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AWARD NUMBER: W81XWH-18-2-0009

TITLE: **Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain**

PRINCIPAL INVESTIGATOR: **Brian M. Ilfeld, MD, MS**

CONTRACTING ORGANIZATION: **University of California, San Diego**
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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation:
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5a. CONTRACT NUMBER

5b. GRANT NUMBER
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6. AUTHOR(S)

Brian M. Ilfeld, MD, MS

5d. PROJECT NUMBER

5e. TASK NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University California San Diego
200 West Arbor Drive
San Diego, CA 92103-8990

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

US Army Medical Research and Materiel Command,
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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 purpose of this two-stage, multicenter, randomized, double-masked, sham-controlled, human-subjects clinical trial is to evaluate the analgesic potential of ultrasound-guided percutaneous peripheral nerve stimulation (PNS) following painful ambulatory orthopedic surgery. The initial 2-year pilot study will estimate the treatment effects of percutaneous PNS on pain and opioid consumption to determine the appropriate sample size of the subsequent pragmatic clinical trial as well as to document the feasibility of and optimize the proposed protocol. The subsequent 4-year pragmatic trial will determine the effect of percutaneous PNS on postoperative analgesia and opioid requirements, as well as physical and emotional functioning, the development of chronic pain, and ongoing quality of life. This investigation has a strong potential to dramatically reduce or obviate postoperative opioid requirements and their resultant negative effects on both individuals and society; while concurrently improving analgesia, increasing the ability to function in daily life, decreasing the risk of transition from acute to chronic pain, and improving quality of life

15. SUBJECT TERMS

Ultrasound-guided percutaneous peripheral nerve stimulation; postoperative analgesia

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU		**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

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

The purpose of this two-stage, multicenter, randomized, double-masked, sham-controlled, human-subjects clinical trial is to evaluate the analgesic potential of ultrasound-guided percutaneous peripheral nerve stimulation (PNS) following painful ambulatory orthopedic surgery. The initial 2-year pilot study will estimate the treatment effects of percutaneous PNS on pain and opioid consumption to determine the appropriate sample size of the subsequent pragmatic clinical trial as well as to document the feasibility of and optimize the proposed protocol. The subsequent 4-year pragmatic trial will determine the effect of percutaneous PNS on postoperative analgesia and opioid requirements, as well as physical and emotional functioning, the development of chronic pain, and ongoing quality of life. This investigation has a strong potential to dramatically reduce or obviate postoperative opioid requirements and their resultant negative effects on both individuals and society; while concurrently improving analgesia, increasing the ability to function in daily life, decreasing the risk of transition from acute to chronic pain, and improving quality of life. If successful, percutaneous PNS could revolutionize postoperative analgesia as it has been practiced for the past century.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Ultrasound-guided percutaneous peripheral nerve stimulation
postoperative analgesia

3. **ACCOMPLISHMENTS:** The 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.

What were the major goals of the project?

1. UG3 Protocol and regulatory preparation Months 1-12 (95% completed)
2. Prepare sites for UG3 enrollment Months 2-12 (95% completed)
3. UG3 Study enrollment Months 9-18 (14% completed)
4. UG3 Data management and analysis Months 2-20 (15% completed)
5. Preparation for UH3 Months 21-24
6. UH3 Study enrollment Months 25-57
7. Data management and analysis Months 1-70
8. Information dissemination and study closure Months 70-72

What was accomplished under these goals?

1. **UG3 Protocol and regulatory preparation**: The protocol has been finalized; the DSMB charter was completed, signed, and instituted; the DSMB began and continues with study oversight; IRBs approved protocol for all enrolling centers; HRPO has granted approval to UC San Diego, Cleveland Clinic and NMCSD; HRPO application has been submitted by WAMC and WRNMMC; the CRADA has been completed for the NMCSD and WRNMMC, and the other 2 MTFs are in the final stages of the process.

2. **Prepare sites for UG3 enrollment:** All enrolling centers have trained regulatory specialists and research coordinators; the randomization lists were created and uploaded to the secure web server; the equipment for all centers other than WAMC and BAMC has been delivered (WAMC and BAMC pending CRADA execution); the order sets have been completed; instructions for subjects have been completed; and the UC San Diego Site Director has been trained.

3. **UG3 Study enrollment:** UC San Diego initiated enrollment 3 months early with 9 subjects to date, and the protocol/database/CRFs are working as anticipated; the Cleveland Clinic and NMCSD have initiated enrollment; the remaining centers will initiate enrollment following HRPO approval and CRADA.

4. **UG3 Data management and analysis:** the case report forms have been created; and, the database has been created and tested and working well.

What opportunities for training and professional development has the project provided?

The Site Directors receive training in the insertion of insulated leads for ultrasound-guided percutaneous peripheral nerve stimulation and management of pulse generators.

The Principal Investigator annually participates in and presents his research at his specialty's premier international conference: the annual conference of the American Society of Anesthesiologists

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals and objectives?

1. **UG3 Protocol and regulatory preparation**: Ensure that the remaining centers have prepared and completed the regulatory process; and, ensure the CRADA process is completed for the two MTFs that have not executed this document.

2. **Prepare sites for UG3 enrollment:** Will continue to train, as/if necessary, regulatory specialists and research coordinators at enrolling centers; order equipment for BAMC and WAMC following HRPO/CRADA approval; and continue to train, as/if necessary Site Directors in the investigational procedure.

3. **UG3 Study enrollment:** Continue enrollment at UC San Diego, the Cleveland Clinic and NMCSD; initiate enrollment this coming quarter at WRNNMC, BAMC and WAMC with HRPO/CRADA approval.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

Nothing to Report

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. If not

previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to report

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

- WRNMMC requested—following IRB approval—approval of their organization-specific HIPAA documents, which is adding additional time before enrollment can commence. The IRB is currently working on approval.

- BAMC has not provided their internally-approved ICF for IRB review; and, therefore, the HRPO and CRADA documents cannot be approved. There is nothing I can do to make the internal BAMC process move faster. The Site Director and regulatory specialists are both aware.

Changes that had a significant impact on expenditures

Nothing to report

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Nothing to report

Books or other non-periodical, one-time publications.

Not applicable

Other publications, conference papers, and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: *Brian Ilfeld, MD, MS*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *0000-0002-6144-3273*
Nearest person month worked: *1*
Contribution to Project: *Oversees all aspects of the project, without exception.*

Name: *Sandeep Dhanjal, MD*
Project Role: *Site Director, Brooke Army Medical Center (BAMC)*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

Name: *Richard Fisher, MD*
Project Role: *Site Director, Naval Medical Center San Diego (NMCSD)*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

Name: *Harold Gelfand, MD*
Project Role: *Site Director, Walter Reed Medical Center (WRNMMC)*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

Name: *Matthew Swisher, MD, MS*
Project Role: *Site Director, University California San Diego (UCSD)*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

Name: *Anthony Plunkett, MD*
Project Role: *Site Director, Womack Army Medical Center (WAMC)*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

Name: *Alparslan Turan, MD*
Project Role: *Site Director, Cleveland Clinic*
Researcher Identifier (e.g. ORCID ID): *no ORCID number*
Nearest person month worked: *0.5*
Contribution to Project: *Oversees all aspects of the project at this center.*

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: Naval Medical Center San Diego
Location of Organization: San Diego, California
Contribution: Facilities and collaboration as an enrolling center

Organization Name: Brooke Army Medical Center
Location of Organization: Fort Sam Houston, Texas
Contribution: Facilities and collaboration as an enrolling center

Organization Name: Walter Reed National Military Medical Center
Location of Organization: Bethesda, Maryland
Contribution: Facilities and collaboration as an enrolling center

Organization Name: Womack Army Medical Center
Location of Organization: Fort Bragg, North Carolina
Contribution: Facilities and collaboration as an enrolling center

Organization Name: The Cleveland Clinic
Location of Organization: Cleveland, Ohio
Contribution: Facilities and collaboration as an enrolling center

Organization Name: Outcomes Research
Location of Organization: Cleveland, Ohio
Contribution: Facilities and collaboration as an enrolling center, data management core, DSMB and statistical core

Organization Name: SPR Therapeutics
Location of Organization: Cleveland, Ohio
Contribution: Training of enrolling centers' Site Directors

Organization Name: Johns Hopkins University
Location of Organization: Baltimore, Maryland
Contribution: Collaboration as part of the Steering Committee

Organization Name: Stanford University
Location of Organization: Stanford, California
Contribution: Collaboration as part of the DSMB

Organization Name: Wake Forest Medical Center
Location of Organization: Winston-Salem, North Carolina
Contribution: Collaboration as part of the Steering Committee

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain [NH170005]

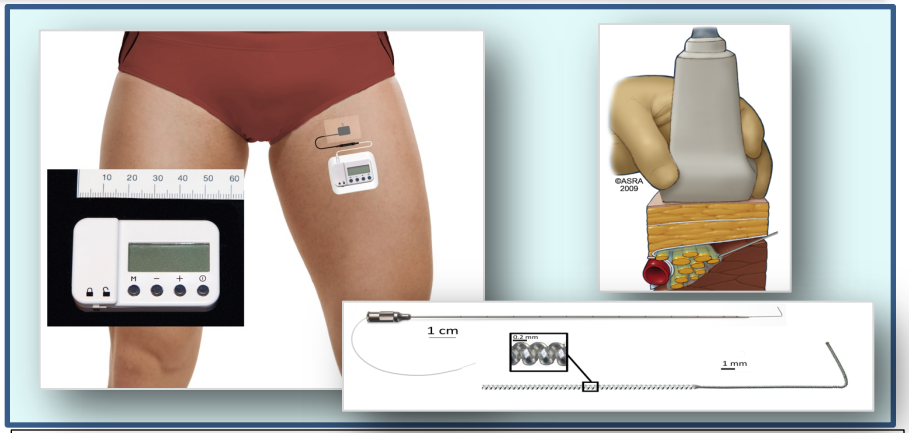
PI: Brian Ilfeld, MD, MS **Org:** University California, San Diego **Award Amount:** $6,971,337

Study Aim

The primary Specific Aim of the trial is to determine the effect of percutaneous PNS on postoperative opioid requirements and analgesia following moderate-to-severely-painful ambulatory surgery.

Approach

- A multicenter, randomized, double-masked, sham-controlled, parallel arm clinical trial
- Percutaneous peripheral nerve stimulation involves the ultrasound-guided insertion of a lead through a needle targeting a peripheral nerve, followed by administration of electrical current using a stimulator small enough to be adhered directly to the skin.
- Subjects will be randomized to receive either active electrical current or sham affecting the major nerve that serves the surgical area
- The primary end points will be cumulative opioid consumption and average surgical pain within the first 7 days following surgery.



Accomplishments: (1) Complete regulatory approval at the Cleveland Clinic and NMCSD; (2) IRB approval for the remaining 3 enrolling centers with HRPO applications submitted for 2; (3) CRADA completed for WRNMMC; (4) enrollment continues at the lead enrolling center, UC San Diego; (5) all centers prepared for the initiation of protocol

Timeline and Cost

Calendar Year:	1	2	3	4	5	6
Regulatory Approvals						
Prepare for Enrollment						
Subject enrollment						
Data collection & analysis						
Budget (million $)	**0.829**	**0.737**	**1.403**	**1.389**	**1.409**	**1.203**

Updated: May 13, 2019

* Goals / Milestones *

Y1 Goal – Regulatory approvals and preparation for enrollment
X Prepare DSMB charter and initiate DSMB meetings
☐ Project approval from HRPO and all enrolling center IRBs
X Prepare data-entry platform
X Each center to prepare for initiation of protocol and enrollment
Y2 Goals – Enrollment for UG3 pilot followed by any necessary revisions
Y3-5 Goals – Enrollment for UH3 study with continuous data collection
Y6 Goal – Complete project
☐ Complete data collection
☐ Data cleaning and final statistical analysis
☐ Manuscript preparation and submission
☐ IRB/USAMRMC/NIH/DSMB final reports and closure

Approximate Budget Expenditure to date
Projected Expenditure: $829,000 Actual Expenditure: $670,000