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

PRINCIPAL INVESTIGATOR: Graham Creasey, MD, FRCSEd

RECIPIENT: VA Palo Alto Health Care System/PAVIR, Palo Alto, CA

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VA Palo Alto Health Care System/PAVIR
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Palo Alto, CA 94304

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of the project is to evaluate the restoration of bladder function using electrical stimulation and block after spinal cord injury in human subjects.
Regulatory compliance has been maintained with the Institutional Review Boards and the Human Research Protection Office and Investigational Device Exemption has been maintained with the Food and Drug Administration.
Nine subjects have been enrolled and four responded to neuromodulation by electrical stimulation via skin surface electrodes. Two did not wish to proceed with surgical implantation of a bladder stimulator, one is considering implantation and one has undergone implantation. In this subject the implant has been successful in restoring micturition without catheterization and continence without medication or rhizotomy for the first time in 41 years. Three clinical sites are now open, in California, New Mexico and Ohio; recruitment is continuing and has identified several more potential subjects who will be evaluated this year, COVID permitting.

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

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TABLE OF CONTENTS

1. INTRODUCTION:

This is a 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 manufactured by Finetech Medical Ltd in England, 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. Higher frequency stimulation will be applied at low amplitude and tested for its effectiveness in blocking sphincter contraction for the purpose of improving micturition.

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
4. Evaluation of continence
5. Evaluation of voiding
6. 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
   First non-veteran subject implanted and undergoing follow-up
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
   b. IRB approval maintained for Stanford University IRB, Santa Clara Valley Medical Center (San Jose, CA) IRB, MetroHealth Medical Center (Cleveland, OH) IRB & University of New Mexico (Albuquerque) IRB
   c. HRPO approval maintained for VA Palo Alto, Santa Clara Valley Medical Center and MetroHealth Medical Center
   d. Information on clinicaltrials.gov has been updated
4) Coordinate study staff for clinical trial
   a. Staff training maintained at VA Palo Alto and Santa Clara Valley Medical Center, San Jose
   b. Staff training at MetroHealth Medical Center, Cleveland, OH and University of New Mexico, Albuquerque, is in process
5) Participant recruitment, screening and surgery
   a. First non-veteran subject has been successfully implanted at Santa Clara Valley Medical Center and has undergone programming of the device and urodynamic evaluation
   b. Other veteran and non-veteran subjects being recruited within limits of pandemic
   c. Existing patients with bladder control implant have volunteered to assist with recruitment
6) Evaluation of continence
   a. The implant has been able to produce continence without anticholinergic medication or rhizotomy in non-veteran subject for the first time in 41 years.
7) Evaluation of micturition
   a. The implant has been able to produce micturition without catheterization or rhizotomy in non-veteran subject for the first time in 41 years
   b. External controller has been modified to test sphincter block for improving micturition
   c. FDA Amendment approved for modification of external controller
8) Data analysis and publication
   a. Data collection and analysis for the non-veteran subject with implant
   b. Publication in Operative Neurosurgery
   c. Presentation at International Neuro Urology Society June 2022
9) Other achievements
   a. Funding of routine costs of clinical trial at Santa Clara Valley Medical Center under CMS National Coverage Determination 310.1 has been confirmed
   b. A request for extension without funding for the next 12 months has been approved by DOD

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

The Biomedical Engineers has received training from the biomedical engineering collaborators in the VA Functional Electrical Stimulation Center in Cleveland Ohio, and the neurosurgeon and urologist in Santa Clara Valley Medical Center have received training allowing them to carry out implants in non-veterans. The neurosurgeons and urologists in Cleveland, Ohio and Albuquerque, NM have also received training. training

How were the results disseminated to communities of interest?

A journal article and video was published by the journal Operative Neurosurgery in January 2020
A presentation was given to the International Neuro Urology Society conference in Innsbruck, Austria in June 2022.

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

1. Maintain existing IRB, HRPO and FDA approvals
2. Continue recruitment, screening, enrollment and evaluation of subjects at all clinical sites
3. Maintain funding of routine costs of clinical trial at MetroHealth Medical Center, Cleveland, and University of New Mexico, Albuquerque, under CMS National Coverage Determination 310.1
4. Implant additional stimulators
5. Evaluate bladder capacity and continence with implanted stimulator
6. Evaluate micturition with implanted stimulator using higher frequencies
7. Expand recruitment through SCI peer support groups and SCI centers

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 internationally. Academic collaboration is in progress with the University of Oxford and University College London in England

What was the impact on other disciplines?

Collaboration with biomedical engineers, particularly at the VA Functional Electrical Stimulation Center in Cleveland, Ohio, is defining new electrical stimulation parameters and protocols for management of the neurogenic bladder. This group is also pursuing supportive studies in animals with separate funding.

What was the impact on technology transfer?

The approval by the Food and Drug Administration of Investigational Device Exemption for evaluation of both continence and voiding in this project will facilitate progress of the project towards technology transfer of the implantable electrical stimulator with modifications to provide alternatives to rhizotomy.

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 a total of four sites in order to increase recruitment of non-veterans who more closely resemble current active-duty service members than the population of veterans initially targeted, who tend to be ageing and less interested in new techniques. We have set up three implantation sites with IRB and HRPO approval and the project is administered through the Palo Alto Veterans Institute for Research.

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

Identification of suitable veteran subjects was initially slow and therefore we obtained FDA approval to expand to non-veterans and to open up to three additional sites. At one of these, the Santa Clara Valley Medical Center, the first non-veteran subject was implanted in June 2019 and is successfully using the implant, without rhizotomy, to produce micturition without catheterization and continence without medication. The other sites, at MetroHealth Medical Center in Cleveland and the University of New Mexico in Albuquerque, have IRB approval and are evaluating subjects as the pandemic allows. A no-cost extension has been approved by the Department of Defense to September 2023.

Changes that had a significant impact on expenditures

In response to the delays caused by the pandemic we have re-budgeted existing research funds to follow up existing subjects and recruit additional subjects, and have confirmed with the Centers for Medicare and Medicaid Services that the routine clinical costs of the trial can be charged to Medicare under National Coverage Determination 310.1. This has allowed expansion of the trial to non-veteran hospitals at no extra cost to DOD.

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**

Presentation to the International Neuro Urology Society Annual Conference June 2022, Innsbruck, Austria, in a workshop on Sacral Anterior Root Stimulation organized by the Principal Investigator, Prof. Creasey.

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

Publication in Operative Neurosurgery 2020: Implantation of Sacral Nerve Stimulator Without Rhizotomy for Neurogenic Bladder in Patient With Spinal Cord Injury: 2-Dimensional Operative Video. Ehsanian R, Creasey G, Elliott C, Abu-Eid C, Ali A, Prutton M & Singh H

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

Clinicaltrials.gov NCT02978638

- **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, MD
Project Role: Project Director
Annualized calendar months: 4
Contribution to Project: Dr. Creasey has worked on: confirming and maintaining regulatory compliance and correspondence with the IRB and HRPO; preparing and submission of FDA supplements and amendments; reworking the SOW and re-budgeting; conducting informational meetings, assembling staff, and logistics for three new investigational sites: MetroHealth System, Cleveland, OH, Santa Clara Valley Medical Center, San Jose, CA, and University of New Mexico, Albuquerque, NM; continuing screening, evaluation, and recruitment of study participants.

Name: Harminder Singh, MD
Project Role: Site Principal Investigator, Santa Clara Valley Medical Center
Name: Arshad Ali
Project Role: Study Coordinator, Santa Clara Valley Medical Center
Contributions to Project: Mr. Ali has been reviewing the database of SCI patients at this SCI Center, the Urodynamic records at this Center and the enquiries from interested potential subjects, and determining which meet the selection criteria. Urodynamic studies are still limited by staff shortages caused by the pandemic.

Name: Dennis Bourbeau, PhD
Project Role: Site Principal Investigator, MetroHealth Medical Center
Name: Kimberly Schach
Project Role: Study Coordinator, MetroHealth Medical Center
Contributions to project: Dr. Bourbeau and Kimberly Schach have been actively reviewing SCI databases during the pandemic and have identified two subjects who appear to meet selection criteria and are interested, in addition to other potential subjects for the study

Name: Reza Ehsanian, MD, PhD
Project Role: Project Manager, University of New Mexico
Contribution to Project: Dr. Ehsanian has obtained a Clinical Trial Agreement with the co-ordinating center at the Palo Alto Veterans Institute for Research at the VA Palo Alto and IRB and HRPO approval, and is actively recruiting subjects locally and nationally.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No

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. 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 at the clinical implantation sites in this project.

Clinicians at the Santa Clara Valley Medical Center in San Jose, the MetroHealth Medical Center in Cleveland and the University of New Mexico in Albuquerque have collaborated in obtaining IRB approval at these sites and recruiting and evaluating subjects.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: See attached

9. APPENDICES:

Restoration of Bladder and Bowel Function using Electrical Stimulation and Block after Spinal Cord Injury
W81XWH-14-2-0132

PI: Graham Creasey, MD **Org:** Palo Alto Veterans Institute for Research **Award Amount:** $998,463

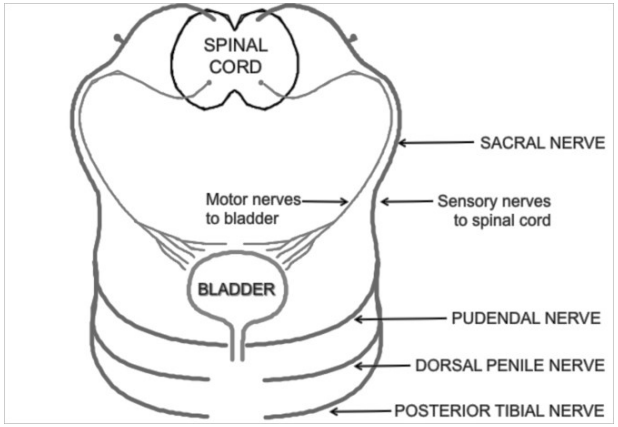
Study/Product Aim(s)

- 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
iii. Achieve these functions by an implanted electrical stimulator without rhizotomy



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, unlike the surgical rhizotomy that has been used in the past.

Timeline and Cost

Activities FY	15	16	17	18	19	20	21	22
Obtain & maintain regulatory approvals								
Stage 1: Recruitment, Surgery, Evaluation								
Stage 2: Recruitment, Surgery, Evaluation								
Expansion of trial to non-veteran sites & identification of subjects								
Estimated Budget ($K)	**$126**	**$333**	**$245**	**$121**	**$171**	**$**	**$**	

Updated: (11/7/2022)

Goals/Milestones

FY15 Goal – Initial Participant Recruitment, Screening & Evaluation
☑ 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
FY19 Goal: Expansion of trial to non-veteran sites
☑ Implant non-veteran
FY20 Goal: Implant further non-veteran subjects
☑ Evaluation and follow-up
☑ Additional site and recruitment
FY21 Goal: Enroll and implant further subjects when pandemic controlled
☑ Identified 173 potential non-veteran subjects
FY22 Goal: Recruit subjects at MetroHealth Medical Center and University of New Mexico and carry out surgical implants

Budget Expenditure to Date

Projected Expenditure: $998,463 Actual Expenditure: $962,957