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

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14. ABSTRACT

The most significant accomplishments in the first year of the grant were three-fold:

1) Completed an exhaustive hardware and software design review by our team of scientists, consultants, and hardware and software engineers. The printed circuit board (PCB) design layout has completed a thorough engineering evaluation and has been released for assembly. The device will undergo additional bench testing in the coming weeks and should be ready for testing human subjects as soon as regulatory approval are received.

2) Received IRB approval for year 2 testing at SIU School of Medicine. Submitted for approval all of the necessary paperwork for IRB/regulatory approvals at each site for year 3 (Madigan Army Medical Center, Portland VA). HRPO application has been submitted and is being reviewed.

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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 year of the DoD grant was to further develop and refine the Gap Device and testing methodology. We then plan 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. 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 SOW proposed four major tasks that we would focus on this year.

SOW Major Task 1 - Prototype Development, using the preliminary findings from the ongoing work at SIU School of Medicine as a guide, was the primary objective of Grant Year 1. Our SOW indicates we were to be working on hardware and software integration, upgrades of prototype, and system documentation. We have also been working on incorporating redundant sound level safety systems to prevent experimenter error or accidental noise overexposure to participants. We have made excellent progress on these efforts for the period ending September 30, 2015. We have completed an exhaustive hardware and software design review by our team of scientists, consultants, and hardware and software engineers. The printed circuit board (PCB) design layout has completed a thorough engineering evaluation and has been released for assembly. The device will undergo additional bench testing in the coming weeks and should be ready for testing human subjects as soon as regulatory approval are received.

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.

SOW Major Tasks 2 and 3 – Dr. Turner and regulatory consultant Dr. Sandra Puczynski traveled to Madigan Army Medical Center and the National Center for Rehabilitative Auditory Research/Portland VA Healthcare System to meet with sub-award research partners at those institutions on Feb 5 - 6, 2015 to review overall program goals and objectives, discuss proposed study protocol, site specific requirements, inclusion and exclusion criteria, data collection and overall logistics. These meetings were held as planned and were very productive. Besides the face-to-face meetings, we have had multiple teleconferences and e-mail communications with our research teams, consultants and sub-award collaborators about key steps in our research plans for the period ending September 30, 2015. Testing at these two sites will be conducted in Year 3 of the grant but we have already submitted the IRB applications at these sites.

Importantly, we decided to conduct Year 2 testing of human subjects at SIU School of Medicine facilities rather than at the OSL facility. We believe that this will yield the greatest participant recruitment numbers and will allow a streamlining of testing from our previous studies in the same laboratory. We are currently holding 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 have fully executed research agreements (subcontracts) in place with the Portland VA Research Foundation and The Geneva Foundation (for the Madigan Army Medical Center). Our research agreement with SIU School of Medicine is near final but was delayed due to modifications we made to budget and plans for conducting Year 2 participant enrollment at SIU rather than at OSL.

SOW Major Task 4 – IRB Approvals. The major regulatory task in the first year of this grant was development and submission of the IRB paperwork for the Year 2 testing at SIU School of Medicine. We received IRB approval by SIU School of Medicine IRB effective August 13, 2015. All IRB applications and related documents have also been submitted to the Portland VA Healthcare System IRB and the Madigan Army Medical Center IRB and are pending approval. Initial HRPO application was submitted this month and is currently under review.

While no results of research are yet available, as the first year of the grant was focused on development of the device and regulatory approvals, we have disseminated a press release about the grant and our efforts to develop a measuring device for tinnitus.

Our major plans during the next year (Year 2 of the grant) include testing our device in human participants at SIU School of Medicine and making any additional modifications of the device before deployment in Year 3 of the grant for testing at Madigan Army Medical Center and Portland VA.

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

The only change in approach is that we are moving our in-house testing to SIU School of Medicine rather than at our OSL facility. SIU is currently conducting other funded research in this same area so it would provide a much more seamless transition and would enable the recruitment of more participants. We have discussed this in prior quarterly progress reports and are currently working on revising the budget with our contract specialist. No changes to the overall budget are requested, as we are simply moving funds from OSL to a subaward at SIU School of Medicine. SIU was already listed as a subaward in our grant so this change just involves moving additional funds to that subaward from OSL.

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

None.

Changes that had a significant impact on expenditures

None.

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. There are no other publications, presentations, patents, or other products to report as yet.

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, and development of the tinnitus testing session/parameters.*

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 prepare to conduct human testing of the GAP Device at three participating sites over the next two years (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.

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.

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