Cover Page to Study Protocol and Analysis Plan

Official title: A prospective, randomized, blinded, placebo-controlled, single center, efficacy study of a Mastoid device in subjects with Ménière's Disease

NCT number: NCT03520322

Document date: 07 August 2018

A prospective, randomized, blinded, placebo-controlled, single center, efficacy study of a Mastoid device in subjects with Ménière's Disease

Principal Investigator – Paul O. Dutcher, Jr., M.D.

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

The purpose of this study is to investigate the efficacy of mastoid oscillation in patients with active Ménière's disease that is not controlled by traditional medical management.

1.2. Background

Since Hallpike and Cairns first described the histologic findings of the inner ear in Ménière's disease in 1938, attention has focused on the cause for these findings. Despite reconfirmation of the histologic findings over the years, such that endolymphatic hydrops is universally accepted as synonymous with Ménière's disease, the etiology for these findings and the clinical symptoms remains elusive.

Paralleling the futile search for the cause, there has been a rich and equally frustrating history regarding the treatment of Ménière's disease. The history and literature is replete with conservative measures attempting to control symptoms without being destructive, as well as more predictable but destructive procedures for recalcitrant symptoms.

One of the more lively and ongoing debates centers around the role and the mechanism of action of endolymphatic shunt/decompression procedures. Those who espouse endolymphatic sac surgeries believe in their value and effect. Naysayers cite the natural history of the disease and the results of the foreshortened sham surgery study completed in Denmark.[1] Even proponents of endolymphatic sac surgery can't agree on the management of the sac, some shunting into the cerebrospinal fluid space, some shunting into the mastoid, some suggesting that fluid pressures can be controlled with valves and others avoiding shunting completely and merely decompressing the sacs. Interestingly, aside from mild variations, all approaches seem to produce similar results. Although foreshortened and resulting in inadequate numbers for statistical analysis, even the sham study[1] seemed to produce similar results. Is there any unifying hypothesis that would explain these observations?

Those who perform endolymphatic sac surgeries believe there is a temporal relationship between the surgical procedure and the improvement in symptoms that the patient experiences. However, the reason for the improvement is unknown. It is merely conjecture that the effect of the endolymphatic shunt is decompressive drainage through the endolymphatic duct and sac. This has never been scientifically demonstrated. In fact, the observation that decompression of the endolymphatic sac without shunting is equally effective would suggest that decompressive drainage may not be the reason that endolymphatic sac procedures work.

The one common factor in all of these surgeries is the use of the otologic drill to remove the bone of the mastoid and expose the endolymphatic sac. In fact, even in the sham study, the otologic drill was used to remove the mastoid cortex, but the surgery was not completed to expose the endolymphatic sac. What effect might the drill have on the process of Ménière's disease?

It is generally accepted that the cause of benign paroxysmal positional vertigo (BPPV) is related to particles/otoconia floating free in the endolymph of the inner ear and becoming trapped in the posterior semicircular canal. These particles have been shown to exist, both histopathologically and clinically. One of the forms of treatment for BPPV is referred to as the canalith repositioning maneuver, designed to move these particles from the posterior semicircular canal back into the endolymphatic system in the

vestibule of the inner ear, thus relieving the symptoms of positional vertigo. These particles have also been known to be trapped in the lateral semicircular canal, but have never been implicated in other forms of pathology of the inner ear.

A hypothesis has been proposed that these particles may become briefly trapped in the outflow tract of the endolymphatic duct from the inner ear (vestibulolithiasis) and thereby produce the endolymphatic hydrops that is felt to produce the symptoms of Ménière's disease. It is likewise hypothesized that, if these particles do jam the endolymphatic duct, *they might be freed by tipping the endolymphatic duct towards the vestibule of the inner ear and oscillating the temporal bone/inner ear structures.*

A pilot study (RSRB 9358) using head positioning and mastoid oscillation has been completed and the results twice reported at the American Academy of Otolaryngology-Head and Neck Surgery annual meeting[2,3]. The results were positive with improvements comparable to the other forms of conservative surgical measures currently practiced in the treatment of Ménière's disease. The only objection to the pilot study was the lack of controls, a standard to which few other available treatments for Ménière's disease have been held. Nevertheless, the current study has been designed to attempt to address this objection.

2. STUDY DESIGN

2.1. Overview

This is a single center, randomized, placebo-controlled trial of mastoid oscillation for treatment of Ménière's disease. Eligible subjects will be randomized using a 1:1 allocation to either mastoid oscillation or placebo (oscillator device that provides the same sound but no vibration of the mastoid) received for 30 minutes at four weekly study visits, with efficacy determination via change in frequency and severity of Ménière's symptoms following the final study visit.

2.2. Rationale for Study Design

The pilot study has already determined that approximately 75% of patients undergoing mastoid oscillation for Ménière's disease refractory to medical treatment significantly improve or resolve their symptoms, compared with less than 10% in a 'waiting list' control group. This means that 75% of patients seen who here-to-fore would have had surgery or a destructive procedure offered now have a non-surgical/non-destructive option available. The ongoing debate that blocks use of this treatment routinely in treatment of patients with refractory Ménière's disease is whether this improvement is better than the natural history of the disease. Therefore, objections demand a control group/study before this form of treatment is accepted as a viable alternative before considering surgical or ablative approaches to the management of Ménière's disease refractory to medical treatment. We have now designed and will have produced a null device (control) which should address this objection/concern. This device will produce the sound of oscillation, but there will be no oscillation delivered. Therefore, the control/null device will be identical to the mastoid oscillator, except that there will be no oscillation whatsoever delivered.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) **Number of Subjects:** We plan to enroll up to 40 subjects in order to accrue 15 randomized to the treatment arm of the study and 15 assigned to the placebo/control arm.

b) **Gender and Age of Subjects:** Subjects 18 years of age and older will be included in the study and there will be no restriction on gender.

c) **Racial and Ethnic Origin:** There will be no restriction based on race or ethnicity.

3.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:**
   a. Adults aged 18 and older
   b. Clinical diagnosis of Ménière's disease, with classical symptoms:
      i. Episodic spinning vertigo
      ii. Fluctuating unilateral low frequency sensorineural hearing loss
      iii. Tinnitus
      iv. Aural fullness
   c. Failure of traditional medical management of Ménière's disease symptoms
   d. English language skills sufficient to provide informed consent to the study

b) **Exclusion Criteria:**
   a. Atypical medical history of Ménière's symptoms and questionable Ménière's diagnosis
   b. Bilateral Ménière's disease

3.3. Discussion of Subject Population

These patients will have already received the standard medical regimen for idiopathic Ménière's disease of diuretics, vestibular sedatives and a low salt/low caffeine diet, but this traditional medical treatment for Ménière's disease will not have resolved their disease symptoms. They will have completed a thorough pre-surgical workup and would normally be offered surgical interventions that would include the endolymphatic-mastoid shunt/decompression, transtympanic Dexamethasone, transtympanic chemical/gentamicin labyrinthectomy or a vestibular nerve section. Subjects entering the study will be offered a non-surgical, experimental and alternative form of treatment, and will be randomized into either the control/placebo arm or treatment arm of the study.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method Of Subject Identification And Recruitment

Patients will be recruited from the clinical practice of the principal investigator.

4.2. Process of Consent

If eligible, patients will be approached by the PI to discuss the study. Candidate subjects will be assured that their decision to participate or not to participate will not affect the medical care that they can expect. If they are interested in participation, they may take the consent form home or they may provide consent at that time. When ready to consent, the teach-back method will be used to ensure that the subject understands their participation in the study. Preferentially, consent will be obtained by study personnel other than the PI, however due to logistics this may not be possible or convenient to the subject, in which case the PI may obtain consent.

Consent will be documented in a consent log in REDCap and signed forms will be stored in the Otolaryngology Department Research Office (SMH 1.5010). The subject will receive a copy of the signed form.

5. METHODS AND STUDY PROCEDURES

The screening visit may take place up to 30 days prior to the first study visit, or may occur on the same day as the first study visit. After providing informed consent, subjects will provide a complete medical and neuro-otological history/exam and the study team would review their standard of care Ménière's work-up. Because subjects are typically established patients of the PI, the history may be obtained retrospectively from the subject's chart.

At the screening visit and at each subsequent visit, the subject will complete the 'Meniere's functional level scale' question (Appendix B).

At the first study visit (which might be the same day as the screening visit) the study team will confirm eligibility and the subject will be randomized to either the oscillation or placebo group, with the study team blinded as to which treatment is received. The study team will be informed whether Device A or Device B are to be used (see 7.2). For treatment, the subject will be in a private room at the Department of Otolaryngology Clinton Woods Clinic. The designated treatment device (oscillator or placebo) will be placed over the mastoid of their involved ear and secured via an elastic/Velcro headband. The subject is positioned so as to place the endolymphatic duct into a gravitationally dependent orientation (the subject lying on their contralateral side with the face slightly tilted towards the floor). The device is turned on and operated for 30 minutes. The subject will be periodically monitored by study staff during this time. Following each treatment, patients will be evaluated for response and untoward side effects.

Study visits 2, 3 and 4 will be 7 days apart. Prior to treatment, a thorough review of the behavior of the subject's Ménière's disease over the preceding week as well as any sequelae of their treatment will be recorded. A complete ENT and neuro-otologic exam will be completed.

Study visit 5 will be two weeks following the final treatment visit (visit 4). Subjects will have a complete medical and neuro-otologic exam and be observed for short-term results of the treatments.

The final study visit will be three months after study enrollment. Subjects will have a complete medical and neuro-otologic exam and be observed for longer-term results of the treatments. Specifically, the frequency and severity of any Ménière's disease attacks will be recorded and compared to pretreatment patterns.

Schedule of Activities

Visit	0 (Screening)	1	2	3	4	5	6 (Final)
Visit Window	-30 days	0 days	7 days	14 days	21 days	35 days	90 days
Obtain informed consent	X	(X)					
Medical and otologic history	X	(X)					
ENT and neuro-otologic exam	X	(X)	X	X	X	X	X
Confirm eligibility/Randomize		X					
Document any recent vertigo		X	X	X	X	X	X
Meniere's functional level scale (Appendix B)		X	X	X	X	X	X
Mastoid Oscillation/Placebo		X	X	X	X		
Document acute response		X	X	X	X		
Adverse event review		X	X	X	X	X	X

5.1. **Efficacy Assessments**

Efficacy will be determined by comparing the frequency and severity of post-treatment Ménière's disease attacks with pretreatment patterns. Clinical response will be classified by AAO guidelines[4]: frequency of definitive vertigo episodes per month, average hearing threshold, word recognition score, and functional level.

5.2. Safety Assessments

As standard of care for evaluation and management of any Ménière's disease patient who has failed medical treatment and who is considering alternative forms of treatment, patients will provide information on their general medical and specific otologic health. They typically receive a thorough ENT and neuro-otologic physical exam per SOC. SOC audiologic testing is conducted if no previous testing in the 3 months prior to their visit is available. SOC ENG/VNG testing is not always necessary in the workup of the patient with Ménière's disease, but might be completed on a case by case basis per SOC. An MRI/MRA scan of the head would be completed on all patients per SOC to assure that there are no incidental tumors or aneurysms. Appropriate SOC screening lab tests would be completed to rule out metabolic, endocrine, inflammatory and autoimmune issues.

For safety assessment, the initial standard of care Ménière's workup described above will be documented when the subject enters the study. At each study visit after the first, subjects will be asked about changes to medical and otologic health, and in particular if they have had vertigo episodes since the last visit, and if so how frequent and of what duration. We will also ask if they experienced any discomfort related to the treatment and the subject will complete the 'Meniere's functional level scale' question (Appendix B).

5.3. Costs to the Subject

There will be no cost for the actual treatment procedure or additional costs related to subjects' participation in this study.Study visits will not be billed to insurance. .

5.4. Payment for Participation

Subjects will not be paid for participating.

5.5. Return of Individual Research Results

Individual research results will not be provided back to subjects.

6. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects will be withdrawn from the research without their consent by the investigator if they are non-compliant (miss scheduled study visits), or if the investigator determines that it is in the best interest of the subject. Also if the subject develops bilateral Ménière's disease during the study they will be withdrawn. There are no additional study activities requiring completion prior to subject withdrawal from the study. Subjects withdrawn from the study will not be replaced.

7. STUDY DEVICE

7.1. Study Device

The Mastoid oscillator is a small device (9 x 6 x 3 cm, ~200g see Appendix 1 for images) custom-made for the PI by Bridgekey Engineering Solutions of Rochester NY. It is secured with a Velcro elastic headband over the mastoid in the post-auricular region of the Ménière's affected ear. The contoured surfaces of the device ensure a smooth fit against the head and also no displacement of the ear. The placebo oscillator replicates the sound of the Mastoid oscillator but without the vibration to the skull. The device runs on a rechargeable battery and there is an on/off button. The start of vibration or sound is delayed by a few seconds after the device is turned on.

Between subject uses the device is cleaned with an alcohol wipe and stored by the study Research Technician in the Clinical Trials office of the ENT department at the Clinton Woods office, within a locked cabinet.

Note that this study is not intended to determine safety or effectiveness for commercial distribution of the oscillator or placebo oscillator. These are custom devices that are ordered by the principal investigator and are not generally available to other physicians. They are not generally available in finished form for purchase or for dispensing upon prescription and are not offered for commercial distribution through labeling or advertising. They are intended to meet the special needs of the principal investigator in the course of his professional practice.

7.2. Subject Enrollment/Randomization

Subjects will be randomized to either oscillation or placebo. The method for assigning study group will be a look-up table that is held in secret for the study personnel by the Chair of the Department of Otolaryngology, who will release either 'Device A' or 'Device B' at time of randomization from a pre-determined table with 1:1 group ratio.

8. RISK/BENEFIT ASSESSMENT

8.1. Potential Risks

1) Physical discomfort: Soreness at the site of oscillation. There is a theoretical risk of worsening of the symptoms of dizziness, however worsening of symptoms never occurred in any of the 66 patients involved in the pilot study. In addition, the vibration of the skull routinely occurs with drilling on the mastoid, something that is performed frequently on patients with middle ear and mastoid disease throughout the world. No complications directly related to the vibration of drilling have ever been reported.
2) Invasion of subject privacy.

8.2. Protection Against Risks

The risks of discomfort will be minimized by having the oscillation procedure performed by trained personnel/otolaryngologists in a professional office setting.

Privacy will be protected by minimizing the number of people with access to the subject's identifying data, which will be stored in REDCap, making use of its built in privacy protections. All study personnel will have training in human subjects protections.

8.3. Potential Benefits to Subjects

There is no benefit to subjects of participating.

8.4. Alternatives to Participation

The alternatives to participation in the study include traditional, time-honored invasive treatments for Ménière's disease.

9. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from the subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for the use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect

at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.
We will exercise the following practices to maintain confidentiality of data and protecting against unauthorized disclosure:

- not downloading identifying information from REDCap except subject ID number (i.e., keep any identifying information separately from any research data)
- locking up research files while they are unsupervised
- using screensavers
- shredding excess copies of paper documents
- protections for codes that link patients to their data
- electronic and physical security of data storage devices and networks
- security measures to protect storage and transmission of electronic data

10. RESEARCH INFORMATION IN MEDICAL RECORDS

Study participation will be indicated in the medical record.

11. DATA ANALYSIS AND MONITORING

11.1. Sample Size Determination

The pilot study[2,3] showed that mastoid oscillation treatment was highly efficacious. Of 66 subjects that were treated, 22 (33.3%) achieved complete control, 30 (45.4%) achieved substantial control, 11 (16.7%) achieved limited control and three (4.5%) had insignificant control. A control group (N=30) with delayed start of treatment had just 2 subjects with improvement of symptoms (complete or substantial) during the wait period (6.6%).
For our sample size projection, we assume that the Mastoid Oscillation arm will have a 75% rate of achieving substantial or complete control, and 12% for the placebo group. With 15 subjects in each group, using Fisher's Exact test, the design has 95% statistical power with alpha of 0.012.

11.2. Planned Statistical Analysis

At the completion of the last study subject, the blinding will be broken and the aggregate results of the treatment and control arm will be compared.

The primary outcome measure is the change in monthly vertigo episodes. Per the AAO guidelines[4], this has a numeric value of X/Y x 100, where X is the average number of definitive spells per month after therapy, and Y is that rate prior to therapy. Categories A-F are designated, and the Chi-square/Fisher's Exact test will be used to compare the treatment and placebo groups.

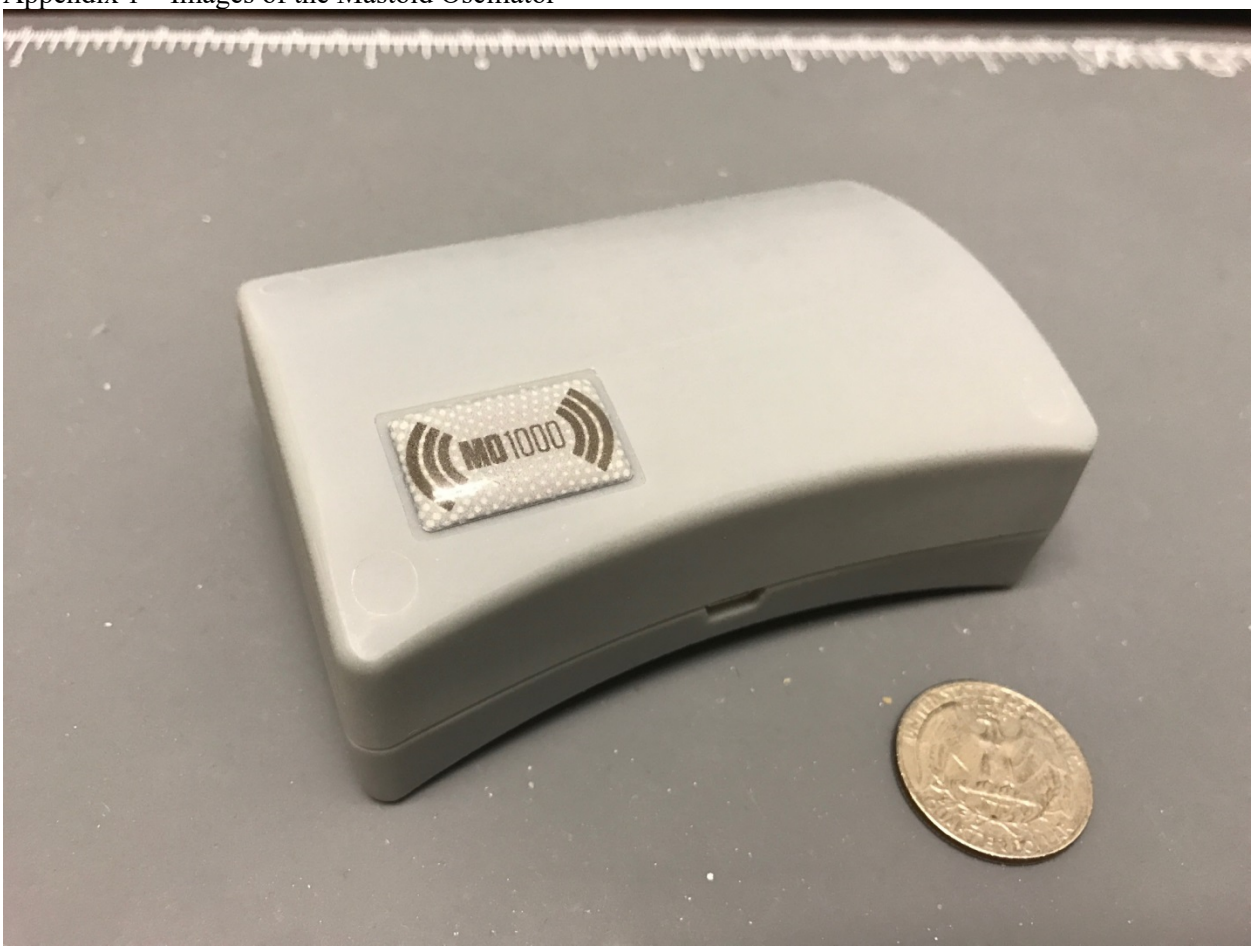
Numeric Value	Class	Description
0	A	Complete control
1 to 40	B	Substantial control
41 to 80	C	Limited Control
81 to 120	D	Insignificant Control
> 120	E	Worsening of symptoms
	F	Secondary treatment initiated due to disability from vertigo

Secondary outcome measures are the average hearing threshold and word recognition score, which will be compared by repeated-measures ANOVA. Another secondary outcome measure is the patient Meniere's functional level before and after treatment (Appendix 2).

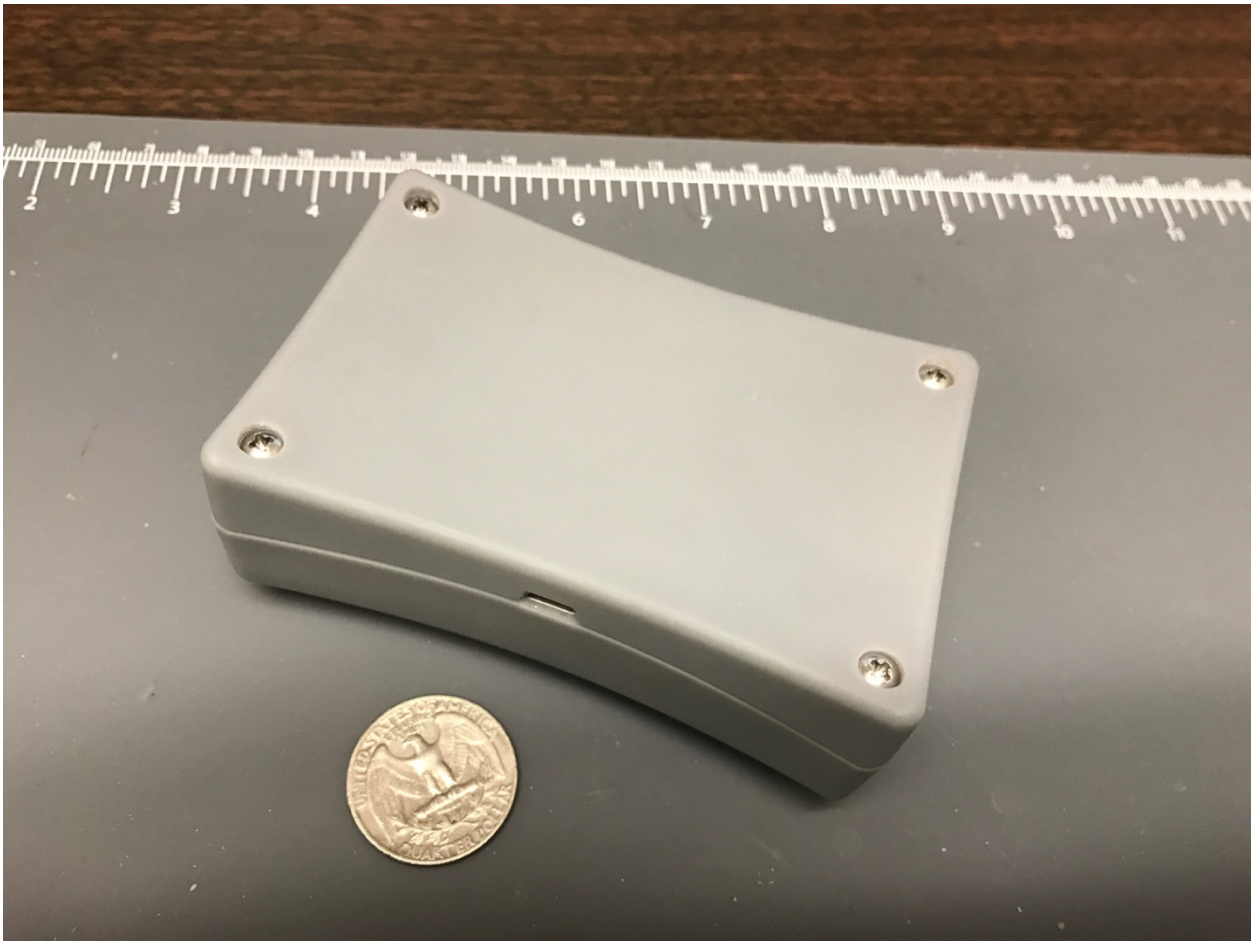
12. REFERENCES

1. Thomsen, J.; Tos, M.; Johnsen, N.J.; Placebo Effect in Surgery for Ménière's Disease; Arch Otolaryngol Head and Neck Surg 107:271-277,1981.
2. Dutcher, P.; Abstract presentation at the American Academy of Otolaryngology Head and Neck Surgery, September 2002.
3. Dutcher, P.; Abstract presentation at the American Academy of Otolaryngology Head and Neck Surgery, September 2005.
4. Monsell, E. M., Balkany, T. a, Gates, G. a, Goldenberg, R. a, Meyerhoff, W. L., & House, J. W. (1995). Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg*, *113*, 181–5

Appendix 1 – Images of the Mastoid Oscillator



The Mastoid Oscillator is a custom device created for the PI by Bridgekey Engineering solutions



The low profile and contoured edges of the mastoid oscillator allow it to fit comfortably over the mastoid bone without displacing the ear.

Appendix 2

Meniere's Functional level scale

"Regarding my current state of overall function, not just during attacks (check the ONE that best applies):

1. My dizziness has no effect on my activities at all.
2. When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
3. When I am dizzy I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
4. I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.
5. I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.
6. I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.