IRB #: 13015-H12
(Assigned by IRB Office)

Approved
12/28/2018
Cleveland VAMC
Institutional Review Board

CPA #: 8333
(Assigned by IRB Office)

***Form Directions**: Form is protected (user has limited access to the fill-in fields). Use the tab key or mouse to navigate the fill-in fields. Formatting is limited in the text fields (no bulleted lists, numbering, etc). In the event that the user is unable to navigate through the protected document or would like to format a document, the user can disable the "protected" feature (select "Review" then "Restrict Ending" then "Stop Protection"). Please do not delete or modify questions..*

Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

.

Section 1 – General Information

1. **Version Date:** December 28, 2018
2. **Title of Project:** A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes
3. **Principal Investigator (PI)** *(name & degrees)*: Ronald J. Triolo, Ph.D.

   E-mail: Ronald.Triolo@va.gov; Ronald.triolo@case.edu

   Pager Number/Cell Phone Number: 216-791-3800 Ext. 4138
4. **Research Contact/Research Coordinator** *(name, degrees)*: Tara Byrd

   E-mail: tara.byrd@va.gov

   Pager Number/Cell Phone Number: 216-791-3800 ext: 4864

Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC);

International studies when the PI is the Lead Investigator list the countries:

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site:

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*: V.A. Merit Review

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
FES	Functional Electrical Stimulation
SCI	Spinal Cord Injury
UECU	Universal External Control Unit
US FDA	US Food and Drug Administration
RPE	Rating of Perceived Exertion scale
URS	Usability Rating Scale
C-Fine	Composite-Flat Interface Nerve Electrode
DEXA	Dual-energy x-ray absorptiometry
ASIA	American Spinal Injury Association
SCI-QOL	Spinal Cord Injury-Quality of Life

8. **Provide a BRIEF SUMMARY of the background for this research.** DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

- *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*
- *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
- *Include the rationale for conducting the research at the VA.*

The overall goal of this project is to improve the functionality, physiological benefits, and safety of FNS systems that stimulate the trunk, hip and lower extremity muscles to restore standing function to individuals with paraplegia. Altering the pattern of activation of the knee extensor muscles promotes prolonged standing time so that users of neuroprostheses can accomplish activities of daily living that require standing for longer durations. Thus, increasing the health benefits associated with increased dosages of weight bearing. The optimal fatigue delaying stimulation regimes will be implemented clinically in 15 subjects to demonstrate the utility and generalizability of the approach.

Currently available FNS systems for standing utilize supra-maximal levels of constant stimulation at the hips and knees. This ensures the knees remain locked during standing, but at the cost of increased fatigue and reduced standing times. In a Phase II clinical trial conducted by our group, small number of the cohort of 18 implant recipients were able to achieve standing times exceeding 10 minutes but most users were limited to much shorter durations due to the rapid onset of muscle fatigue [1]. Standing times for the group averaged approximately 10 minutes with a median of only approximately 3 minutes. For the 11 subjects that continued to participate in the research program for at least two years after implantation, more than half never achieved standing times greater than 5 minutes. While there is no discernible relationship between standing time and factors such as injury level, degree of preserved sensation or time post-injury, the problem is especially pronounced in taller and heavier subjects. [2]

While the relatively short standing times achievable with continuous stimulation are sufficient for facilitating transfers and accomplishing some activities of daily living, many positive outcomes including the health benefits of weight bearing, swing-to gait, and the ability to participate in other important social, work and personal activities necessary to resume an active and independent lifestyle require durations longer than 5 minutes [3].

This project will determine the feasibility and performance of stimulation paradigms that exploit the ability of new multi-contact peripheral nerve electrodes to selectively activate individual portions of different muscles in order to prolong standing duration. Multi-contact nerve cuff electrodes such as the CWRU spiral and the Flat Interface Nerve Electrode (FINE) and the Composite-Flat Interface Nerve Electrode (C-FINE) have already been approved for chronic implantation as part of upper and lower extremity neuroprostheses by the USFDA and the IRBs of both the LSCDVAMC and MetroHealth Medical Center. This new project will continue to utilize these clinically proven technologies and apply their unique ability to efficiently and effectively activate independent motor unit pools within a muscle or independent synergists innervated by a common motor nerve.

[1] V.K. Mushahwar, P.L. Jacobs, R.A. Normann, R.J. Triolo, and N. Kleitman, "New functional electrical stimulation approaches to standing and walking," j neural Eng, vol.4, pp.S181-97, 2007.
[2] R.J. Triolo, S.N. Bailey, M.E. Miller, L. Rohde, J. Anderson, J.A. Davis, J.J. Abbas, L.A. Diponio, G.P. Forrest, D.R. Gater, L.J. Yang, "Longitudinal performance of a surgically implanted neuroprosthesis for lower extremity exercise, standing, and transfers after spinal cord injury, *Archives of Physical Medicine and Rehabilitation.* 93(5):896-904, 2012.
[3] J.J.Eng, S.M.Levins, A.F.Townson, D.Mah-Jones, J.Bremner, and G.Huystion, "Use of prolonged standing for individuals with spinal cord injuries, "Phys Ther, vol.81,pp.1392-9, 2001.

9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*
- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

Neuroprostheses for standing after SCI currently rely on continuous activation of the hip and knee extensor muscles, which results in rapid fatigue and ultimately compromises elapsed standing time. The primary objective of this study is to improve the performance of neuroprostheses for standing by developing and implementing advanced stimulation paradigms that use multi-contact peripheral nerve electrodes to delay fatigue onset and prolong standing duration. The new stimulation paradigms will take advantage of the ability of multi-contact nerve cuff electrodes to selectively activate independent portions of a muscle, or independent muscles that perform the same action. Such a capability will allow one or more muscles (or parts of the same muscle) to rest while the others continue to contract to keep the knee extended and the user upright. Stimulation waveforms that alternate activation to multiple muscles performing the same function, rather than continuously activate the entire muscle group constantly, should allow muscles to rest and recover from fatiguing contractions.

In addition to these important clinical benefits, the project is also of high impact and significance because the methods to be developed will not be specific to any single electrode technology or stimulation system. Any clinical or therapeutic application that requires a sustained muscular contraction or the production of constant joint torques for prolonged periods of time will benefit from the successful completion of this project.

This project is significant because it will:

a) Extend the functionality of standing neuroprostheses and enable more complex and time consuming activities of daily living
b) Allow neuroprosthesis users to receive the full health benefits of weight bearing and upright mobility
c) Improve the overall safety of neuroprostheses for standing.

The Specific aims of this study are:

1) Establish the clinical feasibility of new stimulation paradigms (such as carousel, interleaved and sum of phase-shifted sinusoid among others) for prolonged muscle force production in subjects with SCI.

2) Automate the tuning of the fatigue delaying stimulation paradigms to maximize performance and generate objective methods for ensuring optimal clinical performance.

3) Demonstrate improved functional outcomes of the advanced fatigue-delaying stimulus schemes in terms of standing duration, body weight distribution and subjective and objective measures of stability.

THE HYPOTHESES TO BE TESTED ARE:

- The knee joint torques generated by fatigue delaying stimulation paradigms will be sufficient to keep the knees locked during standing for at least 10 minutes. This will be tested by tracking how long the knee can produce an extension torque on the dynamometer that exceeds a threshold set for each subject based on their body weight. [5.]

- Standing with fatigue delaying stimulation paradigms will be more stable and of longer duration than constant stimulation. This will be tested by recording the elapsed standing times before system users are required to sit due to fatigue of the quadriceps muscles for each of the advanced stimulation waveforms, as well as by monitoring variations in knee angle and subjective impressions of stability while standing.

- Clinical performance of the fatigue delaying stimulation paradigms will be stable over time. This will be tested by repeating the tuning procedures and comparing the optimal parameters over time, repeating dynamometer testing of the same stimulus paradigm at various time intervals, and repeating stand-to-fatigue, body weight distribution and stability tests in the laboratory.

- Objective optimization of control parameters will lead to longer sustained contractions before fatigue. This will be tested by comparing the knee extension torque produced by hand tuning the stimulation paradigms to the outcome applying the automated and objective optimization process for setting up stimulus parameters. These experiments can be performed primarily on the dynamometer and verified during standing in the laboratory.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*

- *The methods must compliment the design of the study and the nature of the data which is being collected.*

This study takes the form of a case series and employs the principles of single-subject research design. Each subject acts as his or her own concurrent (differences among stimulation paradigms for the individual at the same time interval) and longitudinal (initial post-exercise and training measurement versus follow-up values) controls. Primary statistical analyses will be in

comparison to the continuous stimulation case and will be performed on each subject individually. The effect sizes for these analyses were estimated using data obtained from existing 8-channel users and assuming a power level of 80%.

1. The longitudinal stability of the optimal stimulation parameters (pulse width and amplitudes) to ensure selective and non-overlapping activation of different muscles with each contact within the nerve cuffs will be assessed via a two-tailed t-test between initial and follow-up measurements.

2. Differences among the fatigue-delaying stimulation paradigms (carousel, interleaved, sum of phase-shifted sinusoid) and in comparison to continuous stimulation in terms of biomechanical measures of fatigue (T_{50}, $T_{0.21}$) and isometric strength will be determined by ANOVA performed on repeated measures of the outcome variables at each measurement interval.

3. Standing performance in terms of elapsed standing time and body weight distribution on the arms and legs will be compared across stimulation paradigms for each subject via ANOVA.

4. Standing stability in terms of variations in knee joint angle and location of body center of mass while standing with various stimulation paradigms will be assessed via ANOVA. The Wilcoxon Ranked Sum Test will be applied to the seven point ordinal data related to the subjective impressions of stability.

Tests will nominally be repeated three times in random order and the resulting body weight distribution and elapsed standing durations will be compared via ANOVA to determine the relative performance of each stimulation paradigm.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

The number of new subjects (15) to be enrolled in this project and receive implanted neuroprostheses was based on the effect size and variability observed in previous measurements of the outcomes of interest (elapsed standing time, body weight support, knee extension torque) and an assumed power level of 80%. The timing of recruitment and enrollment is based on the time required to fabricate implanted electrodes and stimulators, as well as the time required for implanting, training and testing the subjects who receive the devices. In addition, 10 existing subjects who had already received their implanted systems while enrolled in other approved protocols will be eligible to volunteer for the testing and experimentation portion of the study.

12. **The research involves the following procedures conducted by and for what purpose:**

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-PATIENT SUBJECTS**	☒	☐	☐	☒
Biopsy	☐	☐	☐	☐
Blood collection	☐	☒	☒	☐
Chart review – prospective	☒	☐	☐	☒
Chart review – retrospective	☒	☐	☐	☒
Review of existing data (ex: registry, Database , etc.)	☒	☐	☐	☒
X-ray or Ionizing radiation exposure	☐	☒	☒	☐
Clinical Tests	☒	☐	☐	☒
Device implantation	☒	☐	☐	☒
Drug administration	☐	☒	☒	☐
EEG, EKG , ECG…etc	☐	☒	☒	☐
Gene therapy, Genetic analysis	☐	☐	☐	☐
Pregnancy/Breastfeeding Screening	☐	☒	☒	☐
Interview, Questionnaire, Diary, Survey *(please attach)*	☒	☐	☐	☒
Stool collection, Urine collection, or any Non-surgical Specimen collection	☒	☒	☒	☐
Surgical procedure or Specimen removal during surgery	☒	☒	☐	☒
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*: dual-energy x-ray absorptiometry (DEXA)	☐	☒	☐	☒

- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

13. Please describe the research design and all study related procedures.

- *Describe* ***ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH****. This includes standard of care and research procedures.*

- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for* ***each cohort, including normal controls****).*

Study design:

For all new subjects receiving an implanted neuroprosthetic system, a screening process will occur as inpatient or outpatient, dependent upon the subject's geographic location and level of injury. After the screening, and prior to implantation, an exercise training program will be initiated. Implant surgery may include up to 9 days hospitalization prior to returning home. After the subject has healed from the surgical implant an exercise plan will resume on an outpatient basis to achieve goals using the implanted system. During the final testing and experimentation phase the system will be customized and fine tuned. This final phase may include up to an additional 50 days for customization and system tuning, dynamometer tests of strength and fatigue, standing duration, and body weight distribution and stability.

Screening (Phase I): Participation begins with a screening evaluation and informed consent. After informed consent a series of physical examinations will be performed by a qualified clinical staff to assess medical status and candidacy for the implanted neuroprosthesis. These evaluations include motor and sensory evaluation, nerve and muscle excitability with surface stimulation or intramuscular probe, joint status, bone density, baseline standing capability without FNS or with surface stimulation, and cardiopulmonary status. If psychosocial issues are suspected with a potential participant, he/she will be asked to see their primary care physician who may refer them to a psychologist for screening. The psychologist will use the instruments that, in their best judgment, will yield a diagnosis or resolve uncertainty surrounding a potential participant's suitability for the project. If the psychosocial screening indicates that the potential participant is not well suited to this project in terms of their ability to tolerate uncertainty and cope with the demands of the research project, their participation will be terminated. If the above steps yield satisfactory outcomes, participants will undergo a period of preparatory exercise with surface stimulation followed by muscle strength re-evaluation prior to implant surgery.

Prior to implantation, a medical history review and physical examination are performed, including an ASIA Impairment Scale examination to assess the subject's level of motor and sensory impairment as defined in the International Standards for Neurological and Functioning Classification of Spinal Cord Injury. Blood analysis, urine analysis, EKG and chest X-rays (according to anesthesia standards) may be required to identify any conditions that would rule out the surgery. AP and lateral images of the hips, knees and ankles will be obtained to document baseline joint status and identify any abnormalities that may contraindicate surgery and weight bearing. Measures of bone mineral density via DEXA scan may also be obtained to assess the potential for weight bearing. Copies of the informed consent are provided to each participant for their review.

During the screening evaluation process, it may be discovered that a subject is eligible for multiple studies or that they may be a better candidate for a different protocol. The subject may be referred to other studies they are eligible for.

Screening subjects with previously implanted neuroprosthesis will undergo screening procedures as necessary to determine their eligibility in this study. In addition, existing data will be used for evaluation of eligibility. Repeat testing to determine eligibility in this study may be necessary depending on individual circumstances and the amount of time elapsed since the last exam or test was completed.

Surgical Procedures and Implantation (Phase II):

After identifying key muscles for stimulation, one or more implanted stimulator telemeters (ISTs) will be implanted. Prior to surgery, motor points of the muscles targeted for activation will be mapped with surface stimulation and marked. If selected individuals are not clinically well suited to receive multi-contact nerve cuffs on their femoral nerves, intramuscular electrodes will be inserted at the motor points of each individual head of the quadriceps (vastus lateralis, medialis and intermedius, and rectus femoris) to selectively activate separate and independent motor unit pools.

Nerve cuff electrodes (CWRU spiral, Flat Interface Nerve Electrode (FINE), or Composite-Flat Interface Nerve Electrode (C-FINE) will be deployed in an open surgical exposure of the proximal femoral nerve. Fluoroscopic examination of the lumbar spine (between T11 and L2) will be used during electrode implantation for the erector spinae (trunk extension) or other muscles. The function of all electrodes will be verified intraoperatively before final subcuticular closure and dressing. Anterior-Posterior X-rays of the region from the xiphoid to the mid-shanks will be obtained to document the status of the implanted electrodes, connectors and control device.

Post-operative management, exercise and training includes hospitalization for up to nine days days for monitoring, incision management and therapy to maintain range of motion and increase sitting tolerance, followed by discharge to home with specific instructions to avoid activities that might put stress on the incisions and implanted components, observe the incisions for signs of infection, and note any significant increase or decrease as well as changes in the pattern of spasticity (flexion/extension). Any medical problem suspected after surgery may require an extension to the hospital stay.

At approximately 6 weeks post-surgery, or earlier if incisions are sufficiently healed, stimulated responses will be characterized and exercise with the implanted neuroprosthesis will be initiated. Recruitment properties (stimulus thresholds, manual muscle grades, spillover or reflex activation) of each electrode or contact within a nerve cuff will be recorded. The stimulated responses of the implanted electrodes will be incorporated into initial exercise patterns that will be constructed for each individual. Participants then begin a reconditioning program of progressive resistance strengthening and endurance exercises with stimulation customized to their rate of progress. The exercise program consists of established protocols for both strength training (few repetitions at maximal load via ankle weights) and endurance (high number of repetitions at low loads). These exercises may include contracting the muscles against loads using weights or resistive bands and commercially available exercise equipment. Subjects are expected to complete this exercise program prior to initiating standing, dynamometer and other tests of continuous stimulation or the fatigue delaying stimulation paradigms in order to ensure that their muscles are maximally conditioned and as fatigue resistant as possible.

Standing, pivot transfers and balance training follow the exercise phase until implant recipients demonstrate mastery of basic standing functions with the system, which can take several months. The users will undergo extensive training to learn basic sit-to-stand and quiet standing functions with continuous stimulation. A qualified clinical study staff may measure the strength and range of motion of the voluntary musculature and perform a full ASIA Sensory and Motor Evaluation during

follow-up approximately 1 year after discharge from post-implant rehabilitation. A follow-up DEXA may also be completed approximately 1 year post-rehabilitation to measure change in bone density.

Subjective ratings of physical and medical health, emotional health, social participation, and physical functioning will be obtained by administering a multiple-choice questionnaire, the Spinal Cord Injury-Quality of Life (SCI-QOL), at baseline and at follow-up intervals after rehabilitation and training is completed for comparison against baseline ratings.

Video recordings may be done during all experiments to help with data analysis and for display during talks, seminars and workshops.

All surgical and evaluation procedures will take place at the LSCDVAMC. Dr. Gilles Pinault will be responsible for surgical implantation of the systems and preoperative clinical management, and Dr. Stephen Selkirk will be responsible for medical clearance for recruitment and enrollment and daily management of clinical issues associated with the project. Alternatively, and only if necessary depending on availability of the operating room at LSCDVAMC, implantation can take place at MetroHealth Medical Center at which Dr. Pinault has and maintains operative privileges.

Testing and Experimentation (Phase III):

Once training is completed, the subject will commence with the testing phase to assess the performance of the implanted system.

Implementation of the fatigue delaying paradigms is essentially a three-step process.

1.) Stimulation parameters must be chosen to produce strong muscle contractions with little or no overlap in the populations of motor units activated. This step will be accomplished with the subject positioned in a dynamometer while stimulation parameters are varied by a computer-controlled optimization algorithm to create non-overlapping recruitment curves. [6].

2.) Using the values that specify non-overlapping stimulation as an upper limit, patterns must be tuned to produce the desired profile of joint torque, such as ramping up, plateau time, and ramping down for carousel stimulation, or sinusoidal oscillation frequency and pulse width values for the SOPS paradigm. For the carousel and SOPS paradigms, it is important to ensure that the maximum joint torques generated by stimulating through individual contacts are balanced and roughly equivalent to each other to avoid ripple (jitter or oscillations) in the output when they are combined.

3.) Joint torque will be recorded on the dynamometer during each stimulation pattern and ripple will be quantified to ensure that a constant contraction is achieved.

These three steps can be completed in approximately five two-hour long sessions.

Biomechanical Tests Strength and Endurance: Once stimulation patterns have been hand-tuned to produce strong, low-ripple contractions for each of the fatigue delaying stimulation regimes, tests of their functional impact on fatigue will be performed. To quantify the rate of fatigue of each paradigm isometric fatigue tests will be performed on the dynamometer with the knee held in 20° of flexion. Each fatigue test will consist of approximately 30 minutes of stimulation with a particular paradigm. Fatigue tests for all four conditions (SOPS, carousel, interleaved and baseline continuous stimulation) will be repeated for both legs nominally three times in random order for each subject, with never more than one fatigue test per leg per day.

Standing Time and Body Weight Distribution:

Each stimulation regime will be included in a standing pattern that allows the subject to use maximal continuous stimulation to execute the sit-to-stand transition and then switch the knee stimulation pattern to one of the fatigue delaying paradigms. Hip and trunk stimulation will remain

consistent throughout all trials at the levels that were determined to be most effective clinically for each individual to isolate the effects of the fatigue delaying regimes on knee extension. The subject will be instructed to stand for as long as possible with feet on a set of force plates and hands on a set of load cells to measure the distribution of body weight through the arms and legs. Standing posture can be monitored during these tests with a digital motion capture system to ensure consistent orientation of the body in order to control for variations in hand and foot placement or alignment of the head, trunk and pelvis. No more than one standing test will be performed per day, and the duration of each stand will be recorded. A stand will end either when a subject decides to sit, a physical therapist notes knee buckling, or more than 20% of body weight is supported by the arms for more than 3 seconds. Stands lasting more than 10 minutes will be considered functionally relevant, as this would represent more than a doubling in maximum standing time for more than half of the subjects using continuous stimulation in our prior studies [4].

Stability and User Perceptions of Stability:

Kinematic data collected by the motion capture system during the stand-to-fatigue and body weight distribution trials described above will be used to quantify the stability of the stimulation strategies.

Subjective perceptions of stability will be assessed with the Usability Rating Scale (URS). The URS will be adapted to assess subjective perception of stability and applied immediately after every standing test with each stimulation paradigm. Subjects rate only their impression of the task just completed and are not asked to make mental comparisons to past performance under the same or other conditions. Positive significant differences from zero of the change scores will indicate improved perception of stability while negative significant differences will indicate reduced perception of stability.

Discharge and Follow-up:

A user questionnaire will be administered prior to discharge to home to assess subjective satisfaction with the system. [7,8]. After discharge to home, medical conditions will be monitored on an ongoing basis via regular telephone or other means of electronic contact. While at home, the external controller for the implanted system will monitor patterns of usage and record the number and length of time each exercise or functional pattern is active. External controllers will be returned and exchanged for replacement units in a preventative maintenance program, at which time usage data will be downloaded and stored for later analysis[4].

Self-report of frequency and severity of pressure injuries, spasms, urinary tract infections and other medical conditions are monitored on a continual basis. Subjects may be requested to repeat the tests described above at follow-up intervals of approximately 6 to12 and 18 to 24 months post-implantation. Data from the system monitor built into the External Control Unit will be downloaded during follow-up intervals.

Biomechanical tests of strength and endurance with continuous stimulation and each of the fatigue delaying stimulus paradigms will be repeated on the dynamometer. Elapsed standing times, body weight distribution and stability assessments may also be repeated as described above. Consistency of the stimulus parameters and biomechanical and clinical measures of standing performance will be assessed by comparing these follow-up results to baseline data pre-discharge.

Long term follow-up will include reapplication of the user questionnaire, and repeated measures of the medical and technical evaluations performed at intake. This may include repeat physical examinations, motor and sensory evaluation, bone density assessments and AP/Lateral images of the joints to document any changes due to weight bearing. The integrity and stability of the implanted components will be assessed through repeated measurements of surface potentials and

recruitment properties. Electrode performance will be evaluated by conducting standardized biomechanical measurements including stimulus thresholds and maximal stimulated manual muscle grades, in addition to the dynamometer and clinical tests of standing performance applied at the short-term follow-up interval. The SCI-QOL will be repeated at follow-up intervals after rehabilitation and training is completed for comparison against baseline ratings.

Testing data collected from subjects with previously implanted neuroprosthesis will be used in the current study for comparison.

[5] H. Kagaya, M. Sharma, R. Kobetic, and E. B. Marsolais, "Ankle, knee, and hip moments during standing with and without joint contractures: simulation study for functional electrical stimulation," *Am J Phys Med Rehabil*, vol. 77, pp. 49-54; quiz 65-6, 1998.

[6] L. Fisher, D. Tyler, R. Triolo, "Optimization of selective stimulation parameters for multi-contact electrodes," *Journal of NeuroEngineering and Rehabilitation* – (in press).

[7] S. Agarwal, R.J. Triolo, R. Kobetic, M. Miller, C. Bieri, S. Kukke, L. Rohde, J.A. Davis, "Long term user perceptions of an implanted neuroprosthesis for exercise, standing and transfers after spinal cord injury." *Journal of Rehabilitation Research & Development* 40(3): 214-234, 2003.

[8] L. Rohde, B. Bonder, R. Triolo, "An exploratory study of perceived quality of life with implanted standing neuroprostheses," Journal *of Rehabilitation Research & Development* 49(2):265-278, 2012.

14. Will the research involve the following?

☐ **N/A Chart/Data Review**

Placebo Group	☒ **No**	☐ **Yes** *(describe)*:
Other Control Group	☒ **No**	☐ **Yes** *(describe)*:
Randomization	☒ **No**	☐ **Yes** *(describe)*:
Deception	☒ **No**	☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☐ **No** ☒ **Yes - Radiation Safety Committee approval is required BEFORE IRB can review. Complete the "Application for Human Subject Research Involving Ionizing Radiation Exposure" form and contact the Radiation Safety Officer at (216) 791-3800 ext. 3096**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 7 years.

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:
- 100 SCI subjects will be screened
- 15 new subjects with SCI will be enrolled and receive the implanted neuroprosthesis
- 10 previous recipients of implanted neuroprostheses.

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

N/A SINGLE SITE ☒

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).*

Individual participation for both newly implanted, and previously implanted subjects may last up to three years, or longer until study closure (dependent on available funding).

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☐ **Adults 18 years or greater**

☒ **Specific age range** (list age range): 21 and over.

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending-** ***provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. **Which of the following will be recruited or reviewed for this study** *(check all that apply)*?

☒ **Veteran Inpatients**
☒ **Veteran Outpatients**
☐ **Veteran Families**
☐ ***Normal volunteers**
☒ **Men**
☒ **Women**

☒ ***Non-Veterans;** **Provide justification** SCI is a small, orphan, population consisting of only approximately 250,000 persons in the US. At best 20% of these individuals can reasonably be expected to be eligible for this study due to disqualifying medical comorbidities and secondary complications that would contraindicate participation. Furthermore, approximately 20% of the SCI population are veterans, implying that veterans meeting the inclusion criteria would represent only 4% of all individuals with SCI. The relatively small number of qualifying veterans necessitates recruiting and enrolling non-veterans in this study. We expect approximately 20% of the study cohort, or one out of five participants enrolled, to be veterans which reflects the veteran composition of the SCI population at large. Veterans will benefit greatly from the inclusion of non-veterans, especially those who receive implants at MetroHealth Medical Center and do not require utilization of VA resources.

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. **Which vulnerable population(s) will be TARGETED for recruitment in this study:**

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)
☒ **NONE** (*proceed to Item 26)*
☐ **Medical students, house staff, or Employees of the VAMC or Case**
☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**
☐ **Children – Complete Section 14 "Children as Research Subjects"**
☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**
☐ **Targeting Persons over Age 65**
☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☐ **Others** *(describe)*:

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☐ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☐ **Other - Describe Additional safeguards you plan to use:**

c. Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☐ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☒ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☒ **Investigator's Patient Population**

☒ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☐ **Other** *(describe)*:

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☐ **No** ☒ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:** VISTA/CPRS will be used to identify names, contact information, SSN, and medical history for eligibility determination.

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☐ No ☒ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):*

Physicians associated with SCI are aware of our studies and identify potential subjects who might meet the inclusion/exclusion criteria and are interested in FNS. If the subject is interested, contact information is exchanged. Volunteers will be recruited by integrating the screening and selection process for project participation into the routine for every patient admitted to the SCI Services of the LSCDVAMC.

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☐ **No** ☒ **Yes- check all that apply and submit for IRB review:**

☐ **Letter**

☐ **Information Sheets**

☒ **Questionnaire, Survey, Diary**

☒ **Other** *(flyer, brochure, describe):* A User Manual: Universal External Control Unit for Lower Extremity Implanted Neuroprostheses -Revision 150521

A brochure titled: "Volunteering in Research"

A User Questionnaire, and the Usability rating scale

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*
- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*
- *Provide answers for* ***each cohort****, including normal controls.*

Inclusion criteria for SCI participants:

1. Skeletal maturity (age 21 and above), and ability to sign informed consent
2. Paralysis resulting from neurological disorder such as low cervical/thoracic spinal cord injuries (C6-T12)
3. Time post injury greater than six months to assure neurological and emotional stability
4. Innervated and excitable lower extremity and lumbar trunk musculature
5. Absence of acute or unstable psychological problems, chemical dependency, or substance abuse.
6. Range of motion within normal limits, (full extension at the hip and knee, and ability to attain a neutral ankle position)
7. Controlled spasticity and absence of hip flexion and adduction spasms
8. Appropriate body habitus (not to exceed 300 lbs. or SCI-adjusted BMI less than morbidly obese.)
9. Adequate social support and stability
10. Willingness to comply with follow-up procedures.
11. Full coverage of the acetabulum and minimal knee and ankle laxity

SCI participants who previously participated in another surgical implant FES study may be considered for enrollment in this study.

Exclusion Criteria for SCI Participants:

1. History of vestibular dysfunction, balance problems or spontaneous falls.
2. Acute orthopaedic problems: severe scoliosis or joint dislocation, severe osteoporosis.
3. Acute medical complication: cardiac abnormalities, skin breakdowns, uncontrolled seizures, or immunological, pulmonary/ renal/ circulatory compromise, auto-immune deficiencies, sepsis, active infection, dental caries.
4. Diabetes
5. Non-English-speaking subjects
6. Pregnancy

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

Eligibility will be assessed by members of the study team including the PI, study physical therapists, and research study staff when interviewing potential subjects, inclusion/exclusion criteria will be reviewed and additional medical history will be requested if necessary for review of the subject's history of spinal cord injury and medical /surgical history. Standing is tested with surface stimulation as part of the screening process. Candidates with co-morbid head injuries may be referred for neuropsychological evaluation.

Determination of candidacy may require evaluation by the candidate's primary care physician (PCP) to ascertain baseline physical and psychological status and obtain clearance to apply electrical stimulation. These evaluations may include electrocardiograms, radiographs, respirometry, blood chemistry, urine cultures or other clinical tests as indicated. Candidates with brain injuries will be referred to their PCP for neuropsychological evaluation.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English* ***based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*:

- Pregnancy is an exclusion criterion. This is due to the positioning of the implant on the stomach and lack of scientific data determining the potential risks of neuromuscular electrical stimulation on fetuses.
- Non-English speaking subjects are excluded due to the need to comprehend the complex commands during training

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☐ **No (skip to item #35)** ☒ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☒ **Cash** ☒ **Check** ☐ **Other** -please explain: Cash or check will be used according to subject's preference. Agent cashier.

☐ **Prorated** -provide schedule: ☒ **Fixed** -provide schedule

Subjects will not be compensated for activities related to the screening and intake process or to the installation, maintenance and routine follow-up of the implanted system. Subjects will receive no special compensation for participating in the regularly scheduled aspects of this research project required to install, maintain or monitor the performance of the system. Reimbursement will be limited to legitimate travel expenses paid at the current government rate up to a maximum of $2,000.

When subjects participate in follow-up testing, experiments, teaching sessions or demonstrations other than what is required to install, maintain or monitor the performance of the system, they will receive either $50.00 per session or reimbursement for legitimate travel expenses, paid at the current government rate.

This is expected to be less than $1,000 per year. These may include laboratory data collection sessions pertaining to motion analysis, new controller evaluation, teaching demonstrations, muscle testing, or supervised exercise and ambulation at the investigators' request.

Monthly for mileage related to study activities. No reimbursement for screening phase of the study. If the subject is demonstrating the system, the required forms will be filled in at the end of the demonstration.

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes**- please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

Subject selection will be based on inclusion criteria. As many subjects as possible will be recruited from different races, nationalities, gender and age to increase the diversity of participants. A choice between two equally qualified subjects will be made through a random drawing.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

*Certificate of Confidentiality:

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.

- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

1) **Risks:**

Discomfort and unpleasant sensation:

Individuals with sensation in the area of their paralysis may have some discomfort during electrical stimulation while the proper levels of stimulus parameters are determined. To minimize this discomfort we slowly increase the stimulus pulse width to remain within the subject's comfort level. After comfortable levels are found, there should be no additional discomfort or pain when the stimulation is applied.

Surgery:

There are associated risks with any surgical procedure including bleeding and the use of anesthesia. Other risks include puncture of a vessel and blood loss, irritation of a nerve, pain and bruising, or an adverse reaction to the anesthesia agents. Although it is possible to injure a nerve during implantation, there have been no instances of permanent nerve damage from the implant procedure or from the electrodes themselves. Some muscle tissue is destroyed during surgery. The increases in muscle strength with exercise using electrical stimulation usually compensate for any loss of muscle tissue during implantation. During surgery, monitoring will be accomplished by a qualified anesthesiologist to assure safety. There is a possibility of nerve injury while installing nerve cuff and other electrodes. Nerve damage can lead to pain, burning sensations, sweating, extreme sensitivity to temperature or touch, local heating or cooling, or other changes in the skin, nails or hair of the affected area. These symptoms can usually be treated effectively with drugs, exercise or other therapies. Squeezing the nerve too tightly can cause a compression injury that can result in numbness, tingling, aches and/or muscle weakness that may last for days or weeks after the surgery. This could also trigger muscle spasms and reflexes that cause stomach upset, dizziness, sweating or other unusual symptoms. This situation can usually be detected during implantation or the first several days after surgery. Removing the pressure usually corrects the condition, such as in carpal tunnel syndrome, and these symptoms usually resolve over time. Accidental damage to a nerve from a scalpel or surgical instrument may also result in permanent loss of sensory or motor function.

Infection:

There is a risk that the implanted stimulator could be infected. To reduce the likelihood of infection, special steps (including extensive cleaning of the skin prior to surgery, taking antibiotic medication before and after the operation, and performing the procedure in an operating room) will be taken. As with any other implanted material, there is the risk that the blood can carry bacteria or other infectious agents to the location of the stimulator(s) or electrodes where they can collect and multiply long after the time of surgery. An infection of this type is a known complication for artificial joints and other implants. An aggressive antibiotic treatment would be prescribed to treat the infection and if unsuccessful the device

would be removed in a second surgical procedure. This has occurred once with a lower extremity implant and the subject fully recovered after the device was removed.

To reduce the risk of such systemic infections, it is important for participants to seek medical treatment quickly for any cold, flu, or respiratory or viral infection. Open wounds, burns or dental cavities should also be treated rapidly since they can be sources of infection. Subjects should monitor themselves for urinary tract infections or pressure injuries, and take the other reasonable precautions required for someone with paralysis to remain in good health.

Device malfunction:

There is a risk that the implant(s), electrodes, connectors or leads could fail to operate properly. If a failure should occur, the investigators will analyze the malfunction to help decide whether to replace the failed component, leave it in place, or have the entire system removed. There is a potential for interference when using the wireless fingerswitch; therefore, the user can always employ the buttons on the main controller enclosure as a backup or default alternative if needed.

Tissue erosion:

Pressure over the implant(s) or leads could erode the skin and expose the internal components of the system. The implant size is kept as small as possible and edges are tapered to reduce possible mechanical abrasion. The surgical placement of the devices(s) and leads is designed to reduce the possibility of erosion by locating them in deeper tissue layers for additional protection. If the tissue were to erode, the subject would be counseled regarding the nature of the problem and the device or lead would be removed or replaced. The entire device could be removed if deemed appropriate by the surgeon.

If any part of the device is too close to the skin surface, the subject may notice redness, swelling, or a break in the skin with fluid drainage. If this occurs, the laboratory staff must be contacted immediately for counseling and treatment. Treatment may include oral antibiotics, diagnostic x-rays, or surgical removal or replacement of the component.

Nerve or vessel injury:

The usual dangers of any hypodermic injection are present at the time the electrodes are inserted. These include puncture of a blood vessel, irritation of a nerve or breaking of the needle in the body. In more than 15 years of experience, there have been no instances of permanent nerve damage from implanted procedure or from electrodes themselves. These risks are extremely small and have not been encountered in the previous applications of this technology. Nerve cuff electrodes have been associated with nerve compression injuries. There can be several causes for nerve compression: incorrectly sizing the cuff during implantation, swelling to the nerve within the cuff after surgery, build-up of scar tissue around the cuff, bending of the nerve around the edges of the cuff, and external pressure applied by the surrounding tissues to the nerve through the cuff. Nerve compression may not develop for days or weeks after implantation and can change the patterns of spasms, eliminate tendon tap reflexes and diminish the responses of the muscles to stimulation. Compression can also trigger autonomic dysreflexia or other reflexes that cause stomach upset, dizziness, sweating, blood pressure changes, pain, muscle weakness, burning sensations and other unusual symptoms. The nerve can recover from compression with removal of the applied pressure, and symptoms usually resolve over time as in carpal tunnel syndrome. However, high pressures applied for prolonged periods of time can result in permanent nerve damage. At the recommendation of the research team, the device may need to be removed.

Skin irritation abrasions and pressure injuries:

The conductive gels used with surface electrodes, the adhesives on bandages, or the tapes used to secure surface electrodes or sensors to the body may irritate skin. It is possible to experience a temporary redness under surface electrodes or other dressings in contact with skin. Occasionally, braces may need to be used in portions of this study. With the use of braces, there is a risk of scrapes and blisters. Similar risks are associated with the straps and pads to stabilize limbs in the machines that are necessary to test the strength and endurance of stimulated muscles. Braces will then be modified to minimize undue pressure on the skin, and the muscle testing apparatus will be adjusted or padded to alleviate the pressure points. Muscle testing devices used in this study have built in safety limits and emergency shut-off switches that minimize the possibility of injury.

Pressure injuries are a common complication of paralysis, especially spinal cord injury. Almost one-third (33%) of all persons with spinal cord injury can expect to develop pressure injuries. There is no evidence that the implanted material increases the risk of pressure injuries and indeed, FNS has been shown to reduce the risks of such injuries.

Electrode movement and/or breakage:

Another risk is that the electrodes could move or break internally. The chance of this occurring depends on the design of the electrode, how it is anchored in the tissue, and the length of time in the body. When an electrode moves away from the nerve it activates, it can stimulate a different muscle, produce an unwanted reflex, cause pain, or result in a weaker contraction. When an electrode breaks, it can no longer conduct electricity and is not effective in producing contraction. The amount of material left behind upon removal will vary, but is usually benign and well tolerated. The body may try to expel a fragment of retained electrode. This is a foreign body rejection reaction and does not indicate the presence of an infection. After migrating to the skin surface, the fragment can be removed and the open sore treated to prevent infection. If a failed electrode significantly compromises standing performance, it can be removed and replaced in a separate surgical procedure.

Scarring:

Tissue around the implanted components could become excessively scarred from the surgical procedure or the presence of the implanted material. It is also possible that the application of electrical currents for long periods of time might result in scarring of the tissue. If such scarring interfered with the function of the device(s) or presented a safety problem, the subject would be notified, the problem component could then be removed or replaced with the subject's approval. In our experience with human and animal studies involving implanted devices leading up to this study, such tissue changes have never been encountered.

Device rejection:

The implanted components are made from materials that have been used in other medical devices and are not toxic or dangerous to the body tissues. They include stainless steel, titanium, platinum, and other substances accepted by the FDA for human use. There have been no instances of allergic reactions or toxicity due to the implanted materials in this study to date. It is still possible that the device may be rejected through some yet unknown process. If this were to happen, subjects would be counseled regarding the nature of the problem and the device would be removed.

Burns and electrical hazards:

There is a possibility of an electrical shock including electrical burn, whenever electricity is used to stimulate or to power the instruments necessary to record test results. Stimulators and measurement instruments are designed to prevent any current flow at levels that could produce tissue damage To further minimize these risks, the electrical safety officer associated with the research group will check and certify all experimental set-ups and custom laboratory instrumentation, including stimulation systems for electrical safety before they are applied to you.

It is also possible to receive a chemical burn if the material inside the stimulator batteries comes in contact with your skin. The batteries are sealed inside the cases of the external stimulators, and contain materials that are less likely to cause chemical burns. All batteries are located outside of the body. The implanted components of the systems being tested are passive and do not contain batteries.

Risk to the heart and the nervous system:

There is an extremely low risk of abnormal heart rhythms or autonomic dysreflexia (sudden increases in blood pressure and heart rate). If there is a history of cardiac problems, the candidate should consult with a cardiologist. The issue would need to be cleared by the cardiologist prior to further evaluation. Similarly, if a heart problem develops during the course of this investigation, the investigators must be notified immediately and stimulating would be stopped. The risks are minimized by screening patients for any cardiac abnormalities, by placing electrodes far from the heart, and by carefully monitoring during experimental procedures. The electrical stimulation used in this study is similar to that routinely applied therapeutically in the clinical setting.

Blood pressure changes and muscle fatigue:

Dizziness associated with lower blood pressure can occur while standing, walking or exercising with FNS. If this occurs, further attempts to stand will be made with expressed consent of the research participant only after resting, drinking fluids and consulting a medical professional. Fatigue and shortness of breath can result from prolonged walking or strenuous exercise with electrical stimulation. The standing and walking required for these studies has been shown to be well below the threshold for such a response.

The body can fatigue from prolonged strenuous exercise with electrical stimulation and the subject may experience shortness of breath. The muscles of the hands, arms, and shoulders may tire when walking with stimulation because of the weight placed on the walker, support frame or parallel bars. Soreness of the muscles in the upper extremities should resolve with rest.

Fracture and falls:

Individuals with paralysis generally have weaker bones than able-bodied individuals. Because of this, up to one-quarter (25%) of all persons with SCI may experience a bone fracture at some time after injury. Therefore, based on subject's paralysis, there is a risk for a bone fracture.

Exercise, weight bearing and muscle testing in these studies will place stresses on the bones that can lead to fractures or soft tissue injuries. Tendons and soft-tissues can also be ruptured by the mechanical stresses produced by FNS. Two out of about 50 FNS users (less than 5%) have experienced minor fractures in the laboratory over the past 20 years. Both were unrelated to FNS and healed without permanent injury. To minimize the risk of fracture to bones or injury to tendons, it is important to follow the exercise program prescribed by the research staff and observe precautions for safe FNS use. During standing there is a risk of sprain or joint deterioration resulting from overuse, especially when there is an absence of sensation. After daily

use of the system for many years no deterioration of joints has been noted. There is also a risk of falling and mechanical injury while exercising and standing with stimulation. The risk of injury is reduced when proper precautions are taken. Subjects will be closely supervised by a member of staff during standing and experimental procedures and will be given detailed instructions and training on safe use of their FNS system. In addition, subjects will be placed in parallel bars or a safety harness for stability during testing. All experimental procedures will use standard clinical equipment and any external electric or mechanical testing devices will be set up and tested in advance so the safety officer associated with our research group can qualify their safety.

In addition, there is a risk of falling and mechanical injury while exercising, standing or walking with stimulation. Sprains, joint damage, or other injury from overuse is also possible as there is a lack of sensation in the joints and lower extremities. There have been no injuries resulting from falls in the studies leading to this investigation.

Ionizing Radiation Exposure:

Subjects will undergo procedures involving ionizing radiation exposure in excess of what they would if not enrolled in the study. The various procedures will occur just prior to, and after surgery. Procedures and the number for each are as follows – prior to surgery, 4 X-rays of both hips, knees, and ankles, 2 bone densitometry (DEXA) scans of either the femoral neck, distal femur, or proximal tibia and one chest X-ray (for medical clearance if indicated). During surgery one session of fluoroscopic visualization of the spine between T11 and L2, inclusive will be taken. After surgery, one X-ray of the region of the body from the xiphoid to the mid-shanks will be taken. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation each patient will receive in this study is about 5.2 mSv or 520 mrem, and is approximately equivalent to a whole body exposure of 630 days (1.7 years) of exposure to natural background radiation. This use involves minimal risk and is necessary to obtain the research information desired.

Pregnancy and birth defects:

The effects of using functional electrical stimulation during pregnancy and on the developing fetus are not known at this time. It is possible that the electrical currents used to stimulate the nerves and muscles of a pregnant woman could affect the health of the developing fetus. There may be a risk of birth defect, miscarriage or other unanticipated side effects of electrical stimulation during pregnancy. It is recommended that women of child-bearing potential should not become pregnant during the course of the study. If a subject who has an implant becomes pregnant, the subject must stop using the stimulation system and notify study personnel as soon s possible. Subjects should advise their OB/GYN and primary physician of the situation and consult with the research staff about the best course of action. This might involve removing all implanted electrodes. Although extra lengths of lead wire are placed under the skin when the electrodes are inserted to allow some movement and growth, they may not be long enough to accommodate the changes the body goes through during pregnancy. The implanted electrodes and leads are not designed to stretch as pregnancy progresses, and may put pressure on the skin or internal organs that would not normally exist. It is also possible that the implanted electrodes could be damaged as a result of pregnancy or during a Cesarean delivery.

Magnetic Resonance Imaging (MRI)

An MRI should not be performed on any part of the body as the implant stimulator and electrodes have not been tested for safety within an MRI machine.

Ultrasound imaging and/or sonogram

Ultrasound imaging and or sonograms should not be applied directly over the implant stimulator.

Surface stimulation such as Transcutaneous Electrical Nerve Stimulation (TENS) or Neuromuscular Electrical Stimulator (NMES) could cause current flow through the implanted stimulator that could result in damage to the device.

Diathermy

Diathermy is a deep tissue heat treatment, and should not be performed in the area of the stimulator or electrodes. It is important to contact one of the investigators before undergoing any surgery near the implant or before undergoing implantation of orthopedic or cardiovascular devices such as an artificial hip or a pacemaker. Study investigators should be contacted before scheduling nuclear imaging procedures.

All other surgical procedures that will not take place near implanted devices must also be reported.

Other potential discomforts or risks:

Some of the SCI-QOL questions focus on personal or difficult topics. Subjects may experience mild discomfort answering these questions, but no significant health risks are anticipated.

A qualified clinical study staff will perform the ASIA exam to measure the subject's level of intact movement and sensation. A rectal exam is included to test for sensation and contraction. The clinical study staff will insert a gloved finger into the rectum. This portion of the exam will only take seconds to complete. They may feel a slight momentary discomfort during the test. The exam is not expected to cause any significant pain or damage.

Metabolic testing involves using a nose clip and mouthpiece that might cause claustrophobia or discomfort in some individuals. The duration of the metabolic tests will be short and they will be discontinued if found to be intolerable. If blood needs to be drawn for testing there may be some temporary discomfort and the usual risk of local bruising, infection, or blockage of the vein. Occasionally fainting can occur. The chances of these things happening are no more than with routine drawing of blood samples in a general medical setting. Suitable precautions will be taken to minimize these risks. Compartment syndrome is a death of muscle tissue due to the buildup of large pressure within the limb that prevents blood from flowing. Other studies have shown that exercise with FNS produces pressures that are well within safe ranges and therefore should not increase the risk of compartment syndrome beyond that of the SCI population at large. Only four complaints of lower limb swelling after stimulation have been reported, all of which subsided with rest. Another potential risk is that the subject develops unreasonably high expectations of the FNS system that may lead to depression if the expectations are not met. As part of the screening process for admission into the project we repeatedly stress that there is no guaranty that the FNS system will provide any improvement in function. If a subject should get depressed as a result of this project he/she will be referred for counseling.

Subjects may notice that the strength of spasms increases after using FNS to exercise. This is most likely due to an increase in strength and general health of the muscles involved in the spasms. Several FNS users have reported experiencing fewer, but stronger spasms, although no date exists to support this observation. Similar subjective reports suggest that exercise and standing with FNS does not adversely affect the number or severity of urinary tract infections (UTIs).

Unsupervised use of the FNS system can pose additional risks, especially if subjects ignore the exercise prescription and general precautions as explained by the research staff. It is possible to injure muscles by over-using them. Alternatively, not exercising enough can compromise strength, endurance, and performance with the FNS system. This may ultimately risk the safety of the heart, bones, joints, and skin. It is the subject's responsibility to follow the guidelines for responsible FNS system use. Since this is an investigational study, there are unknown risks.

Protection of privacy and confidentiality

The identifiable information will be used or disclosed only by the principal investigator and authorized study members of the research team or representatives from internal hospital operations (for example quality assurance). Also, authorized representatives of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center may have access to personal health information for the purpose of filling orders (for example lab tests, X-rays, operating room implantation procedure, short stay unit); addressing correct payment for tests and procedures ordered; and/or processing payment for travel. If any incidental findings which affect the subject's general health are discovered during the medical record review or physical exam, the clinical study staff will discuss them with the subject and communicate with a physician of the subject's choice for follow-up. This study poses minimal risk to the privacy of the subjects because: a) The identifiable information including name, hospital ID number, home address and telephone number, photographs, digital images, videotapes, video files, and experimental data will be protected from improper use or disclosure by storing them in locked filing cabinets in a locked office in the Motion Study Laboratory, room B-B322/C-15 and in computers with password protection; and b) The identifiers will be destroyed at the earliest opportunity consistent with the research. The authorization to use your PHI will be good indefinitely as specified in the approved HIPAA authorization, or as required by law. The identifiable information will not be reused or disclosed to any other person or entity outside the Veterans Health Administration other than those identified in the protocol, except as required by law, for authorized oversight of this study, or as specifically approved for use in another study by the IRB.

2) <u>Benefits</u>

Subjects may not directly benefit from participating in this study since the devices involved are experimental. No specific improvement in baseline condition can be guaranteed, but it is reasonable to expect to receive the benefits of being able to exercise, and stand for prolonged periods of time with electrical stimulation. Additional benefits may be increased muscle bulk and improved skin circulation, therefore resulting in a reduction in pressure injuries. Additional benefits may include an improved cardiovascular fitness, stronger bones, and reduced excessive muscle tone and spasms.

The knowledge gained during the course of this study may help make implanted FES systems available to others with similar disabilities in the future. The results of these studies will identify limitations in the performance that will be critical for optimizing the design in the future. The potential societal impact includes reduction in health care costs associated with prolonged disability, personal assistance or nursing home admissions. Increased independence with the implanted neural prostheses may also allow individuals to return to work or engage in other roles associated with a healthy and productive lifestyle.

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

Standard of care procedures that minimize risk include: Prior to the surgical implantation, standard of care pre-operative procedures including review of medical/surgical history, physical examination, laboratory and EKG are reviewed by the research team and the surgeon to minimize the risk to the participant. During procedures where the physical therapist is working with the subject, contact guarding is used to minimize the risk of falls. Standard physical therapy practice guidelines are applied when using electrical stimulation. Universal precautions are used for all subjects.

41. Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.

No alternatives exist. This is not a treatment study.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. Please give your overall risk classification for the research:

☐ **Minimal Risk**

☒ **Greater than Minimal Risk**

43. Will subjects receive any direct benefit from this research?

☐ **No** ☒ **Yes** -describe the direct benefits:

There are significant medical, economic and social costs of paralysis and impaired mobility. Preliminary work indicated that FNS holds great promise for restoring function, improving health, and increasing the independence of individuals with SCI. The increased mobility resulting from FNS may prevent or postpone institutionalization in persons with disabilities. Because the technology is still experimental, no specific improvement in the condition of any one individual can be guaranteed. Participants may receive the benefits of being able to exercise and stand with stimulation. Secondary benefits to exercise may be increased muscle bulk, better cardiovascular fitness, improved bladder and bowel function and stronger bones. The exercise of partially paralyzed muscles is difficult especially when coordination is poor or when there is uncontrollable muscle tone. In some cases the tone can be reduced with medication. But in most cases there are no alternative methods for exercising the lower limbs with active muscle contractions other than electrical stimulation.

44. Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?

The knowledge gained during the course of this study may help make FNS systems for exercise and walking available in the future. Alternatives to FNS for walking include bracing to fix the joints during standing and the use of the upper body and arms supported by walking aids to swing the legs forward. Often this requires excessive effort, forcing individuals to rely exclusively on their wheelchairs. FNS can support the body against collapse, thus obviating or reducing the need for bracing, and provide active contractions in muscles not under voluntary control. FNS can also reduce the excessive muscle tone that may prevent active movement.

Although the risk to the participant is greater than minimal, due to the surgical implantation phase, the only alternatives to FNS for standing include bracing to fix the joints during standing and using the upper body and arms supported to prevent a fall. Often this requires excessive effort, forcing individuals to rely exclusively on their wheelchairs. FNS can support the body against collapse, thus obviating or reducing the need for bracing, and provide active contractions in muscles not under voluntary control. FNS can also reduce the excessive muscle tone that may prevent active movement. Prolonged periods of inactivity and immobility resulting from paralysis compromise the function of almost every organ system and pose serious threats to overall health and general well-being; including pressure injuries, deep vein thrombosis, joint contractures, cardiac deconditioning, and increases susceptibility to immune deficiencies. The potential benefit from improved health due to exercise, as well as scientific knowledge and understanding of SCI rehabilitation interventions is significant. The risk/benefit ratio is acceptable.

Section 6 – Informed Consent

45. Type and number of Consent-

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study*:

☒ **Written Informed Consent –number used in this study** 3 Total

1. Screening Phase I
2. Implant & Training Phase II
3. Testing Phase III

☐ ***Oral Script/Letter/Information Sheet- number used in this study** ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. Will all adult subjects have the capacity to give informed consent?

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☒ No ☐ Yes -please explain:

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

All conversations occur within a private room.

At the time of first contact with an interested individual, the details of participation and potential risks are described verbally and can be followed by distribution of printed materials such as the Informed Consent Form. Questions are encouraged and telephone contact might continue over several sessions as the risks and benefits of the research procedure are explained to the potential participant. Potential participants and their families or caregivers interact one-on-one with members of the research team as all procedures and potential risks and benefits are explained. Candidates are asked directly if they comprehend all aspects of the study throughout the process.

Discussions of the research with study staff are encouraged and all questions can be written down by the potential subject with an expectation of explanation from study staff prior to signing the Informed Consent form. The documents are signed, and originals are maintained on file while participants are provided signed copies.

An additional consent will be requested for video/voice recording to assist with analysis of movement both pre- and post-implant.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☒ **Yes** ☐ **No** - please explain:

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

PI, study Physical therapist, study coordinator, and other study staff as appropriate.

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

N/A. Subjects must be able to read and comprehend English to participate.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

The person obtaining informed consent will determine the subject understands the study by asking questions and having the subject describe the risks and potential benefits of the study.

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy
- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.

To protect the privacy of participants, the HIPPA Authorization form is discussed with the subject and their significant other/s in the Motion Study Lab in a private room. Only study staff receives and uses the information. The nature of the information they give is their own medical history, their disability, and how it affects their daily life. The information is used to assess appropriateness of the individual to enter the study. Only study staff receives and uses the information. The purpose of collecting the medical history is to review needed information about inclusion/exclusion criteria, evaluate their disability and how they could improve by using the

Implant, discuss goals for using the system, and evaluate their overall health and its effect on their disability. Purpose of the data is to conduct scientific research and that no personnel involved in the study may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. All information provided by subjects is kept in a locked cabinet in a locked office.

54. Will researchers have access to identifiable private information about potential subjects outside of this research project? *Ex. PI is provider who has access to medical records for clinical care*

☐ **No** ☒ **Yes- please explain:** The study physician may deliver care to an enrolled subject as part of their routine clinical practice.

55. Will Researchers collect identifiable private information on anyone other than the subject?

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. At the time data are transcribed or recorded for this study they are?

☐ **Fully identifiable- list identifiers to be collected:**

☒ **Coded with a unique identifier- describe the code:** a unique identifier is assigned at the time of enrollment. The identifier is a random group of numbers(s), and letters.

a. Who will have access to the key? PI, study Physical therapist, study coordinator, and study staff.

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. In a locked cabinet, within a locked room of the Motion Study Lab (B-B322/Room C-15).

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. How will electronic research data be secured while the study is active?

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☒ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician- (VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: Consent forms and other hard copy data will be kept in a locked file cabinet in a locked room of the Motion Study Lab (B-B322/C-15).

60. Is identifiable information physically or electronically sent TO the LSCDVAMC from other institutions or locations?

☒ **No** ☐ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

- ☐ **M: drive; whose?**
- ☒ **S: drive**
  - ☒ **Folder access password protected**
- ☐ **Other drive location** *(for example P: drive)*:
  - ☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☐ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored:
LSCVAMC, of the Motion Study Lab (B-B322/C-15) Room C-15

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.
- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

*CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☐ SKIP TO #65

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board:**

☒ **Data Monitoring Committee**

☐ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

We will empanel a Data Monitoring Committee, which will be chaired by a knowledgeable independent observer (e.g., Dr. Brian Cmolik, Chief of Surgery) and consist of members uninvolved with the study (e.g., Dr. Ronald Riechers, Chief of Neurology). The Committee will meet annually to review study procedures and outcomes, and analyze adverse events to identify potential trends that indicate previously unanticipated issues that may affect the risk profile for our subjects. This Data Monitoring Committee will be organized and facilitated by the Regulatory Specialist for the APT Center.

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body:

The VA is the sponsor of this study. External audits and monitoring are anticipated once during the course of the study and will take place in accordance with all applicable policies and procedures of the Medical Center. If necessary, external entities will be contracted to perform independent data monitoring with project funds.

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**

☒ **Serious adverse event**

☒ **Pregnancy**

☒ **Subject withdrawal**

☐ **Study closure by sponsor or FDA**

☐ **Other-describe:**

☐ **Medical condition worsened**

☐ **Intolerable complications**

☒ **Investigator's clinical judgment**

☒ **Subject uncooperative or noncompliant**

☐ **Refusal to suspend breast-feeding**

☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

If participants withdraw from the study prior to implantation, there should be no increased risk related to the study. If the participant is implanted and chooses to withdraw, we retrieve the external equipment which prevents further use of the Implant. The implant can remain in place or can be removed, depending on the desire of the participant. The implant can remain in place without causing health problems for the participant.

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of <u>any</u> drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.
- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☒ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☐ **Drug**

☐ **Biologic or Other:**

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV** ☐ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for each drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☐ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☐ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☐ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** *(Proceed to Section 11)*

☒ **Device**

74. List the device-include name and manufacturer:

Implantable Stimulator Telemeter (IST 16)	TDL (Technical development laboratory of the Cleveland FNS Center)
External Controller • UECU/UECU Lite • Wireless Finger Switch/Sensor • Wireless accelerometer/gyroscope • Communicating Coil • Charger • Stimulation Software	Ardiem Medical, Inc. 1125 Wayne Ave. Indiana, PA. 15701-3513 724-349-0855
	TDL- Technical Development Laboratory Case Western Reserve University 11000 Euclid Ave. Bingham 306 Cleveland, Oh 44106 216-368-3207

75. FDA Regulatory Status of the Device:

☐ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ New Indication of an FDA Approved Device

- A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.

☒ Investigational - Investigational Device Exemption (IDE)

- An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.

Provide the following:

a. **IDE Number:** IDE# G040214 & IDE#G900108

b. **IDE Sponsor or Holder:** VA Research Office

If the PI holds the IDE, complete the following:

i. **The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor**

☐ Yes

ii. **As the PI, you will comply with the regulatory responsibilities of a sponsor**

☐ Yes

c. **FDA or Sponsor Device Risk Determination**

☐ Non-Significant Risk

☒ Significant Risk

d. **Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).**

☐ Humanitarian Use Device (HUD)

- An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.

Provide the following:

a. **HUD Number:**

b. **HUD Sponsor or Holder:**

c. **Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.**

☐ 510(k) Status –

- A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.

a. **Provide the name of an equivalent device and sufficient documentation to justify 510(k)**

76. Attach device information (i.e., brochure, device label)

Device labeling requirements are not applicable to the devices used in this study. Subjects are provided with a User Manual: Universal External Control Unit for Lower Extremity Implanted Neuroprostheses - Revision -150521, which provides user information for the external controls that power the implanted components of the FES system.

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

The Investigator will control the investigational device inventory. The investigator will maintain an inventory log of their clinical investigational devices. (see example log sheet attached). The log must be maintained in the project files or the project's regulatory binder for the time period required by the federal regulations or as indicated by the sponsor. The full names, titles, position, signatures, and/or initials of all VA personnel responsible for maintaining or documenting in the logs must be indicated on the cover letter or log itself.

Elements of the investigational device inventory log will include at a minimum:

- Device logs Study name
- IRB protocol #
- Sponsor name or funding agency
- Type of device
- Model number
- Serial number
- Lot number, if applicable
- Date received. (If the devices were not specifically ordered for the research protocol, but are utilized in the research protocol the date received would be the date the device is implanted in the research subject) [6.2, 6.3]
- Research participant name and Medical Record Number (for internal tracking purposes)
- Research participant study I.D. number
- Date implanted or used
- Disposition. If product is returned to the sponsor or destroyed, documentation of why, when, and persons involved.
- In the event of research software, disposition may include the date the software was deprogrammed from the device (e.g. an approved pacemaker in implanted and programmed with experimental software the date disposition would be the date the subject's pacemaker is re-programmed with approved software, or in the event of an investigational software used to operate a laser the disposition should be indicated as the date removed from the machine and returned to manufacture)
- Names of all the persons who received, used, or disposed of each device.
- Date of expiration of the device

The investigational device inventory list will be updated to reflect deployment of devices to research subject, or return of devices from research subjects.

Investigational devices will be inspected for correct investigational device labeling.
Labeling will state (per 21 CFR 812):

- The name and place of business of the manufacturer, packer or distributor.
- The quantity of contents
- The statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use"
- The label shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions as necessary.
- If the labeling is incorrect the devices will be quarantined until correctly labeled.
- Investigational devices will be stored in locked areas (offices, cabinets, drawers, etc.) away from general hospital supply areas.

Only study staff and assigned regulatory specialists will have access to these areas.
The investigator will do an investigational device inventory, at a minimum, once yearly.

REFERENCES
21 CFR 812, Investigational Device Exemptions
LSCDVAMC Policy 151-015

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ **No genetic testing** (*Proceed to Section 12)*

☐ **Yes- complete the following:**

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study

c. Describe the accuracy of the test

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

☐ **Has a specific condition**

☐ **Is at risk for a specific condition**

☐ **May be at risk for a specific condition**

☐ **Has, is, or may be at risk for some other outcome**

☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

☐ Is not at risk for a specific condition

☐ Is at a lower risk for a specific condition

☐ Is at a population risk for a specific condition

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ No ☐ Yes- please explain:

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ No ☐ Yes- please explain:

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ No ☐ Yes- indicate who will conduct the counseling and whether there are any additional charges:

85. Will DNA samples be stored?

☐ No ☐ Yes--describe where, how, and for how long the samples will be stored:

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ No ☐ Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ No ☐ Yes- please explain:

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. **What identifying information will be required?**

b. **What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?**

c. **What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?**

d. **How long will the information and/or specimens be stored?**

e. **Is the storage facility an on-site or off-site location?**

f. **Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository?** *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:**

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☒ **Not applicable**