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TITLE: VAGUS NERVE STIMULATION: A NON-INVASIVE TREATMENT TO IMPROVE THE HEALTH OF GULF VETERANS WITH GULF WAR ILLNESS

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APPLICANT ORGANIZATION: ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT

Gulf War Illness [GWI] is a condition occurring in some veterans who served in the 1990-1991 Gulf War. To date there is no specific treatment for it. A major complaint of veteran subjects with GWI is widespread pain and achiness. Currently some drugs are available to treat these symptoms, but these treatments have three major drawbacks – they don't work on all patients; their effect often does not last more than a few months; and the side effects they produce are often so bad that patients stop taking them. The purpose of this study is to test a new method of test a new method of treating the widespread pain complaint of Gulf Veterans with GWI using a hand-held neuro-stimulator device that activates a nerve in the neck called the vagus. The goal of this study is to determine whether the active device (which does stimulate the vagus nerve) reduces widespread pain in veterans with GWI in comparison to using an inactive device (which does not stimulate the vagus nerve). We will also test to see if the active device improves migraine which commonly occurs with widespread pain in GWI.

15. SUBJECT TERMS
GULF WAR ILLNESS, VAGUS NERVE, NEUROSTIMULATOR, WIDESPREAD PAIN, MIGRAINE, GULF WAR VETERAN

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Gulf War Illness [GWI] is a condition occurring in some veterans who served in the 1990-1991 Gulf War. To date there is no specific treatment for it. A major complaint of veteran subjects with GWI is widespread pain and achiness. Currently some drugs are available to treat these symptoms, but these treatments have three major drawbacks – they don't work on all patients; their effect often does not last more than a few months; and the side effects they produce are often so bad that patients stop taking them. The purpose of this study is to test a new method of treating the widespread pain complaint of Gulf Veterans with GWI using a hand-held neuro-stimulator device that activates a nerve in the neck called the vagus. The goal of this study is to determine whether the active device (which does stimulate the vagus nerve) reduces widespread pain in veterans with GWI in comparison to using an inactive device (which does not stimulate the vagus nerve). We will also test to see if the active device improves migraine which commonly occurs with widespread pain in GWI.

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

1. Gulf War Illness 5. Migraine
2. Vagus Nerve 6. Gulf War Veteran
3. Neuro-stimulator
4. Widespread pain

2. **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?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The major goal of this study was to determine if an active neuro-stimulator device that uses vagus nerve stimulation (VNS) reduces widespread pain of Gulf War Illness in comparison to an inactive sham device which does not use VNS. We also planned to test to see if the active device improves migraine which only occurs with widespread pain in GWI. The Food and Drug Administration (FDA) has recently approved this neuro-stimulator device for treating acute migraines and cluster headaches in adult patients.

Phase 1: Recruitment/Identification at EO VA – 29 veterans were identified, fulfilled criteria for participation, and signed informed consent to participate in the study; two decided not to participate further and so never came to ISMMS.
Phase 2: Randomization at ISMMS – Twenty-seven subjects came to ISMMS, were randomized and enrolled into the study. Of those, 20 subjects completed the blinded phase. Seven subjects withdrew or were lost to follow up during this phase. Of these seven, six participated through the entire blinded phase but would not come in for the final face to face visit – thus not providing usable data for this study.
Phase 3: Open Label – 15 subjects have completed the study. Five subjects withdrew or were lost to follow up during this phase.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

We started with 29 veterans who were recruited at the East Orange VA and who signed their consent to participate; of these, 27 actually came to ISMMS where they signed their informed consent and were randomized. Of these 27 potential research participants, 20 veterans completed the blinded phase of the study and 15 completed the entire study including open trial.

We have ceased enrollment. We had a tremendous problem from the start of the study identifying Gulf vets who would participate in this study. We had originally hoped to recruit 40 evaluable subjects but at study end achieved only half that number. In finding subjects for this study, we met with veteran groups, worked with local VA officials in state and local government, went to VA support groups to talk, etc. Those methods really were not too effective. We invested in CBS to help identify suitable candidates – an effort that was not successful. We then began working with We Health Co., a company that uses social media to identify subjects for clinical trials. That method was moderately successful in increasing recruitment for the enrollment of several Veterans by advertising our study flyer onto their website that aimed at a community of Gulf War Veterans.

Asking individual investigators to develop their own method of recruiting Gulf vets is extremely costly in time and effort. If DoD is to continue funding in this direction, DoD should help investigators with a method to identify Gulf veterans interested in participating in research.

Primary outcomes for effective treatment during the blinded phase were median values of widespread pain ratings measured by five assessments using a VAS one week prior to study enrollment and compared to the median of ratings collected one week prior to the end of the blinded phase. Secondary outcomes included a comparison across groups for ratings on the Patients' Global Impression of Change (PGIC) and a pre- to post-intervention comparison across groups of the number headache days and average intensity of headaches for 30 days prior to study enrollment and 30 days prior to the end of the blinded phase.

Accomplishments cont'd

Comparing the average pain VAS rating using a Time (Pre vs. Post) by Condition (Active vs. Sham) MANOVA model, a significant main effect for Time was identified (Pillai's Trace, $F_{1,18}$=7.312, p=0.015) indicating a reduction in pain ratings pre- to post-intervention averaged across Condition (6.25 ±0.91 vs. 4.95 ±2.21). Effects for Condition and the interaction were not significant, suggesting no differential impact for the intervention. Average ratings for the PGIC 7-itme scale were not significantly different between conditions (Active: 3.43 ±1.90; Sham: 4.00 ±2.14), suggesting no difference between conditions for patients' perception of their improvement. Comparing number of headache days and average headache intensity using Time by Condition MANOVA models, no significant main or interaction effects were noted ($p > 0.05$).

Preliminary analysis of all our primary and secondary outcome measures showed no significant difference in favor of VNS. Therefore, the trial cannot support the use of VNS in treating the widespread pain or headache of veterans with Gulf War Illness.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach

Since study onset 4,598 veterans haven been contacted via letter, 75-140 new mailings biweekly were sent out for recruitment, as well as a total of 2,797 phone calls were made to individual veterans with multiple follow up calls. Members of our team attended Veteran Advisory Board meetings to share information about our study to Gulf War Veterans. WeHealth Co., a wellness website, advertised our study on a portion of their website aimed at a community of Gulf War Veterans. We plan to present the negative results of this study to the meeting of Gulf War researchers to be hosted by DoD later this year.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to report

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge,

VNS is currently approved for the treatment of acute migraine and we had hoped that VNS would reduce migraine frequency and/or severity. Unfortunately, this was not the result; moreover, we did not find a significant treatment effect on widespread pain either. Therefore, despite positive findings in non-veterans with widespread pain and/or with migraine headaches, we could not extend those results to Gulf veterans with Gulf War Illness.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

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:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Identifying and recruiting appropriate research subjects had been an issue since the start of this project. We had tried to deal with this by speaking to vet groups across the city of New York as well as by working with state and local governmental representatives involved in veterans' issues. We did try one recruitment method using CBS Local Digital Media which used an email direct strategy to veterans within a 30-mile radius of our center. That method was not successful in the recruitment of Gulf Veterans with Gulf War Illness. We also used the DMDC data base to identify Gulf veterans within our catchment area. Because the phone numbers on this data base often are not accurate, we have developed a way to update these so that we can directly contact appropriate veterans. Our most successful recruitment effort was by using a health organization by the name of WeHealth Co., to advertise our flyer on to a specific portion of their website designated for Gulf War Veterans.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

There are no significant changes during this reporting period. IRB approval for the revised consent form and protocol was granted on August 22, 2019. Enrollment has ceased for this study. There are no active study participants in this study. The study remains open for further data analysis and preparation of these results for publication in the medical literature.

Significant changes in use or care of human subjects

Revision of consent form and protocol to include updated risks provided by the device manufacturer - ElectroCore. The company uses this updated information when the device is prescribed for clinical use within the USA. The device has recently received FDA approval for the acute treatment of pain associated with both cluster and migraine headaches.

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

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.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

There are no publications or presentations to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

There are no books, or other non-periodical, one-time conference publications to report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

There are currently no publications, conference papers or presentations to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://clinicaltrials.gov/ct2/show/NCT02791893?term=nct02791893&rank=1 ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study. Studies are generally submitted to the Web site (that is, registered) when they begin, and the information on the site is updated throughout the study. In some cases, results of the study are submitted after the study ends. This Web site and database of clinical studies is commonly referred to as a "registry and results database."

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name:	Benjamin Natelson, MD
Project Role:	Primary Investigator
Research Identifier:	N/A
Nearest person month worked:	No change
Contribution:	Dr. Benjamin Natelson is the Principal Investigator for this study. He is responsible for the conduct of the study.
Funding Support:	N/A

Name:	Michelle Blate, APN
Project Role:	Nurse Practitioner
Research Identifier:	N/A
Nearest person month worked:	No change
Contribution:	Ms. Blate is the nurse practitioner for this study. She conducts the medical evaluation at ISMMS. She also trains every randomized veteran on the use of the device and diary.
Funding Support:	N/A

Name:	Gudrun Lange, Ph.D
Project Role:	Consultant
Research Identifier:	N/A
Nearest person month worked:	No change
Contribution:	Dr. Lange consults on regulatory matters.
Funding Support:	N/A

Name:	Sarah Khan
Project Role:	Study Coordinator
Research Identifier:	N/A
Nearest person month worked:	No change
Contribution:	Ms. Khan oversees all aspects of the study administration and implementation with study subjects.
Funding Support:	N/A

Name:	Michelle Deluca
Project Role:	Research Assistant
Research Identifier:	N/A
Nearest person month worked:	6 months
Contribution	Ms. DeLuca oversees study implementation at WRIISC and participates in the recruitment process.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

August 22, 2019 – received IRB approval the Continuation Review Report of all revised study documents and the replacement of physician Drew Helmer to Anays Sotolongo at the NJVA.

June 1, 2019 – Dr Natelson began an NIH R-21, covering 10% of his time, to study sleep in civilians with chronic fatigue syndrome.

September 1, 2019 – the additional support offered by ElectroCore stopped. This support was replaced by a donation to Dr Natelson's laboratory.

January 1, 2020 – the federal grant provided by the Department of Defense has expired.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or

commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name:

1. War Related Illness and Injury Study Center (WRIISC)
2. ElectroCore LLC [their support terminated as of 9/1/19]

Location of Organization

1. VA New Jersey Health Care System, 385 Tremont Ave, 11th Floor, East Orange, NJ 07018
2. 150 Allen Road, Suite 201, Basking Ridge, NJ 07920

Partner's contribution to the project

- Financial support – N/A
- In-kind support – ElectroCore LLC was providing the nVNS devices and related accessories. They also provided the secure MERGE database in order to input study data until 9/1/19.
- Facilities – The WRIISC is providing their facility for recruitment and screening.
- Collaboration – N/A
- Personnel exchanges – In prior reports, we had employed a full-time study coordinator at MSBI for recruitment and study implementation. But requiring this person to split her time between the new location at ISMMS and the WRIISC at the NJVA facility proved unwieldy. So, we split the job into two parts: one in a position filled by Sarah Khan at ISMMS at 60% time and one in a position filled by Michelle DeLuca/William Van Doren at 40% time at the WRIISC.

8. SPECIAL REPORTING REEQUIREMENTS

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.
N/A

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

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.