

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

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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				
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- 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 (97% completed)
2. Prepare sites for UG3 enrollment Months 2-12 (100% completed)
3. UG3 Study enrollment Months 9-18 (67% completed)
4. UG3 Data management and analysis Months 2-20 (50% completed)
5. Preparation for UH3 Months 21-24 (5% completed)
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 and HRPO approved protocol for original enrolling centers; CRADAs, DSAs and SSVs completed for all MTFs; added Cedars Sinai Medical Center [Los Angeles] as an enrolling center; HRPO application has been submitted by Cedars Sinai.
- 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 has been delivered; the order sets have been completed; instructions for subjects have been completed; and the UC San Diego and Walter Reed Site Directors and Research Coordinators have been trained.
- 3. UG3 Study enrollment:** UC San Diego and Walter Reed have initiated enrollment with 41 and 3 subjects to date, respectively; the Cleveland Clinic has initiated enrollment but not enrolled any subjects; the remaining centers MTFs will initiate enrollment following opening after the COVID closings; Cedars Sinai will enroll following HRPO approval. Anticipated enrollment openings: UCSD: currently open; WRNMMC, NMCSD: May; BAMC, Cleveland Clinic, WAMC: June; Cedars Sinai: late July anticipated (based on HRPO approval date).
- 4. UG3 Data management and analysis:** the case report forms have been created; and, the database has been created and is 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 Cedars Sinai secures HRPO approval and begins enrolling.
- 2. Prepare sites for UG3 enrollment:** Will train Site Directors as cases are scheduled.
- 3. UG3 Study enrollment:** Continue enrollment at UC San Diego and WRNMMC; ensure BAMC, WAMC, NMCSD, and the Cleveland Clinic begin enrolling following the COVID first wave; Ensure Cedars Sinai begins enrollment following HRPO approval.
- 4. UG3 Data management and analysis:** We will continue to upload data from the completed CRFs
- 5. Prepare for UH3:** When we complete 20 additional subjects and their 1-month data-collection phone calls, we will analyze the data for the 64-subject pilot study and determine if any revisions are required for the UH3 phase, and then submit those to the IRB and then HRPO.

- 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:

COVID-19 closed enrollment at each of our centers for between 2-4 months.

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

- All 4 MTFs required 19-23 months for DSA execution due to the merger creating the DHA. However, all now have executed DSAs
- COVID-19 closed enrollment at each of our centers for between 2-4 months, but they are opening between now and next month.
- We will be starting the UH3 RCT later than anticipated due to the above two reasons; but, we are adding a high-volume enrolling center to ensure we complete the UH3 enrollment as anticipated.

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 (NMCS D)
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: John Finneran, MD
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.

Name: Alice Vijjeswarapu, MD
Project Role: Site Director, Cedars Sinai Medical Center
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?

The Site Director at UCSD, Matthew Swisher, MD, MS, was replaced with John Finneran, MD; and, Dr. Alice Vijjeswarapu is the Site Director at the Cedars Sinai Medical Center, our newest enrolling center.

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, data management core, DSMB and statistical core

Organization Name: Cedars Sinai
Location of Organization: Los Angeles
Contribution: Facilities and collaboration as an enrolling center

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

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.