

AWARD NUMBER: W81XWH-15-1-0291

TITLE: Localizing and Assessing Amputee Pain with Intense Focused Ultrasound

PRINCIPAL INVESTIGATOR: Pierre D. Mourad

CONTRACTING ORGANIZATION: University of Washington, Seattle, WA

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

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.**

|  |                    |  |                                   |   |  |
|--|--------------------|--|-----------------------------------|---|--|
| <b>1. REPORT DATE</b><br>October 2020  |                    | <b>2. REPORT TYPE</b><br>Annual Report |                                   | <b>3. DATES COVERED</b><br>15Sep2019-14Sep2020  |  |
| <b>4. TITLE AND SUBTITLE</b><br>Localizing and Assessing Amputee Pain with Intense Focused<br><br>Ultrasound   |                    |  |                                   | <b>5a. CONTRACT NUMBER</b><br>13282005I         |  |
|  |                    |  |                                   | <b>5b. GRANT NUMBER</b><br>W81KWH-15-1-0291     |  |
|  |                    |  |                                   | <b>5c. PROGRAM ELEMENT NUMBER</b>               |  |
| <b>6. AUTHOR(S)</b><br>Pierre D. Mourad, PhD<br>Email: domitt@uw.edu<br><br>E-Mail:  |                    |  |                                   | <b>5d. PROJECT NUMBER</b>                       |  |
|  |                    |  |                                   | <b>5e. TASK NUMBER</b>                          |  |
|  |                    |  |                                   | <b>5f. WORK UNIT NUMBER</b>                     |  |
| <b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b><br>Department of Neurological Surgery<br>University of Washington<br>Box 336470<br>Seattle WA 98195-6470   |                    |  |                                   | <b>8. PERFORMING ORGANIZATION REPORT NUMBER</b> |  |
| <b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b><br><br>U.S. Army Medical Research and Materiel Command<br>Fort Detrick, Maryland 21702-5012   |                    |  |                                   | <b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>         |  |
|  |                    |  |                                   | <b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>   |  |
| <b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b><br><br>Approved for Public Release; Distribution Unlimited  |                    |  |                                   |   |  |
| <b>13. SUPPLEMENTARY NOTES</b>   |                    |  |                                   |   |  |
| <b>14. ABSTRACT</b><br>In order to study the differential sensitivity of peripheral pain generators in the residual limb of two classes of amputees, we use our existing research-grade image-guided intense focused ultrasound (ig-iFU) system to stimulate those pain generators. Targets for iFU stimulation include neuromas, intact nerves, TMR (targeted muscle reinnervation) sites, and patient-identified 'sensitive areas'. We have successfully stimulated intact and transected nerves in our amputee patients and intact volunteers. We have observed significant differences in how the different groups respond to iFU stimulation and how the threshold value of iFU intensity necessary to generate sensations relates to different factors such as overall pain score, neuropathic pain, and the presence of phantom feelings and pain. Specifically, our data suggest that TMR surgery produces transected nerves less sensitive to (iFU) stimulation than 'standard' transected nerves, with those in neuropathic pain showing the greatest difference. We remain short of our enrollment goal of 45 TMR patients, with nearly-completed plans to deploy at Northwestern University to address that shortfall. |                    |  |                                   |   |  |
| <b>15. SUBJECT TERMS</b><br>Image guided intense focused ultrasound (ig-iFU) Intense focused ultrasound (iFU), Targeted Muscle Reinnervation surgery (TMR), limb amputation, Ultrasound  |                    |  |                                   |   |  |
| <b>16. SECURITY CLASSIFICATION OF:</b>   |                    |  | <b>17. LIMITATION OF ABSTRACT</b> | <b>18. NUMBER OF PAGES</b>                      | <b>19a. NAME OF RESPONSIBLE PERSON</b>           |
| <b>a. REPORT</b>   | <b>b. ABSTRACT</b> | <b>c. THIS PAGE</b>                    |                                   |   | <b>19b. TELEPHONE NUMBER</b> (include area code) |
| Unclassified   | Unclassified       | Unclassified                           | Unclassified                      | 7   | USAMRMC  |

## Table of Contents

|   | <u>Page</u> |
|---|-------------|
| 1. Introduction                               | 4           |
| 2. Keywords                                   | 4           |
| 3. Overall Project Summary                    | 5           |
| 4. Key Research Accomplishments               | 6           |
| 5. Conclusion                                 | 6           |
| 6. Publications, Abstracts, and Presentations | 7           |
| 7. Inventions, Patents and Licenses           | 7           |
| 8. Reportable Outcomes                        | 7           |
| 9. Other Achievements                         | 7           |
| 10. References                                | 7           |
| 11. Appendices                                | 7           |

## **1. INTRODUCTION.**

Chronic pain is problematic for many amputees. That pain can have many causes, such as buildup of scar tissue that surround the transected nerves that can then irritate nerve ending. In addition, traditional amputation surgery frequently produces a neuroma at the end of the nerve, itself a source of tenderness and pain. An alternative to standard amputation surgery, called “Targeted Muscle Reinnervation” or TMR surgery cuts the nerve and then implants it into nearby muscle. TMR surgery has anecdotal evidence of reduced pain for amputees relative to standard amputee patients, an important though unstudied finding. Here we seek to address this question directly, through two means. One is use of questionnaires to assess patient’s pain, which gives a general sense of the patient’s experience of their pain; the other uses image-guided focused ultrasound device (ig-iFU) to directly test the sensitivity of cut nerve endings in residual limbs of amputee patients. To support this, we will work with two, 45-participant cohorts of patients: TMR and standard amputation surgeries. We will, in addition, enroll 45 non-amputee participants as a control cohort. Our ig-iFU device uses ultrasound imaging to locate neuromas, nerves, and tissue, and individual, short pulses of high-intensity ultrasound to stimulate the nerve endings in the residual limbs. In this way we will directly determine which are more sensitive: those of standard amputee patients or of TMR patients. An important outcome of this study is determination of the relative merits of each surgical procedure with regard to their relative impact on patient pain.

## **2. KEYWORDS:**

- Image-guided intense focused ultrasound (ig-iFU)
- Intense focused ultrasound (iFU)
- Targeted muscle Reinnervation surgery (TMR surgery)
- Limb amputation
- Ultrasound

### 3. OVERALL PROJECT SUMMARY.

**Research Objective #1:** Determine the iFU threshold value required for reliable sensation induction and characterize those sensations, for intact peripheral nerves within healthy volunteers as well as within individuals with unilateral amputations, with or without TMR.

**Task 1.** Amend existing human subjects' protocol at HMC to include the more extensive studies described here.

- Completed: IRB and military HRPO approval have been obtained for work at UW.
- Completed: Obtained IRB approval at Northwestern University to increase our TMR patient subpopulation.

**Task 2.** Identify and consent volunteers with unilateral standard and/or TMR amputations or intact volunteers.

- Completed: We have identified and consented our allotted intact volunteers and standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Task 3.** Amend our existing ig-iFU device as necessary.

- Completed: We have completed design and construction of a final ig-iFU device.

**Task 4.** Image and thereby locate with our ig-iFU device an intact major peripheral nerve in the appropriate contralateral limb of standard and TMR amputees or of controls.

- Completed: We have imaged and located major peripheral nerves for all of our intact volunteers and standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Task 5.** Determine the iFU threshold value for an intact peripheral nerve and record the type and duration of the associated sensations.

- Completed: We have determined the threshold value and recorded associated sensations for all of our intact volunteers and standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Research Objective #2:** Determine the iFU threshold value of transected nerves in all amputee volunteers.

**Task 6.** Image, hence locate the transected nerve ending and patient-identified sensitive areas as appropriate, in the patient's residual limb with ig-iFU.

- Completed: We have imaged and located major transected peripheral nerves for our allotment of standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Task 7.** Stimulate the transected nerve ending of major peripheral nerves in the patient's residual limb with ig-iFU.

- Completed: We have stimulated the transected nerve ending of the major peripheral nerves for our allotment of standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Task 8.** Apply questionnaires to patients to assay their pain.

- Completed: We have applied questionnaires to our allotment of standard amputees.
- Incomplete: We have done so for all candidate TMR patients in the Pacific Northwest. At Northwestern University we will add sufficient patient numbers to complete this Task.

**Task 9:** Write up all results for publication and presentation.

- Completed: We have written up our results that compare the iFU threshold stimulation value for intact volunteers and standard amputees (Mourad et al, 2018; Bobola et al, 2019). We have also written a review paper that summarizes how ultrasound in many forms may contribute to the diagnosis and alleviation of pain, including ig-iFU (Bobola et al, 2018). Finally, we have documented the apparent reanimation of a TMR nerve with ig-iFU (Ezekeke et al, 2019)
- Incomplete: We have not completed our comparison of the iFU threshold stimulation value for intact volunteers versus standard amputees versus TMR amputees due to an insufficient amount of data from TMR amputees. We provided last year an interim report of the analysis that we could perform. Importantly, it shows that our requested work at Northwestern University will likely give us sufficient number of TMR amputees to complete our analysis.

**Task 10.** Visit Northwestern.

- IRBs approved at the University of Washington (UW) and at Northwestern University (NU).
- Documents submitted to HRPO; Correspondence on-going between UW/NU and HRPO

**Research objective #3:** Develop specifications of a clinical device that embodies intense focused ultrasound.

**Task 11.** Identify first-order ultrasound protocols and associated devices necessary to TAP.

- Completed: We have summarized this design in our review paper and last-year's report.

#### **4. KEY RESEARCH ACCOMPLISHMENTS.**

1. In support of that desire to collect data from more TMR amputees, we have obtained local IRB approval at Northwestern University and the University of Washington to deploy our ig-iFU device there to capture the last TMR patient data we need to complete our work.
2. We have under construction an NIH proposal that uses our image-guided iFU procedure to treat sleep apnea, an important problem for our wounded and aging worriers.
3. We also anticipate working with FUS-Mobile to identify tender tissue in and around the spinal column, tissue amenable to ultrasound-based ablation therapy, with funding sought from the Focused Ultrasound Foundation.

#### **5. CONCLUSION**

The well-known communication problems between some universities (such as UW) and DoD resolved by January 2020. At that point we immediately began discussions with Northwestern University to establish our research program there. Unfortunately, the onset of the pandemic virus shut everything down – administratively – starting in March 2020. In July 2020 we continued those negotiations, achieving local IRB approval at UW and NU by the end of the summer. We successfully submitted our documents to the DoD HRPO before the close of this grant. We have asked for yet another no-cost extension. All is ready to perform our studies at Northwestern *except* HRPO approval.

## 6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

Bobola M, Chen L, Ezeokeke CK, Kuznetslova K, Lahti AC, Lo W, Schimeck N, Selby M, Mourad PD (2018) Towards use of intense focused ultrasound for pain diagnosis and treatment: a review. *Current Pain and Headache Reports: Neuromodulation*. Jul10;22(9):60-72.

Bobola MS, Ezeokeke CK, Kuznetslova K, Lahti AC, Loeser JD, Olmstead TA, Friedly JL, Mourad PD (2019) A pre-clinical study of the response threshold of intact and transected nerves to stimulation by transcutaneous, intense focused ultrasound. *Ultrasound in Medicine and Biology*. Aug;45(8):2094-2103. doi: 10.1016/j.ultrasmedbio.2019.04.014.

Ezeokeke CK, Bobola MS, Selby M, Ko JH, Friedly JL, Mourad PD (2020). Case Study of an Amputee Regaining Sensation and Muscle Function in a Residual Limb after Peripheral Nerve Stimulation by Intense Focused Ultrasound. *Under revision at Brain Stimulation*.

Mourad PD, Friedly JL, McClintic AM, Olmstead TA, Loeser JD (2018) Intense focused ultrasound preferentially stimulates transected nerves within residual limbs: pilot study. *Pain Medicine*, V19:541-549. ePrint Sep 7 2017; doi: 10.1093/pm/pnx188.

Mourad PD, Bobola M, Ezeokeke CK, Selby M, Lahti AC, Loeser JD, Olmstead TA, Ko J, Friedly JL (2019) Interim report for W81XWH-15-1-0291 "Localizing and Assessing Amputee Pain with Intense Focused Ultrasound"

Various presentations on campus, some informal, one presented at the UW Neurological Surgery Grand Rounds.

## 7. INVENTIONS, PATENTS AND LICENSES.

Nothing to report.

## 8. REPORTABLE OUTCOMES.

- Image guided intense focused ultrasound (ig-iFU) can identify and help locate deep and focal pain generators, as demonstrated in residual limbs of amputee patients.
- Ig-FU can locate peripheral nerves thanks to their enhanced sensitivity relative to surrounding tissue, typically muscle, ligaments and bone.
- Spatial patterns in the sensitivity of peripheral nerves ipsilateral and contralateral to an amputation might convey information about spatial patterns in central sensitization, a major contributor to chronic pain in the amputee population.
- The presence versus absence of neuropathic pain in TMR patients strongly differentiates those with versus those without sensitivity of their TMR nerves to iFU stimulation. This is not true for standard amputee patients in our cohort.

## 9. OTHER ACHIEVEMENTS.

We have in hand a draft grant applications of various sorts that use the technology we have successfully deployed here. Our current focus is on treating sleep apnea by stimulating the hypoglossal nerve, known via invasive electrical stimulation to open the airway of human patients via FDA-approved technology. We also anticipate working with FUS-Mobile to identify tender tissue in and around the spinal column, tissue amenable to ultrasound-based ablation therapy.

## 10. REFERENCES

See above for citations to our publications.

## 11. APPENDICIES

None added.