Epidural Neuromodulation for Spinal Cord Injury

Protocol Identifying Number:

Principal Investigator: David Darrow

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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PI	Principal Investigator
QOL	Quality of Life
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
VRI	Volitional Response Index
WHO	World Health Organization

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)
- ICH GCP E6
- Completion of Human Subjects Protection Training

PROTOCOL SUMMARY

Title: Epidural Neuromodulation for Spinal Cord Injury

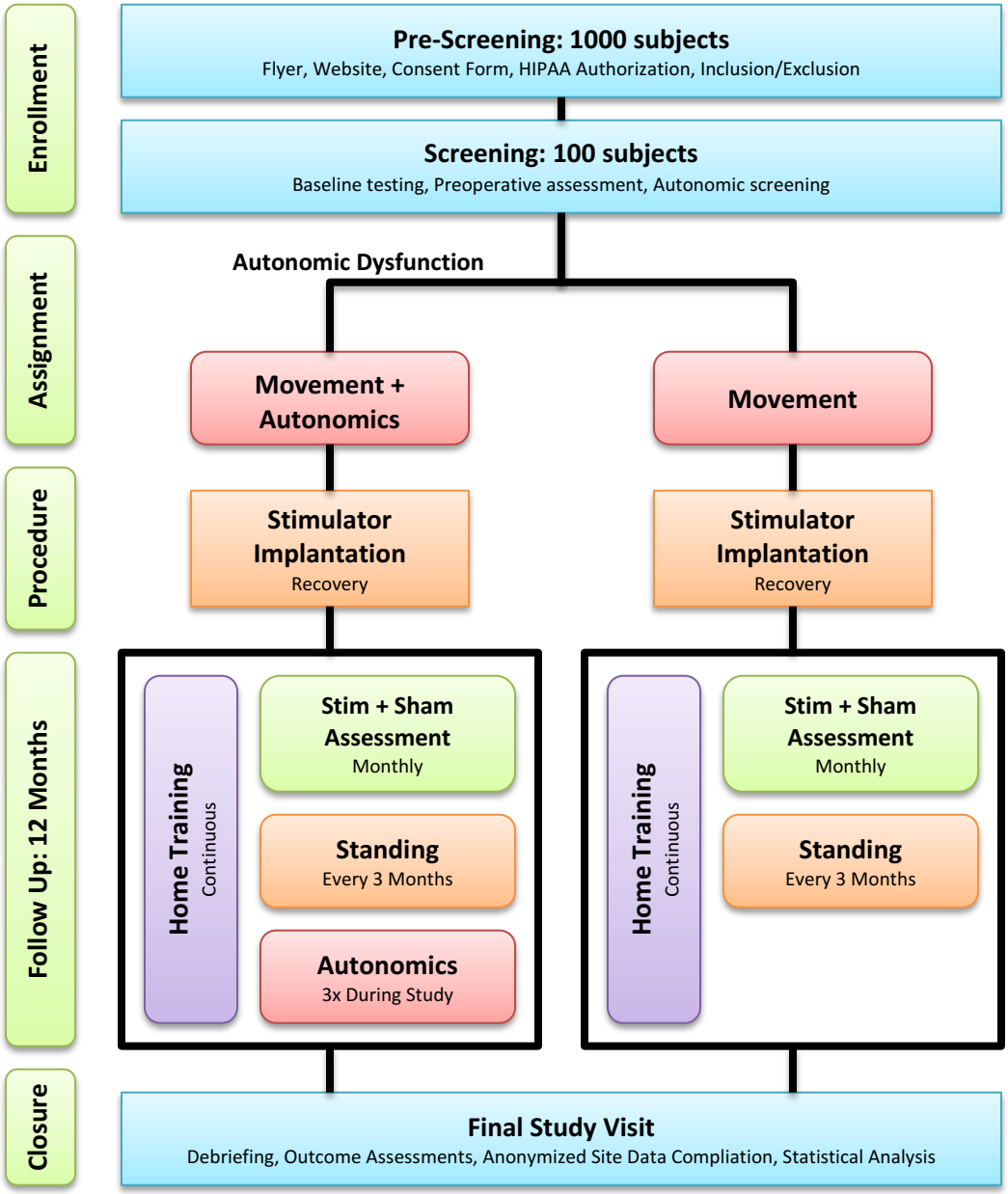
Short Title: ESTAND

Objectives: Primary

1. Investigate the use of epidural stimulation to facilitate volitional movement as measured by surface EMG through the Brain Motor

	Control Assessment (BMCA) Volitional Response Index Magnitude in patients with chronic spinal cord injury and motor paraplegia Secondary 1. Map the parameter space of epidural stimulation using accelerometers to create a Clinical Decision Support System (CDSS) for patient programming 2. Investigate the ability of SCS to enable standing 3. Assess the effect of spinal cord stimulation (SCS) on the cardiovascular system Exploratory 1. Explore the effect of SCS on urinary control 2. Explore psychiatric and quality of life (QOL) endpoints in patients with chronic spinal cord injury undergoing SCS
Endpoints	**Primary:** Lower extremity brain motor control assessment volitional response index magnitude **Secondary:** sEMG power generated during standing Classification of the parameter space Cardiovascular system endpoints: blood pressure, cardiac function, arterial stiffness Cerebral autoregulation and associated cognition **Exploratory:** Psychiatric metrics Quality of Life **Safety:** Physical Examination Blood Pressure Adverse Event Incidence Modified Ashworth Scale Score
Population:	Chronic motor-complete paraplegic patients
Phase:	2
Number of Sites enrolling participants:	3
Description of Study Agent :	St. Jude Medical Tripole™ 16 Lead epidural stimulator paddle, extension wire, and Proclaim™ Elite implantable pulse generator
Study Duration:	5 years
Participant Duration:	15 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The goal of this proposal is to establish and investigate epidural spinal cord stimulation in paraplegic patients to facilitate volitional movement. The facilitation of volitional movement through epidural spinal cord stimulation was nearly found by accident while investigating this form of neuromodulation to facilitate standing and ambulation through central pattern generation.[1] This finding represents a paradigm shift in the understanding and future treatment of spinal cord injury and demands timely investigation and optimization for a malady with currently no therapeutic intervention and significant morbidity.

Spinal cord injury is a devastating complication of trauma, often producing paraplegia or quadriplegia. In the United States, the incidence of acute spinal cord injury is relatively stable at 54 cases per million people, which was approximately 17000 cases in 2012.[2] stable incidence of spinal cord injury has resulted in a prevalence of approximately 273,000 patients suffering from spinal cord injury.[3]

Spinal cord injury carries significant chronic medical complications as well as socioeconomic ramifications. Patients with spinal cord injury of all types have significantly reduced life-expectancy with the majority deaths caused by pneumonia and septicemia.[3] The chronic complications of spinal cord injury are extensive and include all physiologic systems. In particular, patients suffer from cardiovascular complications, respiratory complications, urinary and gastrointestinal complications in addition to complex pain syndromes and morbid pressure ulcers.[4]

Caring for patients with spinal cord injury requires significant healthcare utilization.[5] During the first year of spinal cord injury, there is significant variation of cost based on type of spinal cord injury, ranging from $340,787 for incomplete motor function to $1,044,197 for high cervical injuries.[3] The estimated lifetime costs range from 1.1 to 4.6 million depending on the age of injury and location.[3] These costs do not include lost wages or productivity. Even after the first year of spinal cord injury, patients require frequent physician contact and harbor numerous medical complications such as urinary tract infections and decubitus ulcers.[5] Despite the significant cost and impact on society and numerous clinical trials, there have been no significant strides made in the treatment of spinal cord injury.[6]

Much of the comorbidity from spinal cord injury is secondary to immobility, and it has long been hoped that facilitating ambulation would stymie progressive comorbidity. Locomotion has long been known to be inherent within the spinal cord.[7] Central pattern generators of the spinal cord underlie spinal cord circuitry capable of facilitated locomotion.[8] These findings have fueled the search for a method of neuromodulation capable of

utilizing intrinsic spinal cord locomotion to facilitate ambulation. Gait training has been found to confer significant improvement in the ability of the spinal cord to facilitate walking in animal models, which has led to a modern understanding of the neuroplasticity within spinal cord circuitry.[7]

Humans with incomplete spinal cord injury have been found to benefit from similar gait training, but complete spinal cord injury remains refractory to these interventions.[1] Until recently, complete spinal cord injury was thought of as spinal cord tissue neurologically isolated the brain.[9] Hence, there have been significant efforts to develop novel methods to bridge these gaps in order to re-establish functional connectivity or prevent secondary damage.[10] Due to the nature of degeneration after spinal cord injury and the complexity of structural organization of the nervous system, bridging damaged segments of the spinal cord has been found to be a difficult problem with no current successful therapies, though many in the translational pipeline.[10]

Epidural stimulation has relatively recently been investigated as a possible therapeutic method of modulating spinal cord circuitry to facilitate locomotion.[1] While the focus of this approach towards improving outcomes in spinal cord injury has been to provide a platform through which to support central pattern generation and potentially provide a mechanism of sustained walking in complete spinal cord injury, during testing of subthreshold stimulation in a preliminary study of human patients, volitional movement was discovered.[9]

2.2 RATIONALE

The evidence is now mounting that for spinal cord injuries that do not involve complete transection, viable tracts may remain that are unable to overcome inherent spinal cord inhibitory networks. With targeted epidural stimulation, it is possible to facilitate volitional activation of motor units of these remaining circuits.[9]

This ground-breaking finding provides a glimmer of hope for the most common mechanism of spinal cord injury, which is a crush injury from spinal fracture after motor vehicle accident. While epidural stimulation has only been performed in a very small subset of spinal cord injury, the preliminary results are astonishing with the ability to stand in patients categorized as AIS A and AIS B, essentially complete spinal cord injury, years after their original injury.[9]

Epidural spinal cord injury has been used since 1967 in patients suffering from pain.[11] While multiple devices are available for implantation either as percutaneous electrodes or paddles, it is a safe and quick procedure that may have long-lasting effects on neuropathic pain and its psychological manifestations for a specific subset of patients.[11] As a neurosurgical procedure, it is routinely performed under MAC anesthesia, usually involving the patient during the procedure to provide tailored coverage of complex pain distributions. Epidural stimulation has been found to be a relatively safe procedure for patients with neuropathic pain.[12]

Considering the paucity of treatments available for patients suffering from spinal cord injury, our proposal aims to make steps towards creating a platform for implementation and rigorous investigation of spinal cord stimulation in Minnesota. Given the long history of safe use of spinal cord stimulation for neuropathic pain, our clinical expertise in treating patients with spinal cord injury, and experience in the implantation of spinal cord stimulators, we believe expanding on the existing population of humans implanted is essential in understanding how we can improve the lives of Minnesotans with spinal cord injury. Unfortunately, we routinely care for patients after poly-trauma who suffer spinal cord injury. On an almost weekly basis, we provide stabilization procedures for patients with complete spinal cord injury at cervical and thoracic levels. We are frequently reminded of the lack of treatments available for our patients suffering from spinal cord injury. Through a partnership between Hennepin County Medical Center and the University of Minnesota, linked through a long-standing relationship as the two

main training sites for Neurosurgery residents, our proposal draws on considerable experience with clinical, basic science, and translational research.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The primary risks of this intervention are related to the implantation of an epidural spinal cord stimulator. While in use for many decades for the treatment of chronic pain, it is being used in this study for chronic spinal cord injury.

Surgical risks for implantation of an epidural spinal cord stimulator include bleeding, infection, spinal cord damage (though presumed nonfunctional in this population, cerebrospinal fluid leak, need for further surgery, need for blood transfusion, and rarely death. Subjects will undergo anesthesia for implantation which also harbors risk including heart arrhythmia, pneumonia as well as rare risks such as heart attack, stroke, and death.

Device Associated Adverse Effects

Surgical risks for implantation of an epidural spinal cord stimulator include bleeding, infection, spinal cord damage (though presumed nonfunctional in this population, cerebrospinal fluid leak, need for further surgery, need for blood transfusion, and rarely death. Subjects will undergo anesthesia for implantation which also harbors risk including heart arrhythmia, pneumonia as well as rare risks such as heart attack, stroke, and death.

In addition to those risks commonly associated with surgery, the following risks are associated with implanting or using this neurostimulation system, in order of likelihood and impact:

Likely (more than 10 out of 100 people)

- Lead migration, causing changes in stimulation or reduced pain relief. Retrospective study incidence is 14%. Prospective studies report rates between 10-59%.[13–15]
- Lead breakage. Retrospective study incidence is 17%. The incidence for one prospective study is 4%.[15]

Less Likely (1 to 10 out of 100 people)

- Infection. Retrospective study incidence is 3%. Prospective study incidence is 3-4%.[14,15]
- Hardware malfunction. Retrospective study incidence is 3%. Prospective study incidence is 2-6%.[13,15]
- Over or understimulation: 2.6% incidence.
- Battery failure: 1.9% incidence.
- Persistent pain at the electrode or IPG site: 1.1% incidence. In one prospective study, 8% of subjects reported discomfort.[14]
- Loose connection: 1% incidence.

Rare (less than 1 out of 100 people) or low impact

- Unpleasant sensations or motor disturbances, including involuntary movement, caused by stimulation at high outputs
- Stimulation in unwanted places (such as radicular stimulation of the chest wall)
- Epidural hemorrhage, hematoma, spinal cord compression, or paralysis from placement of a lead in the epidural space
- Cerebrospinal fluid (CSF) leakage

- Paralysis, weakness, clumsiness, numbness, or pain below the level of the implant
- Seroma (mass or swelling) at the IPG site
- Allergic or rejection response to implant materials
- Implant migration or skin erosion around the implant

Potential Adverse Effects from Testing

- Skin abrasions
- Muscle damage from transfers
- Injury from Fall
- Hypotension
- Stroke

Participating in this trial is a significant commitment without guarantee of any benefit. Undergoing surgery, rehabilitation, and testing is a significant physical risk. Daily training and monthly appointments garner potential associated economic, social, and psychological risks including required travel for appointments and medical care, dissatisfaction with medical benefit, and prolonged postoperative recovery.

The risks associated with this study are warranted in humans because of the potential direct benefit of the study participants and the spinal cord injury community. There are no known alternative epidural spinal stimulation therapies to offer instead of surgical implantation.

Autonomic Testing

Many SCI subjects will likely sustain skin irritation from the recording electrodes. These conditions are considered to be minimal risks and are reversible.

There is some chance that subjects may sustain lowering or elevation of blood pressure, dizziness or skin abrasion from hand placements of the trainers. If these events occur, the experiment would cease immediately and the principal and co-principal investigators will be alerted if the condition persists. These conditions are considered to be minimal risks and are reversible.

It is highly unlikely that a subject would feel chest pain or high blood pressure would occur that did not resolve within several minutes. These events have not occurred in our past experience. However, if this did occur the individual would be immediately transported to the respective hospital's Emergency Unit and the principal and co-principal investigator will be notified. It is also highly unlikely that a subject would suffer a muscle strain, joint sprain or fracture from standing. These conditions are considered to be moderate risks but rarely occur. However if these events should occur, the subject would immediately stop standing training and would be evaluated the principal or co-principal investigators or the physician investigator administering the procedure. Standard medical procedures will be provided. The subject's primary physician would be notified as needed. These conditions are considered to be moderate risks and are reversible.

Orthostatic Stress Test: While undergoing this test, participants may experience dizziness, changes in blood pressure and heart rate or shortness of breath. Each participant will be closely monitored for any drastic changes in the recordings of their blood pressure, heart rate or breathing or show visible flushing of their cheeks or face.

There are no identifiable psychological, sociological, economical or legal risks to the participants.

2.3.2 KNOWN POTENTIAL BENEFITS

Preliminary studies have demonstrated regaining ability of volition movement in some muscle groups in these paralyzed patients. In addition, improvements in urinary function and cardiovascular stability has been observed in preliminary reports. A potential benefit of this study includes regaining volitional movement while stimulation is occurring. It is unknown whether autonomic benefits will occur from stimulation. There is no payment for participating during any aspect of the study.

3 OBJECTIVES AND PURPOSE

Epidural spinal cord stimulation for the purpose of facilitating volitional movement is a new and novel neuromodulatory treatment. Epidural SCS has a long history of use for chronic pain with established medical device platforms. The purpose of this study is to investigate and establish the use of SCS for volitional movement. Specifically, establishing the disinhibitory effect of SCS in a greater population with inherent greater variability.

In addition to establishing the disinhibitory effect of SCS for cSCI, our study attempts to explore the parameter space of the spinal cord stimulator platforms in order to optimize stimulation settings for patients through the creation of a clinical decision support system (CDSS). Preliminary evidence suggests benefit to autonomic function, and this study also begins to explore the effects of SCS on cardiovascular function, urinary function, psychiatric outcomes, and quality of life, which all offer significant potential for patients suffering from chronic spinal cord injury.

In summary:
Primary

1. Investigate the use of epidural stimulation to facilitate volitional movement as measured by surface EMG through the Brain Motor Control Assessment (BMCA) Volitional Response Index Magnitude in patients with chronic spinal cord injury and motor paraplegia

Secondary

1. Map the parameter space of epidural stimulation using accelerometers to create a Clinical Decision Support System (CDSS) for patient programming
2. Investigate the ability of SCS to enable standing
3. Assess the effect of spinal cord stimulation (SCS) on the cardiovascular system

Exploratory

1. Explore the effect of SCS on urinary control
2. Explore psychiatric and quality of life (QOL) endpoints in patients with chronic spinal cord injury undergoing SCS

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a quasi-experimental study of chronic spinal cord injury patients using same-subject preoperative and sham controls to determine primary and secondary outcomes. Testing of sham vs. stimulation phases during visits will be randomized and double blinded.

4.2.1 PRIMARY ENDPOINT

The primary endpoint is the BMCA VRI magnitude.

4.2.2 SECONDARY ENDPOINTS

Secondary endpoints include:

1. sEMG power generated during standing
2. Classification of the parameter space
3. Cardiovascular system endpoints: blood pressure, cardiac function, arterial stiffness
4. Cerebral autoregulation and associated cognition

4.2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints include:

1. Psychiatric metrics
2. Quality of Life

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 22 years of age or older
2. Able to undergo the informed consent/assent process
3. Stable, motor-complete paraplegia
4. Discrete spinal cord injury between C6 and T10
5. ASIA A or B Spinal Cord Injury Classification
6. Medically stable in the judgement of the principal investigator
7. Intact segmental reflexes below the lesion of injury
8. Greater than 1 year since initial injury and at least 6 months from any required spinal instrumentation
9. Willing to attend all scheduled appointments

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Diseases and conditions that would increase the morbidity and mortality of spinal cord injury surgery (e.g. cardiopulmonary issues)
2. Inability to withhold antiplatelet/anticoagulation agents perioperatively
3. Significant dysautonomia that would prohibit rehabilitation or assisted standing or any history of CVA or MI associated with autonomic dysreflexia.. A single tilt table test with syncope, presyncope, or SBP < 50 or >200.
4. Other conditions that would make the subject unable to participate in testing/rehabilitation in the judgement of the principal investigator
5. Current and anticipated need for opioid pain medications or pain that would prevent full participation in the rehabilitation program in the judgement of the principal investigator
6. Clinically significant mental illness in the judgement of the principal investigator
7. Botulinum toxin injections in the previous 6 months
8. Volitional movements present during EMG testing in bilateral lower extremities
9. Unhealed spinal fracture
10. Presence of significant contracture

11. Presence of pressure ulcers
12. Recurrent urinary tract infection refractory to antibiotics
13. Current Pregnancy

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited via flyer made available at each site through the neurosurgery and PM&R clinics. We anticipate limited enrollment during the first year to establish and test trial infrastructure. Expansion through the additional sites and capacity should double each year until target enrollment. After securing the initial funding source, our clinic receives weekly inquiries about the status of the proposed trial, highlighting the existing potential recruitment network. We anticipate flyers to be widely disseminated throughout this network.

Patients with chronic SCI are highly motivated and very involved in their care. Subjects will be in continuous contact with the study as they complete their home rehabilitation regimen and will be seen on a monthly basis for testing.

Subjects will receive appointment reminders the week prior to their appointments and regular phone calls if their home rehabilitation progress becomes delayed by more than one week.

Subject recruitment will be divided into two phases. In phase 1, 10 subjects will be recruited per protocol. After the recruitment of the 10^{th} subject, recruitment will be temporarily halted. After the 6 month timepoint data collection for these 10 subjects, the safety endpoints and adverse event reports will be submitted to the FDA in a summary format. Recruitment will not continue until FDA review and approval, though additional subjects may be screened and potentially scheduled.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Subjects may withdrawal from the study at any time. Subjects that choose to withdraw early from the study will be voluntarily surveyed for reasons for withdrawal. They will be asked for permission to continue to utilize the data collected up to the point of withdrawal for research purposes. Should they decline, all data past the note of withdrawal will be deleted from the record system. Subjectss will not automatically have their stimulation device removed. Spinal cord stimulator devices will be removed electively, if the device malfunctions, or if the device poses a significant risk to the subject's health.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 STUDY PRODUCT DESCRIPTION

6.1.1 ACQUISITION

The spinal cord stimulator system (epidural stimulator, extension lead, and Tripole paddle) will be obtained directly from St. Jude Medical. The devices and accessories will be shipped from their production facilities to Hennepin County Medical Center and the Minneapolis VA Health Care System and will be disbursed to the principal investigator according to a Material Transfer Agreement to be arranged between Hennepin County Medical Center, the Minneapolis VA Health Care System, and St. Jude Medical.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The products are the St. Jude Medical Proclaim™ Elite Implantable Pulse Generator and Tripole™ 16 Lead paddle leads. The Implantable Pulse Generator and lead accessories will be enclosed in separately packaged kits including accessories necessary for surgical implantation. The kits will use the commercial box appearance, which includes the name of the product, the model number, a description of the product, safety, use, and storage information, and manufacturer contact information. A label will be affixed on each product box with large text stating that the products are for a clinical study and the name of this clinical study. In addition to the device kits, the standard product manual package insert will be included, which details prescription and safety information, a description of the product, directions for use, technical support, product specifications, regulatory statements, a component list, and packaging symbol and definition legends. On this insert, an affixed label will instruct users to consult an additional study specific package insert that will also be included for use modifications. This package insert will contain the name and description of this clinical study, new directions for use detailing the study indications and study procedure, and contact information for the study investigators.

This product is commercially marketed and FDA approved for use in chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome and intractable low back and leg pain. The products will be used without pre-implantation modification, but the method of implantation will be modified as described in 6.1.4.

6.1.3 PRODUCT STORAGE AND STABILITY

No seal will be broken until the operating surgeon is ready to implant the devices in the surgical field. Expiration dates will be verified before any seal is broken. Products will be housed in a locked cabinet according to the instruction manual specifications for temperature, humidity, and pressure. The cabinet will be accessible to only the principal and co investigators until use if delivered before the planned surgery.

Products will be housed in the Hennepin Central Core storage facility managed by Don Langness. Products will be housed in the Minneapolis VA Central Core, 2M-2Q, managed by Kim Buress, the head of OR. Products will be housed in the University of Minnesota Medical Center Central Supply, managed by Ernie Nickels.

6.1.4 ADMINISTRATION OF STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Surgical implantation of the product will be similar to implantation for patients with chronic pain, which is a routine neurosurgical operation. A single level laminectomy will be performed to allow placement of the paddle electrode under fluoroscopic guidance at the T11-T12 area to cover spinal cord segments L1-S1. Intraoperative neuromonitoring with EMG will be performed to verify the coverage and placement of the epidural stimulator paddles with suprathreshold stimulation. A subcutaneous pocket will be created where the neurostimulator will be placed. The paddle electrode wire will be tunneled in the subcutaneous space to the pocket and connected to the neurostimulator. Surgery will be performed in the standard fashion, under sterile conditions.

6.1.5 MODIFICATION OF STUDY INTERVENTION/INVESTIGATIONAL PRODUCT FOR A PARTICIPANT

The device will not be modified for any subject at any time.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

The St. Jude Medical Proclaim™ Elite 7 Implantable Pulse Generator (Model 3662ANS) is 66.8mm x 50.2mm x 13.5mm. The St. Jude Medical Tripole™ Paddle Leads (Model 3219) are 57.0mm x 10.0mm x 1.6mm with a 60cm lead wire. The pulse width, frequency, and amplitude programming settings of the implantable pulse generator will be within the established parameters in the commercial product manual, and the settings for each study member will vary according to the experimental protocol (as optimization of stimulator settings is one of the main study aims). The duration of implantation will be for 6.5 years (the longevity of the device battery) or until device malfunction or complications / medical issues requiring explantation of the device. Exposure to stimulation is detailed in the study procedures, but is summarized as an average of 2 hours of intermittent stimulation per monthly session and up to four hours per day, 5 days a week for home training sessions over the course of 15 months.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Devices will be distributed to the Hennepin County Medical Center, University of Minnesota, and the Minneapolis VA Health Care System according to a Materials Transfer Agreement between these sites, which will specify device ownership, storage, and use. The products will be shipped two at a time prior to the surgical implantation procedure for each pair of subjects after recruitment once the subjects have been fully screened.

The products will be received by hospital personnel trained in the safe handling of this equipment and informed of proper interim storage requirements, and the senior study investigators will receive these devices from interim

storage to place in the locked appropriate operating room storage area. Documentation of the proper receipt and transfer of all study products will be maintained by the hospitals and study personnel according to the standards of the Materials Transfer Agreement and hospital policy. Should study products be unused and not defective or expired, they will be assigned to the next applicable study subject should the product not expire before the anticipated next surgery date. Otherwise, the product will be disposed of or returned to St. Jude Medical. Defective, damaged, or expired products will be reported to St. Jude Medical and disposed of or otherwise processed according to hospital and manufacturer policy.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

The following is a list of procedures to be performed at various time points throughout the study according to the schedule in Table 1.Please see that table for information about timing. Most assessments are in concordance with the NIH NINDS SCI CDE recommendations in addition to the NIH NIBIB Working group on epidural stimulation trials.

Table 1

Categories	Data Element Name
Demographics	General Core
	Demographics
General Health History	Medical History
	Prior and Concomitant Medications
	Family History
Epidemiology/Environmental History	Alcohol and Tobacco Use
	Alcohol Use Disorders Identification Test (AUDIT)
	Substance Use
History of Disease/Injury Event	History of Injury
	Rehabilitation Therapies
Physical Examinations	Clinical Assessment
	Physical Exam
	Braden Scale for Predicting Pressure Sore Risk
Vital Signs and Other Body Measures	Vital Signs Tests
	Laboratory Tests
Spinal Imaging / Spinal Cord Imaging	Imaging SCI
	Magnetic Resonance Imaging
Treatment / Intervention Data	Assistive/Mobility Devices & Orthosis
	Rehabilitation Therapies
	Surgical and Procedural Interventions
	Other Investigational Treatments
	Home Training Remote Accelerometer Assessment
Neurological Outcomes	International Standards for Neurological Classification of SCI Worksheet

	Modified Ashworth Scale
	NINDS Myotatic Reflex Scale
Electrodiagnostics	Brain Motor Control Assessment
	Device electrode mapping
	Standing Training Assessment
Functional Outcomes	Capabilities of Upper Extremity Questionnaire
	Spinal Cord Independence Measure
	Wheelchair Skills Test
	Falls Diary
	Neurogenic Bladder Symptom Score
	Neurogenic Bowel Dysfunction Score
Autonomic Assessments	Sympathetic skin responses (SSR)
	Tilt Table Testing
	Home Blood Pressure Monitoring
	Orthostatics
	Cardiac Structure and Function Assessments
	Cerebrovascular Assessment
	Arterial Stiffness
	Arterial structure: Wall thickness and lumen diameter
Cognitive	Visual Neurocognitive Assessment
Pain	International SCI Pain Basic Data Subset
Psychological	Patient Health Questionnaire - 9 (PHQ-9) Depression Scale
Quality of Life	Spinal Cord Injury - Quality of Life (SCI-QOL)
	World Health Organization Quality of Life Assessment (WHOQOL-BREF)
Sleep	Epworth Sleepiness Scale (ESS)

STANDARD PROCEDURES

Standardized CRFs will be administered in content groups according to the above organization. What follows is a description of the procedures of each content group. Content groups with simple administration guidelines will be administered according to the practices outlined in current CDEs that will be used and will not be further explained here.

Participant History and Family History

Medical History will be obtained preliminarily from patient medical records, with incomplete entries to be filled during the second subject encounter. The timeframe for eligible history elements will be complete as possible with no limit on the age of diagnosis onset. Medication history will include current medications only, with the exception of botulinum toxin according to the exclusion criteria. A questionnaire about alcohol use including the AUDIT will be administered via interview. The subject will be appropriately informed of the results of the alcohol and drug screening tests and referred to counseling if indicated.

Disease/Injury Related Events

A history of injury will be obtained from the subject's medical records and from the subject, with medical records taking priority when descriptions of the event diverge. Rehabilitation therapy history will apply to all events occurring after the initial injury.

Assessments and Examinations

A full physical examination will be performed. An SCI-focused clinical assessment will be completed from the patient medical records, subject interviews, interviews of trusted collateral individuals with subject verbal consent, and from the full physical examination. The Braden Scale will be used in a clinical determination of the subject's ability to participate in all elements of the study.

Complete vital signs will be obtained during enrollment. These measures include: height, weight, pulse, blood pressure, and temperatureHeight, weight, pulse, blood pressure, and temperature will be taken at the beginning and the end of every 3rd month visit (3, 6, 9, 12, 15) to screen for autonomic dysreflexia. Laboratory tests will include only a lipid profile.

The scan date, time, and type of imaging study of one high quality spinal imaging study at the time of spinal cord injury and all subsequent spinal imaging studies will be obtained according to the Imaging SCI Case Report Form. This information and the content of the imaging study as analyzed by appropriately trained members of the investigation team and/or the impression by the reading radiologist will be obtained for one high quality spinal MRI at the time of spinal cord injury and the most recent study after the event. If there is no high quality MRI after the time of spinal cord injury, the subject will be scheduled for a spinal MRI study during enrollment.

All procedures listed in this section will be explained in detail in the MOP, and will be performed according to standard clinical procedure in the institution. The subject will be informed of the results of these clinical tests, and their primary care provider will be informed. The results of these tests will be entered into the subject's chart.

SCI Classification

The international standards for neurological classification of SCI will be obtained in full during a complete physical exam. A spasticity assessment will be obtained during physical exam for all major limb movements. After the surgical intervention, spasticity assessments will be used at the beginning and end of every 3rd month visit (3, 6, 9, 12, 15) to screen for uncontrolled spasticity in the lower limbs. Peripheral reflexes will also be measured during every 3rd monthly visit.

Functional Outcome

The Capabilities of Upper Extremity Questionnaire and Spinal Cord Independence Measure will be administered during a screening/enrollment clinical visit using subject responses. The Wheelchair Skills test will be administered by a clinician investigator during a screening/enrollment clinical visit.

Autonomic Assessments are all study specific and will be explained in the modified procedures section.

The International SCI Pain Basic Data Subset will be administered during a subject interview.

The Patient Health Questionnaire Depression Scale and Hospital Anxiety and Depression Scale will be administered during a subject visit. Positive psychiatric screening will result in a referral to the appropriate services. Positive suicidal / homicidal ideation or intention to harm self or others will result in a referral to the appropriate services and immediate prompting of the proper authorities.

The Epworth Sleepiness Scale will be administered during a subject interview.

Falls Diary

The falls diary will be a subject-maintained log of fall events. The information will include the time and date of the fall, the activity prior to the fall, the estimated height of the fall, the presence of head or bodily injury after the fall, and subject recorded medical information such as the need for hospitalization and diagnoses related to the falls.

Urinary Function

Urinary function will be assessed through the Neurogenic Bladder Symptom Score (NBSS) survey.

Bowel Function

Bowel function will be assessed through the Neurogenic Bowel Dysfunction Score survey.

MODIFIED PROCEDURES

Modified procedures are listed in detail below. All procedures are explained in working detail in the MOP.

Treatment/Intervention Data

Home Training

Home training allows use of the epidural stimulator while completing a computer-guided accelerometer-based task. Subjects will fasten two wireless accelerometers to their feet to detect plantarflexion and dorsiflexion as well as gross translational movement in the legs.

Our group has a developed an android app that cues the subject to move the left or right foot in a randomized fashion. As the subject moves their legs, the accelerometry data will be collected wirelessly and stored. This data will include the subject number, date and time logs, stimulator setting number, and accelerometry data. The stored data will be automatically uploaded to a HIPAA-compliant and secure server. Post-processing will allow calculation of maximum velocity and fidelity of volition.

After the first visit, subjects will be given detailed instructions on their home stimulation program, which allows up to four hours per day of epidural stimulation. At each follow-up visit, the subjects' SCS programmers will be customized with 5 subject settings. Only experimental stimulator configurations (no sham settings) will be used. Subjects will receive a paper calendar with assigned subject settings for one hour of training 5 times per week. Subjects are expected to turn the stimulator on for training, but can otherwise use the stimulator up to 4 hours per day as needed. Subjects will be instructed to undergo a formal regimen of exercises and will be supplied with a tablet computer capable of cuing subjects with audio and video through the exercises and tracking wireless accelerometer data during the session. Fidelity of the volition cuing will be calculated as a percentage of the training session when the entire training session is completed. Maximum velocities will be aggregated over the training session and parameterized for comparison with repeated measures ANOVA. Stimulator use time will be logged and factored into data analysis.

Electrodiagnostics

Brain Motor Control Assessment. 60 minutes.

The subject's quadriceps, adductors, hamstrings, tibialis anterior, and triceps surae muscles of each leg, as well as the midline over the abdominal muscles at the level of the umbilicus and the lumbar paraspinal muscles will be recorded with multichannel surface EMG. Upper leg and ankle accelerometers will also be monitored to test for presence of movement. Subjects will undergo relaxation, voluntary and passive hip and knee flexion, and voluntary and passive ankle dorsiflexion and plantarflexion during trials of computer controlled patterns and levels of epidural stimulation (or sham). Stimulation and sham programs, defined as stimulator settings that either involve an experimental stimulation configuration or no stimulation through any lead, will be randomly assigned in a group of repeated trials during the session. The BMCA Lower-Limb Protocol elements of Relaxation, Voluntary movements, and Passive stretch will be used to gather quantitative EMG data. Accelerometer data will be quantified by presence and rate of acceleration.

Device electrode custom mapping assessment

To be performed on the first visit after the surgery (month 3). Epidural spinal cord stimulator mapping is similar in concept to a nerve conduction study, with the stimulus coming from one of the epidural stimulator leads as opposed to the same nerve. The purpose of mapping is to define which stimulator leads are associated with the voluntary function of the muscles of interest in the legs, so leads that do not appear to result in any motor activation are excluded from programming trials. The procedure will be performed in the same manner as the Brain Motor Control Assessment, but the computer will stimulate one electrode at a time for each series of volitional tests until all electrodes have been independently stimulated. Electrodes that do not generate a volitional EMG signal will not be included in the set of computer controlled stimulator patterns for the Brain Motor Control Assessment. Accelerometers will not be used.

Standing Training Assessment

The subject will be placed in a standing assist harness in a seated position. The subject's quadriceps, adductors, hamstrings, tibialis anterior, and triceps surae muscles of each leg, as well as the midline over the abdominal muscles at the level of the umbilicus and the lumbar paraspinal muscles will be recorded with multichannel surface EMG. The subject will be given a randomized experimental or sham stimulator setting. During recording, the subject will be assisted from sitting to standing, with parallel bars and research investigators as upper body support. The subject will then shift their weight between the left and right side of their body on cue while their feet are placed on a scale that measures weight distribution. The subject will be assisted back into a seated position. This will be repeated until the set of experimental and sham stimulator settings is complete. Data collected will be EMG signal activation while transitioning to stand, EMG activity while shifting weight, and the changes in weight on the left and right side of the scale during volitional weight shifting.

Autonomic Screening

Screening Tilt Table Testing

The subject will be asked to lay in the supine position on a tilt table. A blood pressure monitor will be applied to the patient. The subject's blood pressure will be taken and considered as the baseline. The subject will then be passively moved to a standing position, while having a blood pressure reading taken every minute for ten minutes. A Systolic Blood Pressure decrease of 20mmHg from baseline is considered positive. A physician investigator will observe the patient during the procedure and ask for symptoms of syncope or presyncope during and after the test. Any signs or symptoms of syncope or presyncope will be considered positive.

Home Blood Pressure Monitoring

The subject will be asked to wear a blood pressure monitor at home for twenty four hours. The subject's Systolic Blood Pressure that was recorded as a baseline for Tilt-Table Testing will be utilized as the baseline for this assessment as well. During the twenty four hour period, a Systolic Blood pressure increase of 20mmHg will be considered positive. A physician investigator will debrief the patient following this period and ask for symptoms of syncope or presyncope during and after the period. Any signs or symptoms of syncope or presyncope will be considered positive.

Autonomic Assessments

Tilt Table Testing

This assessment will be performed during screening. The subject will be asked to lay in the supine position on a tilt table. A blood pressure monitor will be applied to the patient. The subject will then be passively moved to a standing position. Systolic Blood Pressure levels below 50 or above 200 are considered positive. A physician investigator will observe the patient during the procedure and ask for symptoms of syncope or presyncope during and after the test. Any signs or symptoms of syncope or presyncope will be considered positive.

Sympathetic skin responses (SSR)

We will utilize a well-established protocol to record SSR. The SSR will be elicited by stimulation of median and tibial nerves, and recorded bilaterally and simultaneously from both hands and feet to assess the extent of disruption to spinal autonomic pathways. Ten electrical stimuli (duration 0.2ms; intensity 8-10mA) will be applied to the left median nerve and left posterior tibial nerve, in random order and with variable and long-time delays to minimize habituation.

Orthostatic Sit-Up Test. 25 minutes.

On arrival to the laboratory, subjects will be asked to empty their bladder to minimize the influence of reflex sympathetic activation on peripheral vascular tone. In the supine position, subjects will be instrumented with a single-lead ECG (lead II; Powerlab model ML132, ADInstruments). Beat-to-beat systolic (SBP), diastolic (DBP), and mean (MAP) blood pressures will be recorded continuously from the right hand (Finometer; Finapres Medical Systems BV, Arnhem, Netherlands), while discrete blood pressures will be taken every minute from the left arm (Carescape V100; GE Healthcare, Milwaukee, WI, USA). Following instrumentation, baseline recordings will be made during a 10 minute supine rest period. Data acquisition will be performed as detailed above. Subjects will then be passively moved to an upright seated or stand position by the investigators using the cardiac chair or the tilt table. This position will be maintained for 15 minutes, during which recordings of heart rate and blood pressure will be continued.

Cardiac Structure and Function Duration. 20 minutes.

Cardiac assessments will be performed using ultrasound while the subject is in the supine, sitting and standing position. Heart rate will be recorded during the assessment using a single-lead ECG. An ultrasound probe covered in gel will be placed on the subject's chest (Vivid 7; GE Healthcare, Horten, Norway). Cardiac images for 5 cardiac cycles will be collected in the parasternal long and short axes, and apical views. Images will be analyzed offline to determine indices of structure, systolic and diastolic function, and strain. A detailed description of the outcome measures is described in Table 1. These metrics will be recorded at supine baseline, in the seated position and standing with assistance during the aforementioned orthostatic sit-up test.

Cardiac Structure and Function in SCI subjects with Epidural Stimulation Implant

Individuals with epidural stimulation implant would have the above mentioned cardiac structure and function assessment in the following positions:

1) Supine no stimulation

2) Supine Stimulation

3) Sit-up no stimulation

4) Sit-up Stimulation

The stimulation parameters used would be at low voltages not to induce leg muscle contraction and at a frequency that would maintain and/or regulate the blood pressure to within normal ranges.

Neurocognitive Assessment. 15 minutes.

This test can be conducted at the same time as cardiac structure and function.

A visual task will be employed to activate the occipital lobe (while measuring posterior cerebral artery blood flow velocity (PCAv)), and a verbal fluency task to preferentially activate the left cerebral cortex (while measuring middle cerebral artery blood flow velocity (MCAv)), the order of which was randomized. Three minutes of baseline data, as well as a mock practice will be recorded to ensure hemodynamic homeostasis. After this, 10 cycles will occur, each consisting of 30 seconds eyes closed followed by 30 seconds reading. An auditory stimulus will provide notification of 'reading' and 'eyes-closed' periods. The velocity response will be averaged for all 10 trials for each participant. The verbal fluency task has the combined benefit of having been shown to preferentially activate the left MCA, and be a valid and ubiquitous marker of cognition. A PowerPoint (Microsoft, Redmond, WA, USA) slide show will be used, consisting of a series of 10 slides presenting a single letter for 30 seconds followed by the words 'Eyes Closed' for 30 seconds. The ten letters will be M, H, O, I, W, B, T, F, A, S. The letters will be separated into two stages (i.e., self-reported word totals versus verified word totals) separated by two minutes, the order of which will be randomized.

Cerebrovascular Assessment. 20 minutes.

This test can be conducted at the same time as cardiac structure and function.

For each participant, brachial BP will be measured (BpTRU-BPM-100, Coquitlam; VSM Medical, Vancouver, BC, Canada) on the right brachial artery. The following will be sampled at 1,000 Hz using an analog-to-digital converter (Powerlab/16SP ML 795; ADInstruments, CO Springs, CO, USA) interfaced with data acquisition software on a laptop computer (LabChart 7 ADInstruments): non-invasive beat-by-beat BP measurement via finger photoplethysmography (Finometer PRO, Finapres Medicine Systems, Amsterdam, The Netherlands), electrocardiogram (ML 132; ADInstruments), PETCO2 (CO2 Analyzer Gold Edition-17515, Ventura, CA, USA), velocity in the left middle cerebral artery (MCAv) or right posterior cerebral artery (PCAv; Doppler-Box, Compumedics DWL, Singen, Germany). These arteries will be insonated using a 2 MHz probe mounted on the temporal bone and a fitted head strap. As described in depth elsewhere, the P1 segment of the PCA will be insonated at depths between 60 to 70 mm, whereas the MCA was insonated from 45 to 55 mm. Arteries will be confirmed using ipsilateral common carotid artery compression, ensuring an increase in PCA velocity and decrease in MCA velocity. These metrics will be recorded throughout the aforementioned orthostatic sit-up test and following neurocognitive assessment.

Arterial Stiffness. 15 minutes.

aPWV (m/s) is calculated by dividing the distance between measurement sites, by the pulse transit time. Distance between the carotid and femoral arteries will be measured using measuring tape along the surface of the body, held parallel to the testing table. The pulse transit is determined from the arterial blood pressure waves, which are collected at each arterial site. A pen-like device (model SPT-301; Millar Instruments Inc., Houston, TX) will be applied to the carotid and femoral arterial sites using a light pressure to obtain arterial pressure waves. Heart rate will be recorded using a single-lead (lead I) electrocardiogram (ECG) (model ML 123, ADInstruments Inc., Colorado Springs, CO).

Arterial structure: Wall thickness and lumen diameter. 30 minutes.

Brachial and femoral arterial images will be collected using B-mode ultrasound (INFO) for 10 cardiac cycles. Images will be analyzed using internal ultrasound software to determine lumen diameter and intima-media thickness.

Test	Dependent variable	Evaluation of data	Comments
1. Resting hemodynamics and Orthostatic sit-up test	Resting supine arterial blood pressure (BP) and heart rate (HR), BP and HR response to a 10 min sit-up test	The presence of orthostatic hypotension (OH) will be considered when there is a decrease in either systolic BP of 20 mmHg or diastolic BP of 10 mmHg when upright (seated) – based on the definition for OH by the Consensus Committee of the American Autonomic Society and the American Academy Neurology.	The presence of orthostatic hypotension would suggest severely disrupted autonomic control in the evaluated individual.
2. Cardiac structure and function	**STRUCTURE** LV systolic/ diastolic diameters, LV systolic/ diastolic volumes, LV mass, Septal and posterior wall thickness **SYSTOLIC FUNCTION** Ejection fraction, Stroke volume, Cardiac output, Systolic myocardial tissue velocity from the septal wall (S') **DIASTOLIC FUNCTION** Early (E) and late (A) transmitral filling velocity; E/A ratio, Deceleration time (Dt), Isovolumetric relaxation time (IVRT), Early (E') and late (A') myocardial filling velocity from the septal wall, E/E' **2D Strain**	Indices of cardiac structure and function will be determined from offline analysis of ultrasound images using standard analysis packages available on the ultrasound.	Cardiac dysfunctions, identified using echocardiographic (ultrasound) assessments are associated with an increased risk of CVD.
3. Neurocognitive Assessment	**EXCECUTIVE FUNCTION**	Concurrent cerebral blood velocity evaluation	
4. Cerebrovascular Assessment	**CEREBRAL AUTOREGULATION**		

Test	Dependent variable	Evaluation of data	Comments
	Transcranial Doppler evaluation of middle and posterior cerebral artery blood flow concurrent with changes in beat-by **NEUROVASCULAR COUPLING** Transcranial Doppler evaluation during cognitive assessments		
5. SSRs	Number of present sympathetic skin responses, Latency		

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Subjects will undergo outpatient therapy at the same regular interval that was established before participation in the trial. Subjects will be prepared for surgery in the usual manner. Preoperative assessments from their primary care provider will be performed with the necessary preoperative assessments. Postoperative care will also be in the same fashion with routine postoperative pain management if necessary. Postoperative follow-up will also be standard at two weeks for a wound check and suture removal, if necessary.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

In addition to laboratory evaluations required by the study for preoperative anesthesia assessment, the subject will also undergo a baseline lipid profile.

7.2.2 OTHER ASSAYS OR PROCEDURES

Not Applicable

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Complete or verify completion of HIPAA form for release of PHI

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Review imaging to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Tilt table test to assess for risk of dysautonomia / allocation to autonomic dysfunction group
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Obtain urine pregnancy test.
- Obtain baseline information per the assessment schedule, Table 2
- 24 hour blood pressure monitoring to test for allocation to autonomic dysfunction group
- Record vital signs, results of examinations, and other assessments per the assessment schedule, Table 2
- Complete informed consent process
- Schedule preoperative assessment
- Schedule preanesthesia clinic assessment
- Schedule surgery date

7.3.3 FOLLOW-UP

Surgical Postoperative Visit (10-14 days after surgery)

- Physical examination and inspection of the wounds
- Pain control

Long Follow-up Visits (Month 3, 6, 9, 12, 15 +/- 14 days)

- Record adverse events as reported by participant or observed by investigator.
- Record updates in medications
- Wound check
- Focused Physical Examination for spasticity according the Modified Ashworth Scale
- Vital Signs and tests: blood pressure, temperature, pulse
- Home Training Assessment
- Modified Brain Motor Control Assessment
- Device Electrode Mapping Assessment (Month 3 only)
- Standing Training Assessment
- Other assessments per the assessment schedule, Table 2, aside from Autonomics Assessments
- Record participant's adherence to treatment program.

Short Follow-up Visits (Month , +/- 14 days of monthly visit)

- Record adverse events as reported by participant or observed by investigator.
- Record updates in medications

- Vital Signs and tests: blood pressure, temperature, pulse
- Standing Training Assessment
- Home Training Assessment
- Other assessments per the assessment schedule, Table 2
- Record participant's adherence to treatment program.

7.3.4 AUTONOMICS FOLLOW-UP VISIT

Months 3, 6, and 9 +/- 2 months. Only for subjects in the autonomic dysfunction group.

- Record adverse events as reported by participant or observed by investigator.
- Record updates in medications
- Wound check
- Focused Physical Examination for spasticity according the Modified Ashworth Scale
- Vital Signs and tests: blood pressure, temperature, pulse
- Autonomic Assessments as listed under Modified Procedures

7.3.5 FINAL STUDY VISIT

The final study visit will occur on month 15 of overall involvement in the study. The procedures performed during this visit are as described in Section 7.3.7, Schedule of Events. A 14 day scheduling leeway period is allowed for this visit. In addition to the listed procedures to be performed, adverse events will be recorded as reported by the participant or as observed.

7.3.6 EARLY TERMINATION VISIT

Should the subject be terminated from the study for any reason, their final visit will consist of basic safety screening: a complete physical exam, the Vital Signs and Tests assessment and the Modified Ashworth Scale Assessment if the participant is willing. If the subject's device remains intact, it will be interrogated to check impedances.

7.3.7 UNSCHEDULED VISIT

In the event of an unscheduled patient visit, the subject will undergo safety screening – a focused physical exam, the Modified Ashworth Scale test, and the blood pressure, temperature, and pulse elements of the Vital Signs and Tests assessment. Depending on the reason for the visit, the subject may be referred to the appropriate service for possible adverse event follow up. All adverse events reported by the subject or observed by the investigator will be documented and reported. Aside from adverse events, information gathered at these unscheduled visits will not be included in the statistical analysis.

7.3.8 SCHEDULE OF EVENTS TABLE

Table 2

Procedures	Screening	Enrollment	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 13	Month 14	Month 15
Spinal Cord Stimulator Implantation		X													
Demographics	X														
General Health History	X														
Epidemiology/Environmental History	X														
History of Disease/Injury Event	X														
Physical Examinations	X	X	X			X			X			X			X
Vital Signs and Other Body Measures															
Vital Signs and Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests	X														
Spinal Imaging / Spinal Cord Imaging	X														
Treatment / Intervention Data															
Assistive/Mobility Devices & Orthosis	X														
Falls Diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NBSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NBDS	X					X									X
Rehabilitation Therapies	X														
Surgical and Procedural Interventions	X														
Other Investigational Treatments	X														
Home Training			X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Outcomes															
Classification of SCI	X														
Modified Ashworth Scale	X		X			X			X			X			X
NINDS Myotatic Reflex Scale	X														
Electrodiagnostics															
Brain Motor Control Assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Device electrode mapping		X	X			X			X			X			X
Standing Training Assessment			X			X			X			X			X
Functional Outcomes	X														
Autonomics															
Autonomic Screening	X														
Autonomic Assessments			a			a			a						
Sympathetic Skin Responses			a						a						
Cognitive			a			a			a						
Pain	X		X			X			X			X			X
Psychological	X		X			X			X			X			X
Quality of Life	X		X			X			X			X			X
Sleep	X		X			X			X			X			X

Items are grouped according to the major categories of 7.1.1 in blue. Categories containing elements administered at different times in the study are expanded and grayed out. 'X' represents mandatory assessments for all subjects. 'a' represents assessments for subjects selected to undergo autonomics protocol.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not Applicable.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription

medications, over-the-counter medications and non-prescription medications. In particular medications that affect the use of muscles and firing of nerves are particular important including (but not limited to): botulinum toxin injections, muscle relaxants, and antiepileptics.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

In the postoperative phase there is concern for excessive bleeding with blood thinners, anti-platelet agents such as aspirin, or NSAIDs such as ibuprofen. Abstaining from these medications for 30 days after surgery will be discussed with each subject during the preoperative phase.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Treatment with botulinum toxin will not be permitted unless discussed with and approved by the study PI or coinvestigator.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

No prophylactic medications will be administered for this study except local anesthetic and antibiotics during surgery.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

There are no known drugs or interventions to be used for rescue.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

The subject will continue to have the epidural stimulator after the completion of the study unless it was removed for safety. The projected duration of battery life for the stimulators is 5 to 10 years on average. Future battery replacements will remain up to the subject.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety is not a primary or secondary endpoint of this study but safety is a top concern of the investigators. There is significant experience with epidural spinal cord stimulation amongst the primary and co-investigators for chronic pain and there is significant experience with patients with chronic spinal cord injury. Surgical risk, while low, represents the largest aspect of safety concern for this study. Safety during follow-up testing is also a significant concern as it relates to dysautonomia and falls.

While adverse events will be queried at each appointment and serious adverse events will be monitored and reported, there are specific risk parameters that will be monitored conscientiously during the following time periods:

Perioperative

- Hypotension and hemodynamic instability

- Infection
- Bleeding
- Pain
- Cerebrospinal fluid leak

Follow-up Visits

- Hypotension
- Surgical site infection and seroma

These events will be anticipated and, if found, will be recorded in the adverse event database for review. The Adverse Event Incidence Endpoint will reflect the increased vigilance for these safety outcomes.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of the investigators, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include significant postoperative epidural hematoma requiring reoperation.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

8.2.3 EXPECTEDNESS

The principal and co-principal investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All adverse events will be collected and report to the IRB and sponsor regularly and within 30 days.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the IRB and FDA. The principal investigator will be notified of the SAE by the FDA. The principal investigators monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the IRB and FDA.

8.4.3 UNANTICIPATED PROBLEM REPORTING

All possible unanticipated problems will be reported to the IRB within five (5) days of receiving notice of the event if the event requires immediate intervention to prevent serious harm to participants or others. All other possible unanticipated problems will be reported to the IRB as soon as possible and no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

Investigators must promptly report (according to the above schedule) the following events to the IRB if the events occur within thirty (30) days of participants' active participation:

- Adverse events which in the opinion of the principal investigator are both unexpected and related.
- An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
- Information that indicates a change to the risks or potential benefits of the research. For example:
- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
- A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.
- A breach of confidentiality.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- Event that requires prompt reporting to the sponsor.
- Sponsor imposed suspension for risk.
- Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

8.4.4 EVENTS OF SPECIAL INTEREST

Not Applicable.

8.4.5 REPORTING OF PREGNANCY

Subjects found to be pregnant during preoperative testing or during the course of treatment will be excluded until not pregnant at which point re-evaluation can occur at the discretion of the PI.

8.5 STUDY HALTING RULES

Use and implantation of the neurostimulator system will be halted when three grade 3 AEs determined to be "probably related or definitely related." The PI will notify the study sponsor and IRB immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

8.6 SAFETY OVERSIGHT

Safety oversight will be the responsibility of the principal investigator.

9 CLINICAL MONITORING

Clinical site monitoring will be performed by the study monitor. The appointment and responsibilities of the study monitor are defined in section 13.5.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This study explores the effect of epidural spinal cord stimulation on volition movement and autonomic function and represents one of the first studies with little preliminary evidence. The statistical plan is delineated for the primary, secondary, and exploratory outcomes below.

10.2 STATISTICAL HYPOTHESES

Primary Endpoint

Volitional Response Index Magnitude
The hypothesis of the primary outcome VRI magnitude is that epidural spinal cord stimulation will provide a higher VRI magnitude than sham.
H0: mean treatment VRI magnitude = mean sham VRI magnitude
Ha: mean treatment VRI magnitude != mean sham VRI magnitude

Secondary Endpoints
Standing Training Assessment
Hypothesis: standing power will be improved with epidural stimulation
H0: mean treatment standing power = mean sham standing power
Ha: mean treatment standing power != mean sham standing power

Sympathetic Skin Responses (SSR)
Hypothesis: SSR will be unchanged by epidural stimulation
H0: mean treatment SSR = mean sham SSR
Ha: mean treatment SSR != mean sham SSR

Blood pressure
Hypothesis: blood pressure will be increased with epidural stimulation
H0: mean treatment BP = mean sham BP
Ha: mean treatment BP != mean sham BP

Cerebrovascular Assessment
Hypothesis: epidural stimulation will increased cerebral blood flow (CBF)
H0: mean treatment CBF = mean sham CBF
Ha: mean treatment CBF != mean sham CBF

Arterial Stiffness
Hypothesis: epidural stimulation will not change arterial stiffness (AS)
H0: mean treatment AS = mean sham AS
Ha: mean treatment AS != mean sham AS

Visual Neurocognitive Assessment
Hypothesis: epidural stimulation will improve Stroop score

H0: mean treatment score = mean sham score
Ha: mean treatment score != mean sham score

10.3 ANALYSIS DATASETS

Subjects who complete at least 80% of the protocol will be included in the analysis data set.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This study represents a single-arm quasi-experimental, multiple, sham-controlled crossover study. This design is possible because of the rapid onset and offset of the effect of epidural stimulation as previously reported. This protocol provides the opportunity to test outcome measures intensely in each individual subject over different stimulation settings with sham control longitudinally. The intention of the longitudinal assessments is to search for improvements over time with increased understanding of the stimulation parameter space. As such most outcomes utilize the repeated measures ANOVA.

Baseline data relevant to spinal cord injury movement and its adverse effects will be measured in the hopes of providing guidance for future generalizability. Descriptive statistics will be reported as means with standard deviations. Tests will be considered statistically significant when alpha is less than 0.05 for two-tailed tests. All assumptions for statistical tests will be evaluated before use of the test and corrected if necessary and possible.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary outcome is volitional movement as measured by the brain motor control assessment (BMCA). The BMCA uses surface electromyography (sEMG) to track changes in muscle amplitudes relative to a population control in a normalized fashion. In this protocol, the lower extremity BMCA is used to track progress during the trial and is reported as a vector, which consists of the magnitude of the response vector (RV) and the similarity index (SI). The response vector is composed of the magnitudes of the sEMG where each dimension is an included muscle. The similarity index is the inner product of the normalized response vector in controls for a single maneuver with the normalized RV from the subject for that maneuver. The RV is reported in microvolts while the SI is reported as a value between 0 and 1, both continuous variables. As a pair, these are referred to as the voluntary response index (VRI).

The VRI for each maneuver will be averaged over all of the muscle groups at each appointment, resulting in a single sham vector and a single stimulation vector for each regularly scheduled appointment. By design, subjects undergoing the protocol should have response magnitudes and SI of 0 as baseline readings. By normalizing the VRI to (200, 1), it is possible to report a clinically significant change. For example, computing the normalized magnitude for a response magnitude of 50 uV and a SI of 0.2 would result in $\text{sqrt}((50/200)^2+(0.2/1)^2) = 0.32$. Based on the limited data using this particular outcome, we feel a clinically significant change would be a distance of 0.2. This allows muscles groups to coordinate or improve in magnitude.

The primary outcome is whether subjects regain volitional movement during epidural stimulation. The hypothesis is then that the VRI should be higher during blinded treatment when compared to sham stimulation. While the time-course of change and measurements of plasticity are also interesting, the very small amount of pre-existing preliminary data available encourages efforts to focus on major changes in the primary outcome. For each subject,

we assume subjects will be able to attend at least 10 appointments, and, therefore, undergo 10 BMAC tests, resulting in 10 VRIs during treatment and sham.

The repeated measures ANOVA will be used to compare sham and treatment where alpha is assumed to be 0.025 (two tailed) and power 0.95. The correlation between repeated measures is assumed to be 0.5. The ANOVA residuals will be assessed for normality and the groups will be assessed for homoscedasticity. If there are significant violations of these assumptions then Friedman's test will be used instead. The data will be displayed with means and 95% confidence intervals between treatment and sham for each subject and as a group over time.

Missing data will be analyzed to examine for randomness of omission. If the missing data is determined to be reasonably random, then predictive mean matching will be used for imputation. The distribution of the complete data set will be examined with and without the imputed data.

Data from subjects with incomplete data from dropout will be included in the final analysis unless the subject requested removal of their data. Incomplete data will be pooled per session.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Clinical Decision Support System (CDSS)

Optimal programming of the spinal cord stimulator system is seen as a major future barrier to future widespread use, and, as a result, a major goal and specific secondary outcome of the study is exploration of the parameter space of epidural spinal cord stimulation. Current implantable pulse generators offer frequency, pulse width, amplitude, and electrode configuration as programmable parameters of continuous stimulation. While our expectation of future systems is increased freedom in the parameter space with more numerous parameters, more than 32 million settings can currently be programmed, far exceeding the number of parameters that could be evaluated in any clinical trial.

To overcome this daunting barrier to future clinical use, this study intends to populate a probabilistic model of the parameter space that is able to grow with the addition of each patient. Subthreshold testing of the stimulator system during clinical visits reduces the dimensionality of the parameter space by eliminating amplitude as significant, leaving frequency and pulse width.

At each visit, subjects will be assigned 8 randomly chosen clusters from the parameter space as a basis for response surface modeling. Subjects will be programmed 8 randomly sorted settings corresponding to one sample from each of the 8 clusters at each clinical appointment. During the month between clinical appointments, subjects will link their home volitional movement testing to the scheduled setting, which will assess velocity of their movements and fidelity of movement through randomized cuing. In turn, each setting will be assigned outcomes from their home testing. Each of the 8 settings will correspond to one of the 8 clusters being evaluated in the parameter space and each monthly visit will evaluate nearest neighbor settings until the response surface gradient can be calculated. Once the corresponding response surface gradient can be calculated, subjects will be programmed to descend the gradient until the end of the trial.

More specifically, the St. Jude Medical Proclaim Elite neurostimulators currently offer the following parameters:

Frequency: 2-100 Hz by 2s = 50 settings, 110 - 1200 by 10 = 110 settings

Pulse Width: 10-1000 us by 10: 100 settings

Amplitude: 0-25.5 by 0.1: 256 settings

These basic settings result in 4,096,000 possible settings. Up to 8 electrode groups can be given independent constant current settings out of the 16 electrodes implanted, resulting in 32,768,000 independent group electrode settings. Dimensionality reduction and global settings provide a space of 16,000 possibilities. The first generation of the clinical decision support system probabilistic model will evaluate this space.

Standing Training

Subjects will be assessed for ability to provide power during aided standing trials while wearing surface EMG electrodes. Average aggregate power generated will be calculated for the subject during the trial. Statistical testing will be by repeated measures ANOVA to examine for differences in mean.

The ANOVA residuals will be assessed for normality and the groups will be assessed for homoscedasticity. If there are significant violations of these assumptions then Friedman's test will be used instead. The data will be displayed with means and 95% confidence intervals between treatment and sham for each subject and as a group over time.

Missing data will be analyzed to examine for randomness of omission. If the missing data is determined to be reasonably random, then predictive mean matching will be used for imputation. The distribution of the complete data set will be examined with and without the imputed data.

Data from subjects with incomplete data from dropout will be included in the final analysis unless the subject requested removal of their data. Incomplete data will be pooled per session.

Autonomic Function

Multiple measures of autonomic function will be performed during autonomic appointments to characterize changes between stimulation and sham. Measurements made by ultrasound, continuous blood pressure measurement, or electrical response are all continuous measurements. Statistical testing will be by repeated measures ANOVA to examine for differences in mean:

- Sympathetic Skin Responses (SSR)
- Change in Cerebral blood flow (CBF) as measures by Transcranial Doppler during tilt testing
- Mean blood pressure during continuous noninvasive measurement
- Change in mean blood pressure during tilt testing
- Arterial stiffness
- Stroop test

The ANOVA residuals will be assessed for normality and the groups will be assessed for homoscedasticity. If there are significant violations of these assumptions then Friedman's test will be used instead. The data will be displayed with means and 95% confidence intervals between treatment and sham for each subject and as a group over time.

Missing data will be analyzed to examine for randomness of omission. If the missing data is determined to be reasonably random, then predictive mean matching will be used for imputation. The distribution of the complete data set will be examined with and without the imputed data.

Data from subjects with incomplete data from dropout will be included in the final analysis unless the subject requested removal of their data. Incomplete data will be pooled per session.

10.4.4 SAFETY ANALYSES

Safety Endpoints and a summary description are as follows:

- Physical Examination: signs of pressure ulcers, infections, or other relevant emergent findings
- Blood Pressure: change from baseline, before, and after stimulation sessions
- Adverse Event Incidence: as defined by 8.1 Specification of Safety Parameters
- Modified Ashworth Scale Score: changes from baseline, before, and after stimulation settings

Safety endpoints and adverse events will be presented via summary statistics after coding into System Organ Classes (SOCs). As applicable adverse events will only be coded once for each subject. Each adverse event will be described by start date, stop date, severity, relationship, outcome, and duration. AEs will be reported as outlined in 8 ASSESSMENT OF SAFETY.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Most assessments are completed under direct guidance during clinical visits where results are immediately recorded. Compliance with the home rehabilitation program will be completed by measuring the percentage of completed assignments where assignments are at least 80% complete.

Subjects that do not meet this level of compliance will be detected during follow up visits, and they will be contacted upon missing any follow up visit. Subjects will continue to be followed regardless of compliance, which will be noted in data analysis. Subjects will be encouraged to improve compliance when necessary through help with scheduling and troubleshooting with training and rehabilitation.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be described including demographics, medical history, and all baseline assessments of this single-arm study.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

Safety review will be performed by the study monitor (Section 13.5) and analyzed by the Principal Investigator (Section 12.2). The procedure and scope of the safety monitoring parameters will be determined by the Principal Investigator.

10.4.7.2 EFFICACY REVIEW

In this open-label study, interim analysis will be completed after every cohort of six subjects to examine primary and secondary outcomes. These preliminary analyses will have no effect on subject enrollment or early termination of the study due to efficacy.

Formal interim analysis will occur after completion of final outcome of 30 and 60 subjects to assess for efficacy.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Subgroup analyses will be completed with covariates of sex and age for the primary and secondary endpoints. Lesion location will also be used in a sub-group analysis for primary and secondary outcomes, but it is anticipated that there may not be sufficient variation for this analysis to be completed.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

There is only one primary endpoint for which this study is powered. Secondary and exploratory outcomes will provide preliminary information regarding these outcomes in subjects with chronic spinal cord injury undergoing epidural SCS.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Data will be tabulated by individual but represented graphically in groups. It is necessary to demonstrate individual differences over time as trajectories.

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses will be performed to begin to understand how epidural stimulation may affect bladder function, bowel function, measures of depression and anxiety, pain, sleep and quality of life. The study is not powered to examine the effect size of any of these outcomes. These outcomes will be used to explore potential relationships through future research.

10.5 SAMPLE SIZE

Subjects will undergo blinded treatment and sham BMAC testing at each monthly appointment during the course of the trial. Assuming nonattendance to be approximately 25%, we expect subjects to complete at least 9 sessions. With a power of 0.95 and alpha of 0.025 for a two level ANOVA, we assume a correlation among repeat measure of 0.5. By assuming a baseline mean magnitude of 0.3 and a clinically significant change of 0.2 while assuming a within group standard deviation of 0.25 (resulting in an effect size of 0.4), we estimate that we will need at least 56 subjects to demonstrate significance for the primary outcome.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Randomization will only occur during sham-controlled testing during clinic appointments. Subjects and the primary testing physician will be blinded to stimulation versus sham in blocked fashion at each appointment. A schedule of assigned programs will be created and recorded by a study coordinator who will deliver stimulation or sham of deidentified sequential program presets at necessary time points at each clinical appointment. In a set amount of stimulation programs delivered during a session, the testing physician and subject will only be able to see these de-identified labels on the programming device and not the properties of the stimulator settings. Due to the significance of previously reported effects, it is very unlikely that subjects will be able to recognize sham and control periods, but blinding is attempted to remove as much bias as possible.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

The subject and testing physician will be given a case report form that will ask whether or not each program had/did not have stimulation.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Blinding will only be broken during interim and final data analysis.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A Case Report Form will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Any missing or spurious data will be accompanied by a note to file in the subject's record which will clarify the reason behind it and any action taken afterwards.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 TRAINING

The principal investigator and co-investigators involved in the study who have surgery roles have completed training to implant epidural spinal cord stimulator. A co-investigator serving as the site investigator, designated for each site, must be the attending surgeon of record for each surgical implantation. Each surgeon has had significant experience implanting SCS paddle electrodes. The investigator-sponsor is responsible for site visit and training the appropriate personnel at each investigational site. The principal investigator will review the method of identifying and enrolling the appropriate subjects into the study.

The principal investigator will provide the necessary documents and forms to assist each investigational site on subject recruitment, procedural follow-up, and the completion of forms for the study.

Each site shall be responsible for assuring uniform data collection and protocol compliance as required by the study protocol and associated documents.

12.2 QUALITY CONTROL COMMITTEE

The Principal Investigator will be responsible for quality control.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and

regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, sample ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator as allowable by local applicable laws and regulations.

13.2 INSTITUTIONAL REVIEW BOARD

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The consent form will include the following:

- Purpose statement
- Participant commitment
- Costs
- Risks
- Benefits
- Disclosure of alternative
- Statement of confidentiality
- Study contact information

When a clinical site investigator and/or research coordinator identifies a candidate for the study, subject eligibility will be confirmed, and the study investigator or coordinator will approach the individual to offer participation. After a thorough discussion to inform the subject and family of the rationale and objectives of the study and the risks, benefits, and alternatives to participation, written informed consent will be obtained from the subject themselves (subject ≥18 years of age) or a parent or legal guardian (subject <18 years of age). Additionally, assent will be obtained for subjects of appropriate age, according to individual institutional practices. If study participation is declined, then all clinical care will be provided to the child in accordance with institutional practice and judgment.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

All records related to a participant's research will be stored in locked filing cabinets or on computers protected with passwords. The participant's identity on these records will be indicated by a study number rather than by name, and the information linking these study ID numbers with the participant's identity will be kept separate from the research records. The participant will not be identified by name in any publication of the research results.

The collection, transfer and storage of data will be conducted in compliance with the HIPAA Security Rule and structured to minimize risk of PHI disclosure. All recorded data will be entered into a password protected database. All data entry forms will be accessed and completed electronically through a password-protected log-on.

All user interaction with the web-based system, from transmitting access passwords to entering sensitive subject data, is done via 128-bit encryption using the secure HTTPS protocol. Firewalls ensure that only the minimum traffic required for normal operations is allowed to traverse the network of web and database servers. The database production servers will be housed in secure institutional data center facilities and include failover protection designed to minimize potential for server downtime. Minimal required personnel are allowed direct access to production facilities. The study data will remain secure and be maximally protected using production-level data center servers.

13.5 MONITORING

The principal investigator shall select a Monitor(s) qualified by training and experience to monitor the study. A Monitor may be an employee of the principal investigator's organization or an organization contracted by the principal investigator. The Monitor shall assure that the investigators are complying with the signed investigator agreement, the Clinical Investigation Plan/Protocol, IDE regulations and any conditions of approval imposed by the Investigation Site IRB/EC or FDA. Routine monitoring will occur to:

- verify that subject enrollment is being achieved;
- verify that the inclusion/exclusion criteria has been met at enrollment;
- verify that the correct version of the informed consent has been signed by the subject;
- review the medical records of all enrolled subjects to ensure all adverse events have been captured and properly reported;
- verify that the data and imaging are accurate, complete and backed up by source documents;
- verify that all contracts, certifications, and medical licenses for each site are valid through the duration of the study.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Management

The principal investigator will monitor each site's data and interpret the respective imaging. The investigator-sponsor will oversee and process data in the following manner:

- Data Management
  - Design and modify data dictionary (the information that is being collected)
  - Design and modify database
  - Quality Control
- Retrieval and Reports

- Assist in preparation of data quality reports
- Assist in preparation of progress reports

- Design and Analysis
  - Consult with biostatistician in design and analysis of research questions

14.2 STUDY RECORDS RETENTION

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted form FDA 3500 A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol;
- Laboratory certification information;
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Decoding procedures for blinded trials *(incorporate only if applicable)*;
- Master randomization list *(incorporate only if applicable)*;
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by investigator-sponsor;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;

- Subject screening and enrollment logs;
- Subject identification code list;
- Investigational drug accountability records, including documentation of device disposal;
- Retained biological specimen log *(incorporate only if applicable)*;
- Interim data analysis report(s) *(incorporate only if applicable)*; and the
- Final clinical study report.

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IDE have been discontinued and the FDA so notified

14.3 PROTOCOL DEVIATIONS

Investigator-Sponsor or site investigator must not make any changes to or deviate from the protocol, except to protect the life and physical well-being of a subject in an emergency. An site investigator shall notify the Investigator-Sponsor and the reviewing IRB of any deviation from the protocol to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the protocol, with the reason for the deviation and the date of occurrence, must be documented and reported to the Investigator-Sponsor using the appropriate case report form. Sites are also required to report deviations to the IRB per local requirements. Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the Investigator-Sponsor.

14.3.1 DEVIATION CLASSIFICATIONS

For the purpose of consistency and reporting, deviations will be classified according to the scheme outlined below:
• Type A - Deviation to protect the life or physical well-being of a subject in an unforeseen emergency

• Type B - Deviation based on medical judgment

• Type C - Deviation due to misunderstanding of protocol requirements (training was an issue and retraining may be required)

• Type D - Deviation due to a situation that is beyond control

• Type E - Deviation due to an oversight, error or protocol non-compliance.

In the event of trend or pattern observed in a particular deviation type, the Investigator-Sponsor will perform compliance visit. Documentation of such a visit and any subsequent training will be documented in the study Regulatory binder.

14.4 PUBLICATION AND DATA SHARING POLICY

Deidentified data will be shared with St. Jude Medical. Publication is the responsibility of the principal investigator and is not contingent on any outside party. No commercial entity has any right to prevent or change publication of the data. A copy of any manuscripts will be provided to St. Jude Medical before publication occurs.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study PI, the coinvestigators, the PIs of the clinical sites, and collaborators. The Steering Committee will meet in person at least annually.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 LITERATURE REFERENCES

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APPENDIX

Version	Date	Significant Revisions
1.58	09/06/2016	First Draft to be analyzed by CTSI
1.59	09/07/2016	Minor revisions removing references to non-outcome CRFs
1.60	Not known	Not known
1.61	11/17/2016	Changes to inclusion/exclusion criteria
1.62	11/23/2016	Inclusion/exclusion criteria changes, spell check, device storage
1.63	12/04/2016	Added safety analysis endpoints Transferred all safety oversight to PI Renamed individuals involved in the study to 'subjects' Removed references to Urodynamics Removed references to the Neuromusclar Recovery Scale Removed inappropriate CRFs Addition of endpoints to summary Updated device removal section Darrow updates: autonomics exclusion criteria and screening, editing laboratory assessments, statistics, randomization
1.64	12/12/2016	Added FDA 10 subject enrollment safety checkpoint Refined blinding method and added blinding assessment Added two tailed clarification on study endpoint. Added pregnancy exclusion criterion
1.65	12/21/2016	Added clarification of stimulation and sham timing.
1.66	3/1/2017	Removed SSEP, added NBSS and NBDS. Clarified autonomic screening and risk stratification.