

AWARD NUMBER: W81XWH-14-2-0180

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

PRINCIPAL INVESTIGATOR: Jeremy G. Turner, PhD

**CONTRACTING ORGANIZATION: OtoScience Labs, LLC
Jacksonville, IL 62650**

REPORT DATE: October 2016

TYPE OF REPORT: Annual

**PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012**

**DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited**

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2016		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2015 - 29 Sep 2016	
4. TITLE AND SUBTITLE Development of a Device for Objective Assessment of Tinnitus in Humans				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-2-0180	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Jeremy G. Turner, PhD jturner@otosciencelabs.com				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) OtoScience Labs, LLC Jacksonville, IL 62650				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
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-					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	9	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	6
5. Changes/Problems.....	7
6. Products.....	8
7. Participants & Other Collaborating Organizations.....	8
8. Special Reporting Requirements.....	9
9. Appendices.....	9

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 includes 12 major tasks. Progress has been made on tasks #1 and #5. Tasks #2, 3 and 4 are completed.

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 completed a thorough engineering evaluation and was released for assembly. The device was assembled and underwent additional bench testing and it was during that process that we discovered a transient, audible click during certain aspects of the stimulus presentation. We have spent many months determining the source and solution for this problem and are completing the engineering now. We will complete this engineering in the final quarter of 2016 in time for installation and testing at the two outside sites, at the Portland VA Healthcare System (PVAHC) and Madigan Army Medical Center (MAMC).

As described in previous communications with our program officer, we are on schedule to complete the device in time to deliver it to the two external sites by the end of December, 2016. This would allow us sufficient time at those sites to train the personnel on the equipment and for them to do their research. We have been keeping those two sites (VA and DoD) up-to-date on our progress and they indicate that if the device is ready for the beginning of 2017 they will be able to complete their testing of the device in a timely manner and get the grant back onto our original timeline. If the device is not ready by the end of December, we will stop all engineering efforts on our device and revert to a secondary device that we have been using for research purposes. This secondary device is being used for our internal testing in the laboratory and at SIU SOM and it can accomplish the aims of the grant, but would not be suitable for further clinical development post-award. The secondary device would involve additional

efforts in data analysis, but with our existing consultants and budget we can accomplish that step. Our two external sites have agreed that they could share this one device for their testing, if we had to do that.

The key difference between our secondary research 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. If it is not ready by the end of December, 2016, we will seek private funding for the development of the device and continue with our research on this grant with the secondary device.

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 (COMPLETED)– 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, 2016. We have IRB and HRPO approved protocols and consent forms in place for all three participating test sites (Southern Illinois University School of Medicine (SIU), Portland VA Healthcare System (PVAHCS), and Madigan Army Medical Center (MAMC)).

Importantly, we decided to conduct Year 2 testing of human subjects at SIU School of Medicine (SIU) 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 SIU School of Medicine, Portland VA Research Foundation and The Geneva Foundation (for the Madigan Army Medical Center).

SOW Major Task 4 – IRB Approvals (COMPLETED) 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 the SIU and PVAHCS sites. MAMC CR approvals will be due in June (IRB) and September (HRPO) 2017.

Study Site 1 (SIU IRB #15-348)
(HRPO A-18564.a & .b)

Initial IRB approval obtained August 13, 2015
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 Amendment #1: Approved October 6, 2016*

Study Site 2 (PVAHCS IRB #669357) (HRPO A-18564.c)	Initial IRB approval obtained November 24, 2015 Initial HRPO approval obtained March 25, 2016 PVAHCS IRB CR approval obtained September 12, 2016 HRPO Continuing Review approval obtained September 23, 2016
Study Site 3 (MAMC IRB #216040) (HRPO A-18564.d)	Initial IRB approval obtained on June 7, 2016 Initial HRPO approval obtained on September 22, 2016 IRB CR approval will be due June 5, 2017 HRPO CR approval will be due September 21, 2017

*Note. An amendment to the protocol was approved by SIU IRB prior to human testing that reflect modifications made to the inclusion and exclusion criteria and refinements in our methods for measuring tinnitus.

SOW Major Task 5 –OSL Testing of Prototype – As described in our 2015 Annual Report, initial human testing of the study device was changed from OSL to SIU School of Medicine. We recently submitted an amendment (approved Oct 6, 2016) to the study protocol for the SIU site and prior to any human testing of the device. At this stage of device development, we determined a need to use a secondary device to gather additional information about the gap detection system and our methods for measuring tinnitus in humans. We need to better understand two key stimulus settings and whether we can use participants with hearing aids. We plan to use the secondary device at SIU as we refine our methods and complete the final prototype (primary automated) device. Once the final prototype device is ready, we will then use the secondary device system to further validate the information we obtain from the primary prototype device. The secondary device equipment 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. The ultimate 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.

Recruitment/enrollment of human subjects is currently underway at SIU. We have screened 9 potential subjects and 3 passed and are being scheduled for testing. We are also in the process of reviewing medical records from SIU SOM ENT patients who might qualify for our study. We are on target to complete the majority of our testing at SIU SOM in the last quarter of 2016.

No results of research are yet available, as the first two years of the grant have been focused on development of the device, optimizing the study protocol, and securing the various regulatory approvals.

Our major plans during the next year (Grant Year 3) include: 1) completion of the device prototype that will be used for human testing at PVAHSC and MAMC; 2) completion of all human device testing at SIU, PVAHCS and MAMC; 3) and complete data analysis and prepare publications. We expect that we will be able to complete all aims by the end of the 3rd year of the grant.

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 quarterly progress reports and in conversations with our program officer, we have experienced delays in the primary device. These delays are due to health problems with our chief engineer and a technical issue with an audible acoustic transient click in the circuitry which has required substantial engineering efforts to identify and resolve. In order to give engineering the time it needs to resolve these issues we have proceeded with internal testing at SIU SOM using a secondary device. This is allowing us to go ahead and answer some key protocol/methodological questions that will be useful for testing at the two outside sites when the primary device is ready. We expect the primary device to be ready for the beginning of 2017 in time to install it at the two external sites (PVAHC and MAMC) for testing there. We are preparing two identical version of the primary device so the two sites can conduct their work at the same time, in order to save time. We expect that we will be able to catch up and get back onto our original timeline in early 2017.

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

If we do have additional difficulty finalizing the primary device in time for testing at the two external sites in early 2017, our plan is to conduct the research at those two external sites using our secondary device that is being used at SIU. This will slow the completion of the study by a few months but we would still be able to complete

all data collection by the end of the grant. We would likely need a no-cost extension, however, for processing and analyzing the data and preparing it for publication.

Changes that had a significant impact on expenditures

The unexpected health problems of our engineer and the associated delays have resulted in higher engineering costs than budgeted. However, we are working to fund these additional costs through 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 is also being highlighted on an upcoming program called "Innovations with Ed Begley Jr", later this fall. That final episode may refer to the DoD grant in its final version. If it does we will forward that transcript and/or footage to DoD for review before releasing. 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?

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

<i>Contribution to Project:</i>	<i>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.</i>
---------------------------------	---

<i>Name:</i>	<i>Michael Kinder</i>
<i>Project Role:</i>	<i>Co-PI</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	
<i>Nearest person month worked:</i>	<i>6</i>

<i>Contribution to Project:</i>	<i>Mr. Kinder has served as the co-PI on this project, overseeing all aspects of the hardware and software development for the device.</i>
---------------------------------	--

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