Consent Form:

Randomized Sham-Controlled Trial of the Reflux Band in Laryngopharyngeal Reflux

(LPR) UCSD IRB 201945 7/22/2021 - 2/17/2022

NCT04827355

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University of California, San Diego
Consent to Act as a Research Subject

Randomized Sham-Controlled Trial of the Reflux Band in Laryngopharyngeal Reflux (LPR)

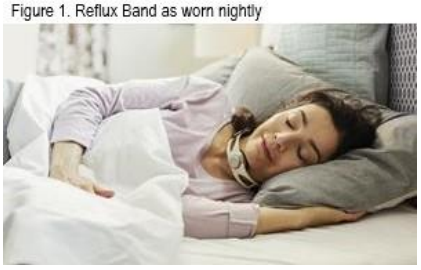
Introduction

Dr. Rena Yadlapati and associates are conducting this research and asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary - whether or not you join is your decision. You can discuss your decision with others (such as family, friends or another physician).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your health care or any other benefits you may be entitled to.
- You can say no even if the person inviting you is part of your healthcare team.
- Please ask questions or mention concerns before, during or after the research.

We are trying to understand if the Reflux Band is an effective treatment for laryngopharyngeal reflux (LPR) in comparison to a sham device. LPR is a syndrome in which acid that is made in the stomach travels up the esophagus and into the throat, causing chronic symptoms including throat clearing, voice hoarseness, sore throat, etc. Participation in the study may or may not benefit you directly, and may result in new knowledge that may help others.

Figure 1. Reflux Band as worn nightly



If you participate in this study, there are 3 - 4 in person visits (2 of which are part of your standard of care) ranging from 30 – 45 minutes each and 2 virtual visits, either by phone or video, each 15 minutes. You will be assigned with a 50/50 chance (similar to a coin flip) via a computer generator to receive the Reflux Band or sham device (a device that will not provide you medical therapy) which you will wear around your neck nightly while sleeping (6+ hours) over a duration of 8 weeks. The Reflux Band, which has been cleared for use by the FDA, applies pressure to the outside of your neck at your cricoid cartilage, at the middle of the neck, and increases the internal pressure of the muscle separating your throat from your esophagus (upper esophageal sphincter). You will only wear the band while sleeping at night and remove in the morning upon waking (Figure 1).
The in person visits will occur at one of these UCSD La Jolla locations: the Perlman Medical Office Gastroenterology clinic, the Center for Voice and Swallowing, Altman Clinical and Translational Research Institute (ACTRI) Clinic.

There is an optional 4 week extension at the end of this study in which your Reflux Band will be refit (if sham) to provide the manufacturer's specified pressure. This portion contains 1 virtual follow up during week 10 and an in person follow up during week 12, in which you would conclude your participation in this study.

The most commonly expected risks of the study are skin reaction, discomfort, and difficulty sleeping. These were generally mild and short in duration.

No serious risks were observed when the Reflux Band was worn around the neck in previous studies.

There are not alternatives to this study.

Additional, detailed information about this research is provided below. Please feel free to ask questions before signing this consent.

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Why have you been asked to participate, how you were selected, and what is the approximate number of participants in the study?
You have been asked to participate in this study because you are exhibiting symptoms of voice hoarseness, throat clearing, cough, and/or sore throat, you are currently taking a proton-pump inhibitor (PPI) for reflux management and your salivary pepsin sample was positive for pepsin. There will be approximately 72 participants at this site.

What will happen to you in this study and which procedures are standard of care and which are experimental?
In addition to the information at the beginning of this form, here are some additional details about will happen to you if you agree to be in this study,

Screening (30 minutes) *Standard of Care*
You will be screened for eligibility to participate during a standard of care clinic visit which will include: review of relevant medical history and collection of saliva sample(s) (each sample is about ½ teaspoon) if not previously collected for salivary pepsin and/or oral microbiome analysis.

> Saliva Analysis: This study analyzes salivary pepsin and oral microbiome. Pepsin is a protein found in your stomach that when found in your saliva may indicate level of reflux present. Oral microbiome analysis will look at the microorganisms that reside in your oral cavity. Human DNA testing will not be performed. You will not receive the results from saliva tests throughout the study and the tests will not be used for your clinical care.
>
> Anti-Reflux Medications: During this study you will be expected to remain on your prescribed double daily dose of PPI (ex. Omeprazole 40mg daily, lansoprazole 30 mg daily, etc) and you cannot make changes to this dose during the study. This PPI dose needs to be stable for <u>at least 4 weeks</u> prior to being assigned to a study group. If needed, you will be given the time to reach this dose between the screening visit and randomization visit. Certain anti-reflux medications are prohibited during this study unless specifically approved by the study investigator. Prohibited medications include: h2-blockers (i.e. Pepcid), gaviscon, or antacids such as tums, rolaids, maalox.

If you meet all eligibility requirements, you will proceed to enrollment and randomization to be assigned to a device group (sham or interventional). If you have already completed salivary pepsin analysis prior to the screening visit, you may complete your enrollment and randomization at this same visit.

Blinded Intervention (Week 0-8)
<u>Enrollment & Randomization (45 minutes):</u>
You will be assigned by chance using a computer generator to a study group. Your chance of being assigned to each group is 1 in 2 (50/50). Neither you nor the researcher(s) can choose the group to which you will be assigned. If you are assigned to the group receiving interventional treatment, the Reflux Band will be fit to apply pressure per manufacturer guidelines. If you are assigned to the group not receiving treatment (sham) the device will be fit to a pressure known not to provide you with therapy. The research coordinator will fit the Reflux Band to your neck

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per your group assignment, provide you with instructions for wear and cleaning, and mark with tamper resistant tape.

At this visit, the research coordinator will send you home with the Reflux Band sized according your group assignment which you will start using the following night.

You will also receive a log that you will complete to record how long you wear the band nightly as well as record taking your daily prescribed PPI. You will be shown how to use this log. It is expected that you will wear the Reflux Band to bed nightly for at least 6 hours for 8 weeks. Completion of your log is expected to take 1-2 minutes a day for 8 weeks. It may take a few additional minutes weekly to clean your band by wiping with a damp cloth.

You will also be sent home with an at home saliva collection kit. You will collect 3 samples total for salivary pepsin analysis (each about ½ teaspoon) at different times throughout the day (15 minutes total). You will collect these the day after you receive your reflux band. You will collect 1 sample first thing in the morning before food or drink, 1 sample 30 minutes after a meal, and 1 sample right before bedtime. You will be provided with instructions and you will return the samples by dropping off or shipping to the research coordinator within 3 calendar days of collecting them. The research coordinator will contact you to remind you to do this. After you finish collecting the bedtime sample, you will start using your Reflux Band that night while sleeping.

Follow Up 1 (15 minutes): You will follow up with the research coordinator during **week 2**, either in person or virtually via video conference. During this visit the research coordinator will 1) inspect the device to ensure it has not been tampered with, 2) ask you to place the device on your neck to ensure that it is fitting you correctly, 3) and ask you about your symptoms.

Follow Up 2 (30 minutes): You will follow up with the research coordinator during **week 4** in person. During this visit, the research coordinator will 1) inspect the device to ensure it has not been tampered with, 2) ask you to place the device on your neck to ensure correct fit, 3 measure the pressure being applied with an external manometer, and 4) ask you about your symptoms. You will also be asked to answer 3 short questionnaires about your LPR symptoms and provide 1 fasting saliva sample for salivary pepsin analysis.

Follow Up 3 (Phone Call, 15 minutes): The research coordinator will call you during **week 6** to discuss symptoms and ensure that you are wearing the Reflux Band nightly and taking your prescribed PPI daily.

End of Blinded Intervention Follow Up (30 minutes) *Standard of Care*: During week 8 you will follow up with your gastroenterology or laryngology physician as standard of care as well as meet with the research coordinator. Your physician will discuss your outcome as well as next steps and clinical care that may be unrelated to your participation in this study. The research coordinator will ask you to answer 3 short questionnaires about your LPR symptoms and ask you to provide 2 fasting saliva samples for salivary pepsin and microbiome analysis. The research

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coordinator will ask you about symptoms you have described throughout the study. Your Reflux Band will be refitted to the manufacturer guidelines.

*If you do not choose to participate in the optional extension, you will be provided with the reflux band and associated fitting equipment and instructions at this visit. It will be your final research visit.

Optional Extension: Known Intervention (Week 9-12)
You will be asked if you would like to participate in an additional 4 weeks of known (un-blinded) intervention in which you will wear the device at the manufacturer's guidelines. During this time, your device may or may not apply more pressure than the previous 8 weeks when you did not know which group you were assigned to. You will still be instructed not to self-adjust your device.

Extension Follow Up 1 (15 minutes): You will follow up with the research coordinator during week 10, virtually via video conference. During this visit the research coordinator will ask you to place the device on your neck to ensure correct fit and ask you about your symptoms.

End of Extension Follow Up (30 minutes): You will follow up with the research coordinator during week 12, who will ask you to complete 3 short questionnaires and ask you to provide 1 fasting saliva sample for salivary pepsin analysis. The research coordinator will provide education and necessary materials for self-fitting the Reflux Band for future adjustments as needed.

Post Treatment Follow Up Phone Call
You will be contacted 3 months after you have completed the research study. During this phone call, the research coordinator will ask you questions about your current symptoms, current anti-reflux management (medications, lifestyle changes), and if you have continued to use the Reflux Band. If you have continued to use the Reflux Band, you will also be asked to answer 3 short questionnaires.

Data Collection
Collection of data as it relates to your esophageal and / or laryngology treatment will include: Identifier: participant name, date of birth, medical record number; Demographics: Gender, race; Past medical and surgical history; Current medications; Results of available esophageal and laryngeal testing.

Your information will be given a unique study-ID that will code your identity. Only research staff directly involved in this study will be able to de-code this information.

What risks are associated with this study?
Participation in this study may involve some added risks or discomforts. These include the following:

1) **Completion of questionnaires:** There exists a small risk of emotional upset when filling out questionnaires. You may experience some anxiety as you are asked to answer

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personal questions or reminded of unpleasant thoughts or experiences during the questionnaire process. You have the right to refuse to answer any question, however the study team shall determine if the extent of refusal may warrant removal from the study.

2) **Saliva Analysis:** Collection of saliva for pepsin and microbiome analysis is non-invasive. There may be a small amount of discomfort when bringing up saliva for collection. These results will not be used in your clinical care.
3) **Reflux Band:** The safety of the Reflux Band has been assessed in previous studies. Some discomforts that were reported after using this device include skin reaction, discomfort, difficulty sleeping, incorrect fitting, and device malfunction. These symptoms were generally mild, short in duration, and the majority of these events were not related to the device. If you experience any of these symptoms, contact the research team as they may be able to help you resolve these issues. There are no additional known risks of the device if used to apply less pressure (as a sham). Studies have shown that there was no effect on heart rate, blood pressure, cardiac rhythm, or intraocular pressure when the Reflux Band was worn around the neck in previous studies. If you experience any symptoms or issues related to the device you should call the research team to discuss the symptoms and how to move forward. The risks of the Reflux Band in pregnancy or breastfeeding are not known. If you become pregnant during the study stop using the Reflux Band and contact the research team immediately.
4) **Potential Loss of Confidentiality:** As with all research there is a risk of loss of confidentiality. This means someone who should not have access to your records may gain access. Procedures are in place to minimize this risk.

You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective than the other study groups(s), or other treatments available for your condition.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Are there risks to the reproductive system or a developing fetus?

It is unknown if the effects of the treatment procedures may pose some unforeseeable risks on the reproductive system (sperm, eggs) or to the developing fetus.

What are the alternatives to participating in this study?

You may elect not to participate in the study and continue with a standard course of treatment for your LPR as discussed with your physician.

What benefits can be reasonably expected?

There may or may not be any direct benefit to you from these procedures.

What happens if you change your mind about participating?

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits that you have already received through this study. If you

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decide that you no longer wish to continue in this study, you will be requested to: contact the study team to indicate that you no longer wish to you participate. The study team may ask you follow up questions regarding symptoms. You will not be compensated for visits you have not completed.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study for the following reasons: Dr. Yadlapati thinks that being in the study may cause you harm, you become pregnant, or you are breastfeeding. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive up to $100 for participating in this research study. You will receive a $25 Visa gift card for completing the randomization visit. You will receive a $25 Visa gift card for completing Follow Up 2 during week 4. You will receive a $25 Visa gift card for completing the End of Blinded Intervention Follow Up during week 8. You will receive a $25 Visa gift card if you choose to participate and complete the Optional Extension Follow Up (Week 12). If you choose to withdraw from study, you will not be compensated for visits you have not completed.

Are there any costs associated with participating in this study?
There will be no research related costs to you for participating in this study. The Reflux Band will be supplied at no cost while you take part in this study. The cost of re-fitting the Reflux Band during the open label is also provided at no cost and you will be provided with the materials for fitting the device yourself. Saliva samples for salivary pepsin and oral microbiome analysis will be collected and processed at no cost to you. You are responsible for the costs of travel and parking.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your condition while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no cost. Before you decide to be in the study, you should check with your health plan/insurance company to find out exactly what they will pay for. Examples of procedures and drugs that may be billed include the following: PPI therapy and standard of care clinic visits.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?

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Research records will be kept confidential to the extent allowed by law. Protection of confidentiality and data security will be accomplished by the following steps following HIPAA regulations:

- Limiting of access of your research data to related study team
- Storing all electronic data on a password protected drive within a secure server
- Storing all paper records in a locked cabinet in a locked office
- Up to date training for all study team members
- Your name will not be recorded or kept in datasets
- Only de-identified is shared. When shared, it will only be as part of an entire dataset, not singled out.

Research records may be reviewed by the UCSD Institutional Review Board (IRB), and the National Institute Health (NIH), and the Food and Drug administration (FDA) and the Human Research Protections Program (HRPP) Office that protect research subjects like you, the study doctor and the rest of the study team, and officials at the institution where the research is conducted and the officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

This research is covered by a Certificate of Confidentiality from National Institute of Health. Researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research *unless* there is a federal, state, or local law that requires disclosure (such as to report child abuse, elder abuse, intent to hurt self or others, or communicable diseases), you have consented to the disclosure, including for your medical treatment; or it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institute of Health which is funding the project or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA). You should also understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research to release it.

Personal identifiers will be removed from the information or biospecimens collected as part of the research. After such removal, the information could be used for future research studies your additional informed consent**.** The de-identified information from your saliva specimens will be used in this research and may be used in other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of this information."

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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.

Will you receive any results from participating in this study?
You will not receive the results of your saliva analyses throughout the study.

Who can you call if you have questions?
Dr. Yadlapati and/or the study team have explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach the research coordinator at 858-246-5236.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____	_____
Subject's signature	Date
_____	_____
Signature of the person conducting the informed consent discussion	Date

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