weissbrod			X					

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### 23. FUNDING SUPPORT FOR THIS STUDY

This study is being supported by the American College of Gastroenterology 2018 ACG Junior Faculty Development Grant. This grant is for \$100,000 for 3 years, from 7/01/2019 until 6/30/2021.

### 24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

There will be no shipping or transport of biological materials during this study.

### 25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

There are no investigational drugs being used in this study.

### 26. IMPACT ON NURSING STAFF

This study will involve the nursing staff from UCSD in endoscopy. The time for study participants will fall within normal scheduling of patients for HRIM and pH-impedance. Research patients will only be scheduled during normal hours within the schedule for these procedures. There is no additional

budget provided for nursing staff training and participation in this study. This study will be done within the outpatient setting and attached is the affirmative statement that the study plan has been discussed with the appropriate nursing supervisor and that they have approved of these services.

#### **27. CONFLICT OF INTEREST**

All investigators and coordinators listed on this application have completed and submitted a UCSD COI disclosure form to the UCSD COI office.

There are no conflicts of interest issues to be disclosed for the investigators or key personnel that relate to this study.

#### **28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES**

This is not a cancer-related study and does not qualify under the California Clinical Trial Law (Section 1370.6 of the Health and Safety Code; Section 10145.4 of the Insurance Code; and Sections 14087.11, 14132.98, and 14132.99 of the Welfare and Institutions Code).

#### **29. OTHER APPROVALS/REGULATED MATERIALS**

Attached is the FDA approval of the Reflux Band (UESAD).

#### **30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT**

Surrogate consent and/or decisional capacity assessment will not be sought for this study.