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TITLE: Development of a Device for Objective Assessment of Tinnitus in Humans

PRINCIPAL INVESTIGATOR: Jeremy G. Turner, PhD

CONTRACTING ORGANIZATION: OtoScience Labs, LLC
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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary device has undergone substantial engineering/bench testing and laboratory testing. Final refinements of the device are being completed in the last quarter of 2016. Secured IRB approvals for all study sites (SIU, Portland VA, Madigan Army Medical Center). HRPO approvals obtained for all study sites. IRB Continuing Review (CR) and HRPO CR approvals also obtained for SIU and PVA. MAMC IRB CR and HRPO CR approvals are not due until June 2017 and September 2017. Optimizing device/test/protocol based on feedback from our pilot work and consultants. Recruitment of subjects for testing at SIU is underway using a secondary device, which allows us to proceed with early protocol development/testing and for validating the primary device when it is ready.

15. SUBJECT TERMS
None provided

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Tinnitus is the perception of sound in the ears or head when no external sound is present. The US Department of Veterans Affairs (2009) reports that tinnitus is the most prevalent new disability claim and the most prevalent overall service-connected disability for those receiving compensation. Despite the prevalence of tinnitus and its sometimes debilitating symptoms, the cause(s) and treatment(s) have been especially difficult to identify. One major obstacle in the development of our understanding of the pathophysiology, prevention, and treatment for tinnitus is the fact that a truly objective measure of tinnitus does not exist. Our goal is to provide an efficient instrument to the DoD that would allow it to screen military personnel for tinnitus before deployment and regularly thereafter as a normal part of their audiological evaluation. This measurement will introduce objectivity into tinnitus assessment, help to limit malingering, and provide a baseline upon which decisions about deployment and disability compensation can be made. The current proposal presents a fundamentally novel approach to measuring tinnitus that measures whether the auditory system is capable of hearing silence, the core deficit in tinnitus. Our measure has already been widely used in animal research to measure tinnitus, and has recently been shown to work to measure tinnitus deficits in humans. With refinement, we believe the technology could be ready to implement as a widely available objective measure of tinnitus by the end of this grant period. The purpose of this current study is to develop an objective way to measure tinnitus. The first two years of the DoD grant was designed to further develop and refine the Gap Device and testing methodology. In the third year of the grant, we began to conduct a multisite research study to determine if people who suffer from tinnitus detect silent gaps that are embedded in background noise differently from people who have some hearing loss, but no tinnitus. We are continuing that work now during our no-cost extension period. Our hypothesis is that subjects with tinnitus will not be able to detect silent gaps embedded in background acoustic noise. Results from this DoD supported research will be used to further develop an FDA approved diagnostic device for assessing tinnitus in humans.

2. KEYWORDS: Tinnitus, Diagnostic Device Development, Human Testing, Multisite Study

3. ACCOMPLISHMENTS: *The Principal Investigator is reminded that the recipient organization is required to obtain prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.*

Our original SOW included 12 major tasks. We submitted a revised SOW on July 14, 2017 along with a request for a 12 month no cost extension (NCE) for this project which was approved on July 19, 2017.

Site Key: OSL - Work to be done at OtoScience Labs; **SIU** - Work to be done at SIU School of Medicine's Center for Clinical Research; **Portland VA NCRAR** - Work to be done at the Portland VA Medical Center National Center for Rehabilitative Auditory Research; **MAMC** - Work to be done at the Madigan Army Medical Center.

Specific Aim #1: Development and testing of single system capable of both a manual button press (subjective) and automated EMG eyeblink (objective) measurement of tinnitus.

Task 1. Prototype Development **(OSL): COMPLETED**
Task 2. Participant Selection and Recruitment **(OSL): COMPLETED**
Task 3. Develop initial protocols **(OSL): COMPLETED**
Task 4. Regulatory Approvals (IRB & HRPO) **(OSL, SIU, Portland VA NCRAR, MAMC): COMPLETED**
Task 5. Perform device testing at SIU **(OSL, SIU):** 50% complete; During our practice sessions at SIU this year, we encountered an artifact in the acoustical background noise with our primary study device. This problem was also detected in our duplicate device during practice sessions by our team at Portland VA NCRAR. The two primary study devices had to be sent back to our engineers and OSL, and our engineers are currently working to correct the problem. Indeed, it appears to have been fixed this week. In the meantime, we had to proceed with human testing using the back-up system (Plan B device).* Testing is currently underway at Portland VA NCRAR and MAMC using the back-up system. Dr. Turner synthesized the 9 audio wav. files necessary for the back-up system. We plan to resume testing at SIU using the primary device as soon as it is ready and possibly conduct some head-to-head comparisons between the primary device and our back-up system.

Task 6. Data analysis, study report, manuscript submission **(OSL, SIU):** 20% complete; expected completion after ALL data at all three sites are collected and analyzed.
Task 7. Prototype Adjustments **(OSL) COMPLETED** – Initial prototype adjustments were completed during the second and third quarters of 2016 and prior to delivery to our study sites. During the training sessions, we encountered some background noise that required some software and hardware adjustments to the device(s). Once these corrections were made, the device(s) were sent back to the study sites to begin testing. During the practice sessions, we encountered a new artifact background noise that had the potential to interfere with threshold and Gap testing. Our engineers are currently working to correct the problem before we re-introduce the primary device. As of this submission, the engineers report that they have fixed the problem in the circuitry and we hope to have it to test soon. The goal remains to both develop a standard button-press audiometric test for tinnitus that can be used seamlessly with a follow-up objective eyeblink-based test to confirm tinnitus hits. Our hypothesis remains that participants with tinnitus will demonstrate deficits processing silent gaps, and that these deficits will be present using the EMG-based eyeblink startle reflex, as well as the traditional button-pressing subjective approach.

Specific Aim #2: Measuring Hyperacusis in participants with tonal tinnitus

Task 8. Assess value of device for measuring hyperacusis **(OSL, SIU, Portland VA NCRAR, MAMC)**: 0% complete; will occur at the time that data collection is finished at each site (tasks 6 and 11).

Specific Aim #3: Measuring tinnitus at external sites

Task 9. System delivery and training at field sites **(OSL, Portland VA NCRAR, MAMC):** 90% complete; We installed the primary device at Portland VA and conducted training sessions that included all study site research staff at a meeting held in Portland/NCRAR in March 2016. Additional training at NCRAR and MAMC has been ongoing.
Task 10. Protocol amendments **(OSL, SIU, Portland VA NCRAR, MAMC)**: **COMPLETED**
Task 11. Perform studies at two external sites (OSL, NCRAR, MAMC): 30% complete; Portland VA NCRAR is recruiting and testing subjects using the back-up system (Plan B device). They are scheduled to complete testing by December 31, 2017. MAMC is also recruiting and testing subjects using the back-up system. We anticipate that they will complete testing by December 31, 2017.
Task 12. Analysis and submission for publication (OSL, SIU, NCRAR, MAMC): 10% complete; we will be processing data as it arrives from each site and analysis and write-up will be completed as soon as data collection is completed. We expect to have this task finished in the Summer of 2018, well within the one-year NCE period.

*Note. The key difference between our back-up system (Plan B device) and the primary device we are developing with this grant funding is the degree to which the device is automated and ready for testing and development for the FDA approval process. The primary device we are developing as part of this grant would be much closer to a clinically useful diagnostic tool and would be ready for a clinical trial of the device and an Investigational Device Exemption (IDE) application to the U.S. Food and Drug Administration. The back-up Plan B device is essentially the same tool used by eyeblink startle researchers.

Further, we identified a contact at FDA, Cherish Guisto, AuD, Clinical Reviewer in Audiology, FDA, CDRH, Office of Device Evaluation, ENT Branch who discussed our plans for developing and testing our tinnitus device with the ENT Devices Branch Chief, Dr. Srinivas Nandkumar. In addition to providing written confirmation from FDA that our non-significant risk (NSR) determination is adequate and that we are not required to submit an IDE to study our device at this time, they provided very helpful information and advice.

Preliminary advice from FDA indicates that our device would likely be classified as a Class II device because FDA has other diagnostic devices with ENT indications that are Class II. They were not able to advise us yet as to whether our device would be appropriate for the 510(k) pathway or would require a de novo application. However, they do recommend that we submit a pre-submission request to obtain formal feedback regarding our proposed regulatory pathway and study protocol. We will do this as we accrue more research on the device and its ultimate features.

We have fully executed research agreements (subcontracts) in place with SIU School of Medicine, Portland VA Research Foundation and The Geneva Foundation (for the Madigan Army Medical Center). We have fully executed contract amendments in place to continue testing at our external sites during the no-cost-extension period.

We have successfully secured initial IRB and HRPO approvals for all study sites (SIU, PVAHCS) and MAMC). Continuing Review (CR) approvals (IRB and HRPO) have also been secured for all sites. No new submissions are anticipated until Spring/Summer 2018.

Study Site 1 (SIU IRB #15-348) Initial IRB approval obtained August 13, 2015
(HRPO A-18564.a & .b) Initial HRPO approval obtained December 29, 2015
SIU IRB Continuing Review (CR) approval obtained June 5, 2016
HRPO Continuing Review (CR) approval obtained September 26, 2016
SIU IRB Protocol Amendment #1: Approved October 6, 2016
SIU IRB Protocol Amendment #2: Approved December 7, 2016
SIU IRB Protocol Amendment #3: Approved February 23, 2017
HRPO Protocol Amendment submitted Mar 13, 2017; Approved April 12, 2017
SIU IRB CR approval submitted April 25, 2017; Approved April 26, 2017
HRPO CR approval submitted May 6, 2017; Approved May 8, 2017

Study Site 2 (PVAHCS IRB #669357) Initial IRB approval obtained November 24, 2015
(HRPO A-18564.c) Initial HRPO approval obtained March 25, 2016
PVAHCS IRB CR approval obtained September 12, 2016
HRPO Continuing Review approval obtained September 23, 2016
PVAHCS IRB Protocol Amendment submitted 3/14/17; Approved 4/25/17
HRPO Protocol Amendment submitted May 4, 2017; Approved May 8, 2017
PVAHCS IRB CR submitted July 3, 2017; Contingent CR Approval 8/4/17; Final CR Approval 8/10/17
HRPO CR Application submitted 8/15/2017; HRPO CR Approval 8/16/2017

Study Site 3 (MAMC & RHC-P IRB #216040) Initial IRB approval June 7, 2016
HRPO A-18564.d) Initial HRPO approval obtained on September 22, 2016
New IRB: Regional Health Command-Pacific IRB (RHC-P IRB) eff Feb 1, 2017
RHC-P IRB CR application submitted Feb 15, 2017; Approved April 12, 2017
RHC-P IRB Protocol Amendment submitted 3/13/17; Approved 4/21/17
HRPO CR application submitted May 4, 2017
- Requested acknowledgement of CR on May 12; no reply
- Resubmitted CR app per HRPO reviewer on May 16, 2017; Additional documents requested 5/22/17; Approved 5/24/17

HRPO Protocol Amendment submitted May 13, 2017; Approved 5/24/17
RHC-P Protocol Amendment (Site PI Change**) – Submitted 5/12/17; Resubmitted 6/19/17; Approved 7/6/17
HRPO Protocol Amendment (Site PI Change**) – Submitted 7/7/17; Approved 7/11/17

**MAMC also experienced a change in their site PI this year. LTC James Crawford, MC was replaced by LTC Nelson S. Howard, MD, MBA. The amendment reflecting the change in site PI was submitted to the RHC-P IRB on May 12, 2017 and approved July 6, 2017. HRPO approval for the change in site PI was approved July 11, 2017. This change in study personnel also required an amendment to the subaward agreement between OSL and The Geneva Foundation. We have a fully executed amendment to the agreement effective June 15, 2017.

Our quarterly teleconference(s) with the research teams from all three sites were held in February, May and August 2017. Our next quarterly teleconference is scheduled to take place in early December 2017. However, we maintain weekly contact via email and/or phone with all study sites. We also hold bi-monthly meetings with SIU's Center for Clinical Research (CCR) to keep progress moving forward, as the CCR has been assisting with preparation and maintenance of regulatory documents, study coordination, project planning and communications with DoD, project

coordination with military and VA sites, conflict of interest management, FDA regulatory support, statistical support, and progress report assistance.

We are on target to complete the majority of our testing by the end of the first quarter 2018. Recruitment/enrollment of human subjects is currently underway at all three sites.

SIU (Study Site #1):

1871 Medical Records reviewed
70 inquiries
63 phone screened
37 eligible (32 tinnitus; 5 controls)

Portland VA NCRAR (Study Site #2):

64 inquiries
64 phone screened
34 eligible (27 tinnitus; 7 controls)
0 tested

MAMC (Study Site #3):

8 inquiries
5 screened
2 eligible (2 tinnitus; 0 controls)
1 tested

No results of research are yet available.

Our major plans during the next year include: 1) fixing the artifact background noise that currently exists in the primary study device; 2) completion of all human testing at SIU, Portland VA NCRAR and MAMC using either the back-up (Plan B) system and/or the primary device; and, 3) complete data analysis and prepare publications. We expect that we will be able to complete all study aims by September 30, 2018.

4. IMPACT: *This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period.*

What was the impact on the development of the principal discipline(s) of the project?

Tinnitus is the most common new disability claim of military personnel and the most prevalent overall service-connected disability. This fact just reflects the surface impacts on military personnel and the minimum monthly disability payments received by veterans do not begin to address the real costs, which include loss of silence and degraded hearing, expensive visits to medical professionals, hearing aids and other prescribed and non-prescribed treatment costs, lost productivity, social isolation, and greater risk for other conditions such as anxiety disorders and depression. In addition, veterans are more than twice as likely to experience tinnitus as age-matched non-veterans.

The DoD and VA could desperately use a tool to measure tinnitus. While fMRI measures of tinnitus have been explored extensively, they have not been shown capable of measuring tinnitus the way many had hoped. This coupled with their high cost suggest a more efficient approach would be desirable. The current proposal presents a fundamentally novel approach to measuring tinnitus that measures whether the auditory system is capable of hearing

silence, the core deficit in tinnitus. Our measure has already been widely used in animal research to measure tinnitus, and has recently been shown to work to measure tinnitus deficits in humans. With refinement, we believe the technology could be ready to implement as a widely available objective measure of tinnitus by the end of this grant.

Congress has mandated DoD to investigate diagnosis and treatment for tinnitus. Our goal is to provide an efficient instrument to the DoD that would allow it to screen military personnel for tinnitus before deployment and regularly thereafter (including once they attain veteran status) as a normal part of their audiological evaluation. This measurement will introduce objectivity into tinnitus assessment, help to limit malingering, and provide a baseline upon which decisions about deployment and disability compensation can be made.

We are already finding that our work is having an impact on our discipline. As others learn that we are exploring the development of an objective assessment of tinnitus, the interest grows, and other ideas emerge. We think one benefit of our funded project is to spur on the development of other research and development in this area, independent of our work.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. ***CHANGES/PROBLEMS:*** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.*
Changes in approach and reasons for change

As has been reported in previous progress reports and in conversations with our program officer, we have experienced delays in the primary device. These delays were originally due to health problems with our chief engineer and a technical issue with an audible acoustic transient click in the circuitry which required substantial engineering efforts to identify and resolve. We spent much of our time this past year further optimizing the study device(s). We encountered a software problem with the prototype device at SIU and had to ship it back to the engineers. This problem was corrected and the device was shipped back to SIU on June 26, 2017. Similar software adjustments were also made to the duplicate device. The duplicate device was re-installed by the engineers at Portland NCRAR on June 12-13, 2017. Again, having two prototype devices permits us to conduct testing at two separate sites simultaneously. The software adjustments were made to the audiogram program to optimize the sound presentation. We also installed a correction table that provides for calibration corrections at different sound frequencies. When the system is calibrated at each frequency used in the audiogram the user enters an "offset" for each frequency so that you get the expected dBs. Our engineers, Michael Kinder and John Kolb made a second site visit to PVAHCS on June 12-13 and Jeremy Turner made a second site visit to PVAHCS on June 29-30 to ensure that the device was working properly and the study team was prepared to begin testing. Because we only have two study devices, we cannot initiate testing at our third site until one of our other two sites competes human testing. We thought this issue had been corrected, but encountered another artifact in the device during our practice sessions (an audible background noise) that had the potential to interfere with threshold and Gap testing. The study devices, were again, sent back to the engineers and they are currently working on this issue. At the time of this submission, our engineers report identifying the problem in the circuitry and have fixed it. In order to give engineering the time it needs to confirm these fixes, we have proceeded with human testing using the back-up system (Plan B device). Dr. Turner had to synthesize the nine audio .wav files necessary for the testing, but they seem to be working well. Currently, we are recruiting at all

three sites, but only testing at our two external sites because we only have two test systems. We are hopeful to resume testing at the SIU site with the primary device and plan to conduct some head-to-head comparisons with the back-up system (Plan B device) currently being used at our two external sites.

Actual or anticipated problems or delays and actions or plans to resolve them

The technical problems that we have experienced with the primary device have contributed to the delays in testing human subjects, however we have moved forward with our back-up system (Plan B device). The back-up system (Plan B device) we are using is functionally equivalent to the primary device we are creating. They only differ with respect to automation, as the primary device we are developing is to be automated as much as possible. Our engineers have identified a problem with the circuitry that is being corrected. Indeed, as of this week we have tested the primary device on three normal listeners and they all confirm the background noise problems are gone, so the primary device appears to be ready to test whenever one of the two sites (MAMC or PVAHCS) is completed with the Biopac and other equipment needed for testing. We still anticipate being able to use the primary device to complete our primary study aims. These technical issues are not completely unexpected when developing a new technology that is designed to objectively measure tinnitus in humans. Our study sites continue to remain enthusiastic about the project and have agreed to continue to assist us as much as possible. We communicate frequently with our study sites and will continue to closely monitor efforts to meet our accrual goals.

We also decided to optimize the time left on the grant with funds that are currently available for our external sites. We are currently concentrating our recruitment and testing efforts at Portland VA and MAMC using the back-up systems. Once the primary device is ready, we plan to resume testing at the SIU site.

Finally, we submitted a request for a no cost extension (NCE) to continue this study until September 30, 2018. The NCE was approved on July 19, 2017.

Changes that had a significant impact on expenditures

The unexpected health problems of our engineer and the associated technical problems that we have encountered with the primary device have resulted in higher engineering costs than budgeted. However, we are working to fund these additional costs through reallocation of funds from other consultants use of overhead funds for these purposes.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None.

6. *PRODUCTS:* *List any products resulting from the project during the reporting period.*

OtoScience Labs' website (www.otosciencelabs.com) has been updated and it now refers to our human tinnitus test development. We also have a DoD-approved press release on the website that refers to our project. OtoScience Labs' tinnitus testing technology was highlighted in February 2017 on the FOX Business News.

7. *PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS*

What individuals have worked on the project?

Name:	*Jeremy Turner, PhD*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*

Contribution to Project:	*Dr. Turner has served as the PI on this project, serving as general oversight over all aspects of the grant, but especially focused on coordinating between consultants and subawards, regulatory paperwork, development of the tinnitus testing session/parameters, and oversight of the testing done at all three sites.*
Name:	*Michael Kinder*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Mr. Kinder has served as the co-PI on this project, overseeing all aspects of the hardware and software development for the device.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Organization Name: Southern Illinois University (SIU) School of Medicine
Location of Organization: Springfield, IL
Partner's contribution to the project: SIU School of Medicine Center for Clinical Research participated in bi-monthly planning meetings as we have been preparing to conduct human testing of the GAP Device at three participating sites (SIU School of Medicine, Springfield IL; Madigan Army Medical Center, Tacoma WA: National Center for Rehabilitative Auditory Research/Portland VA Healthcare System, Portland OR). Research personnel assisted with development of site-specific IRB documents (protocols, consent forms, recruitment materials, and related materials) that were submitted to the SIU School of Medicine IRB.

Organization Name: Madigan Army Medical Center
Location of Organization: Tacoma, WA
Partner's contribution to the project: Research personnel assisted with development of site-specific IRB documents (protocols, consent forms, recruitment materials, and related materials) that were submitted to the MAMC IRB. Research personnel are participating in quarterly conference calls.

Organization Name: Portland VA Healthcare System/Portland VA Research Foundation
Location of Organization: Portland, OR
Partner's contribution to the project: Research personnel assisted with development of site-specific IRB documents (protocols, consent forms, recruitment materials, and related materials) that were submitted to the Portland VA Healthcare System IRB. Research personnel are participating in quarterly conference calls.

8. ***SPECIAL REPORTING REQUIREMENTS:*** *None*
9. ***APPENDICES:*** *None*