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TITLE: Restoration of Bladder and Bowel Function Using Electrical Stimulation and Block after Spinal Cord Injury

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CONTRACTING ORGANIZATION: VA Palo Alto Health Care System, Palo Alto, CA 94304

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14. ABSTRACT

The purpose of the project is to evaluate the restoration of bladder and bowel function using electrical stimulation and block after spinal cord injury in human subjects.

Regulatory compliance has been maintained from the Stanford Institutional Review Board and the Human Research Protection Organization. Investigational Device Exemption has been obtained from the Food and Drug Administration.

Participant recruitment and screening has continued and nine subjects have been enrolled and undergone urodynamic evaluation. Six of these have undergone neuromodulation by electrical stimulation via skin surface electrodes and three are considering implantation of a bladder stimulator in Stage 1 of the clinical trial. Recruitment is being extended to non-veterans.

15. SUBJECT TERMS
Spinal Cord Injuries, Neurogenic Bladder, Electric Stimulation

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1. INTRODUCTION:

This is a prospective Phase 1 clinical trial of an implanted electrical stimulator to improve both continence and voiding in human subjects with chronic spinal cord injury. It will use the existing FDA-approved Vocare stimulator and electrodes, implanting electrodes on the sacral nerves as usual but without performing posterior sacral rhizotomy. Conventional low frequency stimulation will be applied to the sacral nerves at a low amplitude to activate large afferent axons with the aim of inhibiting bladder contraction by neuromodulation, and bladder capacity and continence will be measured. Subjects who show benefit will be offered the implantation of an electrode on each pudendal nerve; these electrodes will be connected to the Vocare stimulator already implanted. The effect of high frequency stimulation of the pudendal nerves through these electrodes to block sphincter contraction and improve electrically stimulated voiding will be measured.

2. KEYWORDS:

Spinal Cord Injuries, Neurogenic Bladder, Electric Stimulation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Maintain Regulatory Compliance
2. Coordinate Study Staff for Clinical Trial
3. Participant recruitment, screening, surgery and evaluation for Stage 1
4. Surgery and evaluation for Stage 2
5. Data analysis and publication

What was accomplished under these goals?

1) Major activities
   Regulatory compliance maintained
   Study staff for clinical trial maintained
   Participant recruitment and screening continued
2) Specific Objectives
   To improve continence by electrical stimulation in human subjects with SCI
   To improve voiding by electrical stimulation in human subjects with SCI
3) Significant results
   Regulatory compliance maintained
   a. FDA approval maintained: IDE supplement approved 12/20/2017; IDE amendment for expansion to up to three additional sites approved 03/15/2018
   b. Stanford University IRB approval maintained: protocol continuation approved 07/24/2018
   c. HRPO approval maintained: continuing review accepted 11/15/17; next continuing review submitted 8/22/2018
   d. Protocol submitted to Santa Clara Valley Medical Center IRB for review as non-veteran site

4) Coordinate study staff for clinical trial
   a. All staff training maintained
   b. Several meetings have been organized by the PI at two new potential sites: Santa Clara Valley Medical Center, San Jose, CA and MetroHealth Medical Center, Cleveland, OH
   c. Research staff (engineers, neurosurgeons, urologists) has been assembled at the two new potential sites

5) Participant recruitment and screening
   Twenty five veteran subjects have been interviewed in detail and informed about the procedures of the clinical trial and provided with Informed Consent Documents. Nine have been enrolled and have undergone urodynamic evaluation. Three of these were found to be unsuitable for electrical stimulation, and six underwent repeat urodynamic evaluation with neuromodulation using external stimulation. Two of these patients are now considering proceeding to surgical implantation of a bladder pacemaker. Approval has been obtained to extend recruitment to non-veterans and three educational presentations have been made to non-veteran spinal cord injury peer support groups, from whom 38 non-veterans have contacted us to express interest and another five potential subjects have been identified.
6) Other achievements
   Extension without funding for 12 months approved in principle by DOD Science Officer and revised Budget, Justification and Statement of Work submitted to DOD Contract Officer.

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

The Biomedical Engineer has received training from the biomedical engineering collaborators in the Functional Electrical Stimulation Center.

How were the results disseminated to communities of interest?

Presentations on the project have been made at the Paralyzed Veterans of America Summit Conference in Dallas TX and the Annual Scientific Meeting of the International Spinal Cord Society in Sydney, Australia.

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

1. Obtain IRB approval for new non-veteran sites in San Jose and Cleveland
2. Finalize subcontracts with new non-veteran sites in San Jose and Cleveland
3. Further recruitment and screening of participants at new non-veteran sites in San Jose and Cleveland
4. Implantation of stimulators for Stage 1
5. Evaluation of bladder capacity and continence with implanted stimulator

4. IMPACT:

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

The use of electrical stimulation to restore both bladder continence and emptying without destructive surgery has generated considerable interest in the discipline of spinal cord injury particularly in Britain, Australia and New Zealand.

What was the impact on other disciplines?

Collaboration with biomedical engineers is defining new electrical stimulation parameters and protocols for management of the neurogenic bladder.

What was the impact on technology transfer?

The approval by the Food and Drug Administration of Investigational Device Exemption for Phase I of this project will facilitate progress of the project towards technology transfer of the implantable electrical stimulator.

What was the impact on society beyond science and technology?

Nothing to report yet.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

FDA approved expansion to three additional sites on 03/15/2018 in order to increase recruitment of non-veterans. 38 non-veterans have contacted us with interest. One non-veteran participant has undergone urodynamic investigation and was found to be suitable for surgical implantation of the stimulator and wishes to proceed with this implantation as soon as IRB approval is obtained at the new site.

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

Identification of suitable veteran subjects was slow and the urodynamic system at the VA broke down and was not available for much of the year but we obtained FDA approval to expand to non-veterans and to open up to three additional sites. We have selected two of these and identified the team members required in both, including a urologist and neurosurgeon. We have submitted an IRB protocol to one of these and expect this to be approved in November 2018. We are preparing the IRB protocol for the second additional site and are in negotiation with a third potential site.

Changes that had a significant impact on expenditures

We have applied to the DOD Contract Officer re-budget existing funds for a 12-month extension without funding to expand the study to up to three additional sites as approved by the FDA.

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.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Conference papers presented at Paralyzed Veterans of America Annual Summit Conference and International Spinal Cord Society Annual Conference

Journal publications, books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Nothing to report

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

Clinicaltrials.gov

- **Technologies or techniques**

Technique being developed for application of high frequency alternating current block.

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

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: *Graham Creasey*
Project Role: *Project Director*
Nearest person month worked: *3.6*
Contribution to Project: *Dr. Creasey has worked on training and coordination of other personnel and on confirming and maintaining regulatory compliance and correspondence with the VA, IRB and DOD and FDA. He has met with potential subjects, provided information to allow them to give informed consent, and carried out screening urodynamics. He has also visited the new sites to select collaborators and educate them about the project.*

Name: *Zoia Latev*
Project Role: *Research Biomedical Engineer*
Nearest person month worked: *6*
Contribution to Project: *Dr. Latev has assisted with maintaining regulatory compliance and preparing reports and supplements and amendments for the VA, the IRB, the DOD and the FDA. She has also visited the new sites to develop collaboration with the technical staff in those sites.*

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?

As planned in the grant application, collaboration has been established with the Functional Electrical Stimulation Center at the VA Medical Center in Cleveland Ohio, which is affiliated with the Bioengineering Department of Case Western Reserve University. This Center developed the technique of high frequency alternating current block in animals and has also studied the use of electrical stimulation for improvement of bladder capacity and continence after spinal cord injury. Both of these techniques are being evaluated in human subjects during this project using implantable electrical stimulators, and the biomedical engineering expertise available from the collaborators at the Functional Electrical Stimulation Center will be crucial in translating their basic research into clinical application in this project.
Clinicians at the Santa Clara Valley Medical Center in San Jose and the MetroHealth Medical Center in Cleveland have collaborated in preparing the documents required for IRB approval at these sites.

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: See attached

9. APPENDICES: NA

Restoration of Bladder and Bowel Function using Electrical Stimulation and Block after Spinal Cord Injury
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PI: Graham Creasey, MD **Org:** Palo Alto Veterans Institute for Research **Award Amount:** $998,463

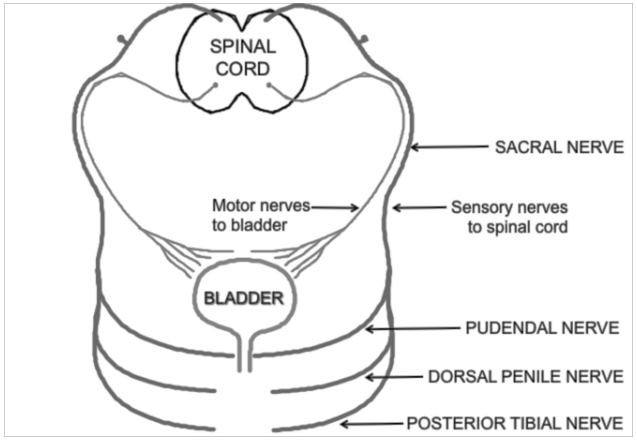
Study/Product Aim(s)

- To improve continence by electrical stimulation in human subjects with SCI
- To improve voiding by electrical stimulation in human subjects with SCI

Approach

The purpose of this study is to improve both continence and voiding of urine by electrical stimulation of nerves in patients with spinal cord injury. Electrical stimulation of the sacral nerves or roots has been used before to produce bladder contraction and improve voiding, but it has usually been combined with cutting of sacral sensory nerves to reduce reflex contraction of the bladder and sphincter. However, cutting the nerves has many undesirable side effects. A new protocol of electrical stimulation of nerves using a surgically implanted system without cutting nerves will now be tested for its ability to:

i. Inhibit reflex contraction of the bladder and improve continence;
ii. Block reflex contraction of the sphincter and improve voiding.



Animal research studies have shown that stimulating sensory nerves can inhibit bladder contraction and high frequency stimulation of motor nerves can block action potential propagation and prevent unwanted external urethral sphincter contraction in order to produce bladder emptying. The effect of stimulation is easily reversible.

Timeline and Cost

Activities / FY	15	16	17	18
Obtain all regulatory approvals				
Stage 1: Recruitment, Surgery, Evaluation				
Stage 2: Recruitment, Surgery, Evaluation				
Data Analysis and publications				
Estimated Budget ($K)	**$239**	**$257**	**$259**	**$242**

Updated: (10/29/2018)

Goals/Milestones

FY15 Goal – Initial Participant Recruitment, Screening & Evaluation
☑ Assemble regulatory documents and research protocol
☑ Coordinate study staff for clinical trial
☑ Recruitment and screening of first participants
☑ Obtain FDA approval for Stage 1

FY16 Goals – Further Participant Recruitment, Surgery and Evaluation
☑ Continue with Recruitment and screening
☑ Evaluate patients in Urodynamic laboratory

FY17 Goal – Participant Evaluation
☑ Expand recruitment to non-veterans
☑ Evaluate continence and voiding in urodynamic laboratory

FY18 Goal – Further Participant Recruitment, Surgery and Evaluation
☑ Obtain FDA approval for non-veteran clinical trial sites
☐ Evaluate Voiding and Continence with implant

Comments: expanding recruitment to non-veteran sites

Budget Expenditure to Date
Projected Expenditure: $998,463 Actual Expenditure: $827,121