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Neuromodulation of motor and sensory spinal pathways in subjects undergoing epidural spinal cord stimulation.

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PROTOCOL TITLE:
Neuromodulation of motor and sensory spinal pathways in subjects undergoing epidural spinal cord stimulation.

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1.0 Objectives/Specific Aims

Each year, an estimated 34,000 spinal cord stimulation (SCS) surgeries are performed worldwide for treatment of debilitating chronic low back and leg pain (CLBLP).[1] Although the commercial application of SCS to treat CLBLP was approved by the FDA in 1989, only in the past decade have significant advancements in stimulator technology been introduced. For instance, traditional SCS devices achieved reduction in pain using a type of stimulation known as low-frequency tonic stimulation (LFTS, below 100 Hz), which was dependent on induction of paresthesias (i.e., a tingling sensation) over the areas of pain perception.[2] However, we now know that LFTS compromises sensory information flowing back to the spinal cord, which can be important in other spinal cord functions such as proprioception and movement. In contrast, recent innovations in stimulator technology now provide the capability to apply stimulation frequencies up to 10,000 Hz along with complex waveform patterns – known as high frequency burst stimulation or HFBS - that can mitigate pain perception without the induction of paresthesias and the negative consequences on proprioception and movement.[3] We propose to study the effects of these recently introduced features in SCS technology on motor and sensory spinal thresholds, proprioception and movement in subjects with CLBLP.

The spinal cord relies on input from the motor cortex as well as sensory information from the extremities to carry out specific actions. For example, recent evidence suggests that preservation of temporally specific proprioceptive information via dorsal column primary afferent fibers is critical for motor behaviors such as ambulation.[3,4] Since the spinal cord is exposed during the placement of the SCS device, information about a subject's motor and sensory spinal pathways can be easily obtained during the regular course of the procedure and compared to proprioceptive and motor responses once the subject is awake and moving with the device turned on. Our lab specializes in electrophysiological recordings in subjects undergoing spinal cord stimulator (SCS) implantation for CLBLP, while MUSC's Locomotion Laboratory specializes in quantifying proprioception and movement in human subjects. In this proposal, we will apply these techniques to subjects with CLBLP to determine effects of spinal neuromodulation on motor and sensory thresholds, proprioception, and kinematics.[5,6] Our plan includes the following specific aims:

Aim 1. Compare the effects of LFTS and HFBS on motor and sensory thresholds intraoperatively. Question: Do HFBS waveform patterns modulate motor and sensory thresholds to allow more information to reach the spinal cord? In this aim, we will measure sensory and motor spinal thresholds in subjects undergoing SCS implantation during stimulation of epidural paddle contacts. *We hypothesize that HFBS will reduce motor and sensory thresholds relative to LFTS during epidural paddle activation.*

Aim 2. Determine the effect of HFBS on proprioceptive afferent signaling from lower extremity muscle groups. Question: Does HFBS, when compared to traditional LFTS, allow for increased spatial limb awareness during passive motion? In this aim, postoperative subjects from SA1 will undergo isokinetic passive proprioceptive testing before, during and after spinal cord stimulation with HFBS and LFTS parameters targeting musculature surrounding the knee. *We hypothesize that subjects will have increased awareness of the lower limb in space through passive movement during optimal HFBS compared to optimal LFTS parameters.*

Aim 3. Determine the effect of HFBS on lower extremity musculature during gait. Question: Does HFBS, when compared to LFTS, differentially affect muscle synergy patterns during gait? In this aim, subjects from SA1 and SA2 will perform treadmill walking before, during and after SCS stimulation. Subjects will be monitored with surface EMG and 3-D kinematic tracking software to quantify any changes in walking pattern. *We hypothesize that subjects will have increased EMG module complexity during gait while experiencing optimal HFBS compared to optimal LFTS or no stimulation.*

2.0 Background

Significance

SCS is currently used to treat chronic neuropathic pain that may arise from spinal injury, disease, and/or previous spinal surgery, for example, in cases of post-laminectomy syndrome, the most common indication for SCS. SCS surgery represents 70% of all neuromodulation cases in the United States and is expected to grow as the intervention shows continued promise to successfully treat neuropathic pain from these and many other etiologies.[1] With the introduction of new charging capacities, stimulation frequencies and waveform patterns, questions about potentially new mechanisms of pain reduction as well as effects on other spinal cord functions, such as movement and balance, have gained urgency.

SCS was originally based on a concept known as the gate control theory of pain. Gate control theory postulates that central regulation of pain involves nonnociceptive fibers (large Aβ fibers in the dorsal column medial lemniscal pathway) that inhibit nociceptive fibers (Aδ and C fibers in the spinothalamic pathway) and thus reduce both pain transmission in the spinal cord as well as perception by higher brain centers.[7] The SCS procedure involves placement of epidural electrodes that when activated recruit lower threshold Aβ fibers that produce a paresthetic sensation along the region of pain. The antidromic projections to dorsal horn interneurons influence two additional downstream targets: fibers that further inhibit pain transmission and ventral motor neuron pools that target specific myotomes .[8]

In 2009 Harkema et al investigated the motor effects from LFTS at intensities strong enough to elicit paresthesias, ranging from 5-60 Hz (frequency), 210 to 450 μs (pulse width) and amplitude ranging from 0.1 to 8.0 V. Using these parameters, LFTS was found to elicit lower extremity muscle activity including co-activation during standing, rhythmic activation during stepping, and mechanically appropriate activation of agonist lower extremity muscles during weight shift in a subject with spinal cord injury.[9] Additionally, Gill et al introduced the application of multiple independent current control (MICC) which allows for different stimulation parameters on the paddle to be delivered in tandem, innervating spatially distinct regions of the spinal cord. The MICC programs supported bilateral tasks, suggesting that complex charge delivery via MICC can enable independent modulation of both spinal sensory and motor neuron pools.

The ability to program customized HFBS patterns may help to address another important factor in potentially expanding the use of SCS to other indications, including movement: preservation of proprioception. The amount of compromised afferent information during traditional spinal cord stimulation via LFTS is dependent upon the quantity of dorsal column primary afferents recruited and is proportional to increases in current and pulse width.[3,10] Traditional stimulation parameters (15Hz-100Hz, 210μs–450μs, 4.5mA–9.0mA) were found to cause decreased interneuron modulation of inhibitory/excitatory interneurons from antidromic collision when amplitudes are high enough to innervate their homonymous motor neuron pool to activation threshold. However, high frequency burst stimulation (HFBS) at 600Hz was found to illicit motor neuron activation with a 39.8% reduction in current amplitude and 15% recruitment of modeled homonymous afferents, as opposed to 45% recruitment utilizing LFTS to elicit similar motor neuron activation.[3]

3.0 Intervention to be studied

Overview

This study will perform the following research-specific procedures:

1) Determination of eligibility through medical chart review
2) Recording and stimulation of spinal potentials during insertion of epidural spinal stimulator paddle
3) Proprioception testing
4) Body weight support and treadmill (BWST) testing

Definitions and nomenclature

Spinal cord stimulation (SCS) will be performed using a 32-electrode paddle array (Boston Scientific, Marlborough, MA) (Figure 1) implanted in the dorsal epidural space along the thoracolumbar region of the spinal cord. The array will be powered by a multiple independent current-controlled (MICC) implantable pulse generator (IPG) connected to the paddle per standard of care procedures for SCS implantation. In addition, as per standard of care, motor evoked potential (MEP), somatosensory evoked potential (SSEP) and electromyography (EMG) will be performed via the IOMAX intraoperative neuromonitoring system (Cadwell, Kennewick, WA) and LR10 (Tucker Davis Technologies, Alachua, FL) recording device. **The SCS system will be placed for clinical purposes, i.e., treatment of chronic pain, however, we will collect data at various points during the placement. The study procedures will add 15 minutes to the surgery.** MUSC's Locomotion Rehabilitation Laboratory – located at the College of Health Professions Building C - houses a Biodex Pro System 4 isokinetic/isometric dynamometer (Biodex Medical Systems, Shirley, NY). The Biodex will standardize application of passive isokinetic knee flexion/extension trials to each blinded subject for proprioceptive investigations, which will be referred to as threshold to detect passive movement (TTDPM) throughout the rest of this document. Finally, MUSC's Locomotor Energetics and Assessment Laboratory – also located at the College of Health Professions Building C – houses a dual belt Instrumental Treadmill (Bertec, Scotland, U.K.) that is coplanar with the floor and will be used during all walking events. The laboratory also has a 12-camera motion capture system (PhaseSpace, San Leandro, CA) that utilizes active infrared LED tracers to track kinematic positioning data and will be used during all walking events. Another tool offered by the lab is a 16-channel EMG system (Motion Labs, Baton Rouge, LA, model MA300-XVI) which utilizes surface electrodes to detect target muscle activity and will also be used during all walking events. In all, we expect total duration of the study to be approximately 30 days.

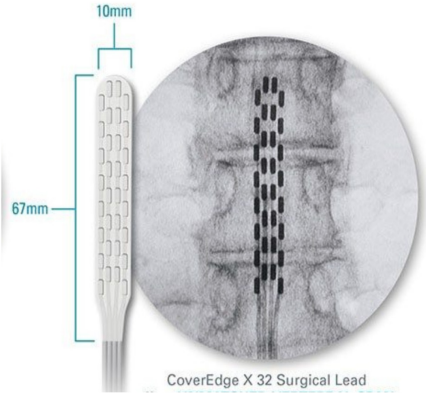

Figure 1: Boston Scientific CoverEdge™ 32 Surgical Lead (left) and fluoroscopic image of the stimulator array after implantation along the dorsal epidural space (right).

Device use

The epidural stimulator paddle (Boston Scientific, Marlborough, MA, model 4x8 CoverEdge™ 32) and IPG (Boston Scientific, Marlborough, MA, model Spectra WaveWriter™) are FDA-approved, commercially available devices designed to treat chronic pain of the back and lower extremities and will be used for their intended clinical purpose – electrical stimulation of dorsal column fibers to mitigate pain perception. The research use of this device, which will add approximately 15 minutes to the surgery, involves recording/stimulating from the device during the standard of care intraoperative neuromonitoring protocol. Regardless of study participation, the stimulator paddle and IPG will be implanted according to standard of care for the pre-planned SCS surgery. The IOMAX intraoperative neuromonitoring system (Cadwell, Kennewick, WA), equipment owned by MUSC and operated by MUSC neurophysiology staff, is a commercially available device used during standard of care spinal surgical procedures, such as SCS implantation. Regardless of study participation, intraoperative neuromonitoring via IOMAX will take place according to standard of care for the pre-planned SCS surgery. The following devices are used for research purposes only. The LR10 is a physiological signal amplifier and analog to digital converter that will be used to record from the stimulator paddle during standard of care neuromonitoring protocols. The Biodex Pro System 4 (Biodex Medical Systems, Shirley, NY), used regularly by physical rehabilitation researchers here at MUSC, is a commercially available device that will be used solely as a research tool to deliver passive isokinetic knee flexion/extension during the TTDPM. The Instrumental Treadmill (Bertec, Scotland, U.K), GAITRite mat (CIR Systems, Franklin, NJ), motion capture system (PhaseSpace, San Leandro, CA), and MA300 EMG system (Motion Labs, Baton Rouge, LA) are all commercially available devices that are used by MUSC researchers at the College of Health Professions to perform extensive gait analysis in subjects with various neurological deficits. Gait analysis is being performed

for research purposes only, and is not standard of care for patients receiving SCS surgery. All medical devices are to be used as they are FDA approved and marketed.

4.0 Inclusion and Exclusion Criteria / Study Population.

All diagnostic procedures will have taken place prior to recruitment as part of the routine diagnosis and care of patients with chronic pain. It is standard of care to require failure of conservative therapy, e.g., 6 weeks of physical therapy and/or 1 or more epidural steroid injections, and SCS temporary trial by a board-certified **pain management specialist** in addition to neuropsychological testing by a board-certified neuropsychologist prior to being considered for permanent SCS implantation.

Eligibility for this study will be based on the following inclusion/exclusion criteria:

Research Inclusion Criteria

- Subjects diagnosed with CLBLP by a **pain specialist** with a documented referral for evaluation of SCS surgery
- Subjects with the ability to walk
- Age 18-80

Research Exclusion Criteria

- Subjects with the inability to consent for themselves.
- Prior history of spinal neoplasm, infection, arteriovenous malformation and/or radiation to the spine

The rationale for these research related criteria are as follows: subjects with prior history of tumor, infection, arteriovenous malformation and/or radiation of the tissues surrounding the epidural space may result in formation of scar tissue which directly alters the resistance of the tissue to passing electrical current, potentially confounding study data. None of the research exclusion criteria would exclude a patient from undergoing SCS surgery for non-research purposes, therefore the exclusion criteria apply only to the research being performed for this protocol.

5.0 Number of Subjects

We propose to study 5 individuals with CLBLP. A prior study conducted by Formento et al, 2018 using SCS and proprioceptive testing published a standard error and 95% confidence interval using successful and unsuccessful SCS trial attempts ($p < 0.05$ among LFTS parameters and no stimulation, with a minimum of 10 trials per stimulation setting.)[3] Based on this, we expect that our small population will exhibit similar variance. The subject sample size is in direct comparison to sample sizes of previous proof of concept studies regarding SCS for spinal cord physiology biomarker sampling.[3,9,11] The research team plans to use a two-way repeated measures ANOVA model in order to investigate the varying differences in stimulation type and kinematic parameters. A Post hoc comparison will be made using a Tukey adjustment.

6.0 Setting

The data pertaining to Aim 1 for this study will be recorded in the operating room at MUSC Main Hospital. Data collected during Aims 2 and 3 will be recorded in the Locomotor Rehabilitation Laboratory and the Locomotor Energetics and Assessment Laboratory respectively, which are both located in the College of Health Professions Building C at MUSC. Coded and identifiable data will be stored electronically on a secure server in separate folders. Signed consent forms will be located in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC. In all, we expect total duration of the study to be approximately 30 days for each subject.

7.0 Recruitment Methods

During the subject's preoperative clinic visit, the PI will ask the potential participant if they would like to learn more about the study. If so, the PI will introduce the study and ask if he can answer any further questions about the study before inviting in the PI's physician assistant (listed as a study team member). The PI will then leave the room and the PI's physician assistant will review a prescreening checklist to determine whether subjects may be eligible for the study (no information obtained during the prescreening will be documented as research data). For the screening, potential participants will be asked to confirm that they are between the ages of 18 and 80, that they have been previously diagnosed with CLBLP by a pain specialist, and whether they have any prior history of spinal neoplasm, infection, arteriovenous malformation and/or radiation to the spine. If potential participants answer no to either of the first two questions or yes to either of the remaining questions, they will be considered ineligible for the study. Otherwise, the PI's physician assistant will review the informed consent form (ICF) with the potential participant and then leave the room in order to give the potential participant sufficient time to read the ICF.

Next, the PI's physician assistant will conduct a brief medical chart review using Epic to confirm that the patient's age is between 18 and 80 and that the patient has a documented referral from a pain specialist to undergo evaluation by the PI to undergo SCS surgery. The Epic 'Medical History' tab will also be checked to rule out prior history of spinal neoplasm, infection, arteriovenous malformation and/or radiation to the spine.

Careful attention will be placed on good communication. It will be emphasized that participation in the study is not necessary for standard of care medical treatment for their condition. It will also be emphasized that the subject can withdraw from the study at any time.

8.0 Consent Process

Once the potential participant has been given an opportunity to review the consent form in detail, the PI's physician assistant will re-enter the room and go over the sections of the consent with the participant. She will answer any questions the potential participant may have. The voluntary nature of the study will again be emphasized. It will also be emphasized that the potential participant may exercise their right to take the consent form home to discuss with family and friends prior to signing. For potential subjects that provide consent to the research study during their clinic visit, a copy of the signed and dated ICF/HIPAA authorization form will be provided to them before leaving the clinic. Original forms will be placed in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC. On the morning of surgery, IRB-approved study personnel will once again review the study procedures and study consent documents – emphasizing the voluntary nature of the study and the ability of the subject to withdraw at any time. Subjects who did not sign the ICF/HIPAA authorization form during their clinic visit and who still wish to participate in the study will be able to sign the forms on the morning of surgery, at which time a copy of the signed and dated forms will be provided to them.

9.0 Study Design / Methods

Step 1: Recording and stimulation of spinal potentials during insertion of epidural spinal stimulator paddle

On the day of the surgery, subjects will first be placed under general anesthesia for the procedure. Next, after positioning the subject on the operating room table, subdermal MEP, SSEP and EMG needle electrodes will be placed throughout the body by the neurophysiology team as determined by standard of care guidelines. Once the epidural paddle is placed by the surgeon, study procedures will begin by (#1) connecting the terminals of the paddle to the LR10 (Tucker Davis Technologies, Alachua, FL) for amplification, filtering and recording of electrophysiological signals. Using this recording setup, (#2) MEP and SSEP protocols will be performed to determine motor and sensory thresholds, respectively. Next, the surgical procedure will resume and after the IPG has been placed, study procedures will begin again and include (#3) activation of both low-frequency tonic stimulation (LFTS) and high-frequency burst stimulation (HFBS) patterns from the inserted paddle while recording EMG signals.[12-13] The surgical procedure being performed (SCS paddle and IPG implantation) for

clinical purposes will not deviate in any way from standard of care. The recording and stimulation study procedures will occur using equipment already present in the operating room used to test the SCS system as per standard of care in addition to the LR10 (Tucker Davis Technologies, Alachua, FL) signal recording machine. All devices will be used for their FDA-approved intended use. Our study procedures are expected to add approximately 15 minutes to the SCS procedure and will be paid for by internal funds. The standard of care versus the research procedures are diagramed below:

Standard of care procedures	Research procedures
Subject is placed under general anesthesia and positioned face down. The neurophysiology team places subdermal needles for MEP, SSEP and EMG measurements and connects the wires to the **IOMAX intraoperative neuromonitoring system** (owned and paid for by MUSC). Skin incision is made. The SCS paddle is placed into initial position.	Once the SCS paddle is in initial position, the research team connects the SCS paddle terminals to the **LR10 machine** (owned and paid for by the Rowland lab, takes less than 1 minute).
The neurophysiology team then performs MEP and SSEP measurements. The surgeon makes small adjustments to the position of the paddle based on this information.	The research team saves data from the SCS paddle as the MEP and SSEP measurements are performed (takes 0 minutes).
Once the SCS paddle is in its final position, the SCS paddle terminals are disconnected from the LR10 machine and reconnected to a **Boston Scientific external stimulator** (owned and paid for by Boston Scientific – leaves the OR with Boston Scientific representative). The stimulator tests the impedance of each contact.	Once the impedances are confirmed, the external stimulator is used to test each contact on the paddle and compare low- and high-frequency stimulation patterns as prescribed by the study protocol (takes approximately 15 minutes).

Step 2: Proprioception testing before, during and after SCS stimulation
All of the following are for research purposes and not considered standard of care for SCS surgery. Following an approximately 30-day recovery period from surgical placement of the paddle and IPG, subjects will undergo

stimulation configuration mapping (SCM)[3,9,11] in the Locomotor Rehabilitation Laboratory at the College of Health Professions Building C at MUSC in order to determine electrode and parameter configurations that elicit activation of lower extremity musculature. For this testing, we will place surface EMG pads on subjects' skin overlying muscles of interest. Using the Boston Scientific external stimulator interface, we will wirelessly activate the implanted spinal paddle and compare muscle activation using LFTS and HFBS patterns by systematically testing each individual contact. Subjects will comfortably lie supine on a large, low-rise rehabilitation mat common to any physical rehabilitation clinic during SCM.

Next, we will investigate the perceived change in knee joint angle and direction of movement reported by the subject in a Threshold to Detect Passive Movement (TTDPM) task.[3,14] The TTDPM protocol will begin with the subject sitting in the Biodex testing seat, with the non-tested leg hanging freely and the tested leg strapped to the rotating arm of the dynamometer at the lower shank. The subject will be blinded as to the mode and intensity of stimulation: HFBS, LFTS, or no stimulation. Furthermore, in order to shield the subject from witnessing initiation, direction and approximate distance traveled of the shank, the subject will be asked to wear a blindfold and headphones playing a soft background noise (Figure 3). The TTDPM will consist of at least 10 trials for each stimulation condition. The subject has control of a switch that immediately halts movement of the rotating arm, which is to be activated once the subject perceives movement **OR** if the subject begins to feel any pain or discomfort throughout the task. Our research team anticipates data collection to last approximately 3 hours per subject for this step (1 hour for supine SCM, 1 hour for TTDPM and 1 hour for set up and breakdown). Proprioception testing will take place before, during and after SCS stimulation.

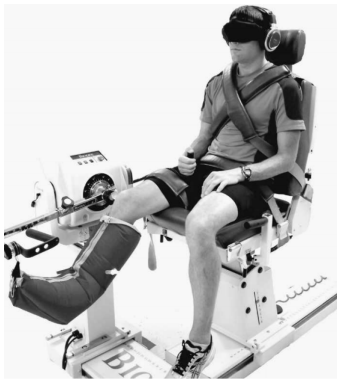

Figure 3: TTDPM test using a Biodex

Step 3: Body weight support and treadmill (BWST) testing before, during and after SCS stimulation

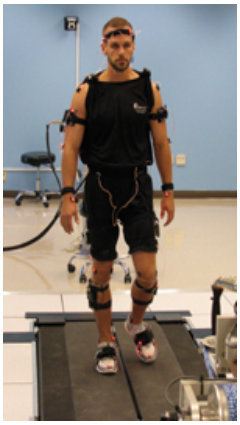

Figure 4: Demonstration of treadmill walking while undergoing 3-D kinematic tracking and EMG capture.

All of the following are for research purposes and not considered standard of care for SCS surgery. The following methods for gait and EMG module analysis have been developed and extensively tested by MUSC researchers at the College of Health Professions.[15-18] Similar to step 2, LFTS and HFBS patterns will be compared by systematically testing each individual contact on the paddle while investigating for changes in stepping speed, pattern and EMG moduling complexity. Regarding EMG module analysis, muscle activity will be recorded bilaterally via surface EMG from the medial gastrocnemius, soleus, tibialis anterior, rectus femoris, vastus medialis, biceps femoris, semimembranosus and gluteus medius. Furthermore, subjects will also have active LED markers placed over their clothes in order to track whole body kinematics throughout this portion of the study.

First, subjects will walk across a GAITRite mat (CIR Systems, Franklin, NJ) to measure self-selected overground walking speed and other spatiotemporal gait parameters. Subjects will then be permitted to practice walking on the Instrumental Treadmill until they feel comfortable. To optimize capture of steady state data on the treadmill, each subject will walk for approximately 10 sec prior to the 30 sec of data collection (40 sec per trial). This will allow capture of at least 10 consecutive steady state gait cycles (depending on cadence) per each amplitude selection for each stimulation delivery technique, which will be defined by parameters found during walking SCM. We will allow as much rest as needed between trials. For all trials, subjects will wear their own low-heeled shoes. A safety harness (Robertson Mountaineering, Fort Collins, CO) mounted to the laboratory ceiling will be worn by the participant to protect them in the event of loss of balance. Our research team anticipates data collection to last approximately 2 hours per subject for this step (1 hour for walking SCM and gait analysis and 1 hour for set up and breakdown). For their participation in step 2 and step 3 of the study, participants will be

remunerated $50.00 in the form of a check ($10.00 for lunch reimbursement and $40.00 for completion of steps 2 and 3).

Through EMG capture and high/low bandpass filtering to extinguish biologic artifact and equipment artifact respectively, segments of EMG that were recorded through functional task can be analyzed with an algorithm that yields hierarchical complexities representative of muscle synergies.[5-6,19] The research team will use previously outlined methodology to define modules through non-negative matrix factorization, where analysis will be applied to consecutive gait cycles.[20]

The Instrumental Treadmill (Bertec, Scotland, U.K), GAITRite mat (CIR Systems, Franklin, NJ), motion capture system (PhaseSpace, San Leandro, CA), and MA300 EMG system (Motion Labs, Baton Rouge, LA) have been used in the same manner described above in the following MUSC IRB approved protocols: **Pro00028941**, Assessment of contributions to impaired walking after neurologic injury; **Pro00088728**, Fatigue and mobility in stroke: a biomechanical and neurophysiological investigation; **Pro00048394**, The effects of impaired post-stroke coordination and motor pathway integrity on mobility performance; **Pro00059390**, A novel mechanics-based intervention to improve post-stroke gait stability.

10.0 Data Management

Once a potential participant is asked if they would like to learn more about the study, they will be assigned a participant ID. Participant IDs will be assigned consecutively. We will maintain a database that accurately reflects all potential subjects that were approached about the study and the results of eligibility evaluation. For eligible subjects, the specific types of data that will be collected include: 1) analog local field potentials from the SCS, MEP, SSEP and EMG electrodes, 2) digital and analog output signals from the IOMAX intraoperative neuromonitoring device, 3) digital, time-stamped, physical displacement data captured from the Biodex machine, 3) digital, time-stamped, positioning data produced by the PhaseSpace software, 5) videography data, and 6) any available imaging data (dicom files). Raw data will remain on our lab-owned data acquisition machines with encrypted hard drives and stored behind a locked door when not directly supervised. Data will be copied from all lab-owned data acquisition machines and/or hospital-owned data servers to a password protected network server accessible from our lab under the IRB protocol number and participant ID. This will constitute the master copy of all data for the lab and will consist of separately stored coded and identifiable folders. The purpose of keeping a copy of the raw data is in case the server is interrupted, and it is necessary to reconstruct the data. Portions of data will be copied to end-user devices (e.g., desktop, laptop, etc) for data analysis, however only the portion needed for analysis will be copied. Any end-user device such as a laptop that physically leaves the lab will be encrypted with MUSC-approved software (BitLocker, Microsoft Corp., Redmond, WA) which uses the AES encryption algorithm in cipher block chaining or XTS mode with a 256-bit key. Desktop machines used for analysis that do not leave the lab and are stored in a locked laboratory will not be encrypted. All data on data acquisition and end-user devices will be deleted at the conclusion of the study. No PHI will be stored on any data acquisition machine or end-user device. A linking database associating the participant ID and subject identifiers will be maintained on MUSC Box, separately from the research data. Subject identifiers to be collected include first and last name, gender, date of birth, social security number, medical record number, mailing address and telephone numbers. Telephone and medical record numbers are required for an approximate 7-day phone call made to subjects following SCS implantation. Additionally, we will collect information pertaining to disease severity for each subject, including Visual Analog Scale (VAS) scores, a common pain scale, and any other available rating scale scores. These measures will assist in correlating our physiological data with severity of disease for each subject. Videography data will be stored in the identifiable folder on the password protected network server. The purpose of this data is to correlate movement dynamics with physiology data. Finally, we will save imaging data on a password protected network server in order to analyze and correlate with our physiological data. Only IRB-approved personnel will have access to the linking database. Consent forms will be stored in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data and Safety Monitoring Plan
The proposed research involves use of a neural stimulation device and warrants oversight by a Data Safety Monitoring Board (DSMB). The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. The overall framework involves biannual review of the enrollment, safety and adverse event data, and quality control data by the DSMB throughout the period of the proposed research.

DSMB composition
The DSMB will be appointed by the PI and will be composed of individuals who are not on the study team and have the following qualifications: (1) a clinical electrophysiologist with expertise in electrical neuromodulation and intraoperative monitoring, (2) a board-certified neuropsychologist who specializes in treatment of pain syndromes, and (3) a biostatistician with expertise in design and analysis of clinical trials. These three individuals bring substantial expertise adequate to monitor data and safety for the proposed research.

DSMB responsibilities
The responsibilities of the DSMB are as follows. Prior to any enrollment, the DSMB will review the study design, protocol, recruitment/enrollment plan, statistical analysis plan, and data and safety monitoring plan. Once enrollment begins, the DSMB will convene every 6 months to review the enrollment data, the safety and adverse event data and quality control data (see below for detailed data description). The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB may provide recommendations for any safety concerns. The DSMB may recommend stopping the study early if the protocol has significant safety concerns. The DSMB will review the results and document their reviews in writing. In summary, the stopping rules are if the study has unanticipated safety concerns. The DSMB will also be able to make recommendations for appropriate action to maintain a reasonable safety profile for the study. The PI will provide a report for the IRB to review that summarizes oversight activities, DSMB recommendations and any concerns regarding participant safety.

Safety reporting to the DSMB
Subjects may report safety issues with the study directly to the PI, any member of the PI's clinical and/or research teams, the MUSC Family Care Liaison, the IRB and/or ORI Director. In the absence of any such reports, the PI will systematically attempt to uncover any safety issues experienced by a subject during the approximate one week follow-up phone call. Any of the following will be reported to the DSMB if noted by the subject during the approximate one week follow-up phone call following SCS surgery (Aim 1): severe lower back or leg pain unresponsive to pain medication, repeated falls/imbalance, excessive bleeding from wounds, lower back irritation or bleeding around the site of paddle or IPG implant and/or return to the hospital. Any of the following will be reported to the DSMB if noted during the approximate 30-day return appointment (Aims 2 and 3): return to hospital, evaluation by another provider for findings related to spinal cord stimulation surgery, imaging, lab values and/or other reports indicating complications from spinal cord stimulation surgery. All the above-mentioned issues are outside of what would be reasonably expected for a normal postoperative course following spinal cord stimulation surgery. In accordance with HRPP Section 4.7, all the above-mentioned issues constitute adverse events and will be submitted to the DSMB for review (at 6 month intervals) in addition to being recorded in an adverse event log. In addition to serious adverse events, events that are unexpected, related or possibly related to a subject's participation in the research and suggests that the research places subjects or others at greater risk of harm than was previously known or recognized constitute Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and must be reported directly to the IRB (in addition to the DSMB). Finally, all deaths will be reported to the IRB within 24 hours of learning of the death, unless the death is expected (e.g., due to disease progression).

12.0 Withdrawal of Subjects
Subjects may be withdrawn from the study without their consent, including stopping participation for safety reasons. For example, if at any point during the protocol it becomes evident that continuing with the study

would present risk in excess of that outlined in this document, data collection for that subject may be terminated. However, any data collected before the incident may still be used in analysis. At any time, subjects may also express desire to withdraw from the study. We will instruct the subjects that, to withdraw from the study, all they need to do is to contact one of the members of the study team and express the desire to be excluded from the study.

13.0 Risks to Subjects

All procedures will follow standard of care guidelines. Research staff will follow up with each participant by phone approximately one week after the surgical procedure, and during the approximate 30-day return, to make sure the participants are not having any problems. Nevertheless, this study still poses certain risks as outlined in the following sections:

Surgical complication – Due to the 15 extra minutes added to the surgery, connection of the paddle terminals outside the surgical field, and extra personnel in the room, there is a slightly increased risk of surgical infection. The extra risk of infection due to the research protocol does not increase this risk beyond the 1-5% overall historical risk of complications from the SCS surgical procedure.

TTDPM

While testing for proprioception retention of the lower extremities, subjects may encounter discomfort due to non-volitional muscle activation that hinders passive movement. To mitigate this risk, the Biodex system has a subject-controlled trigger that immediately stops the dynamometer's passive motion and may be activated at any time a subject experiences discomfort of pain during the test.

Overground and Treadmill Walking

Subjects will be asked to walk on a pressure sensitive mat at self-selected walking speeds and on a treadmill at self-selected walking speeds with each scenario having the subject in an upper thoracic safety harness which is tethered to the ceiling for fall protection. Despite the aforementioned safety measures, there still exists a risk of loss of balance, fall and potential injury. The risk to subjects through these tasks do not exceed risks involved with general physical therapy settings and may result in mild muscle fatigue or discomfort that generally subsides within a few days. Subjects will be given ample rest time and may have additional rest time at any point throughout data collection periods. Furthermore, subjects will be assisted during large movements or during potential transfers across different surfaces by an IRB-approved study member.

Photography and videography

Subjects will be videotaped during performance of supine / walking SCM and EMG moduling protocols. We will also photograph and/or videotape any other aspect of the subject's research participation that will help us correlate the subject's condition with the EMG and kinematic data. The videos and photos we record can include the full face, upper body, arms, and legs. Photography and videography carry a risk of loss of privacy. Photos and videos will be stored on a secure server. Only approved study personnel will have access to these files.

Loss of Confidentiality

Additional risks include loss of confidentiality. To mitigate this risk, a linking database associating the participant ID and subject identifiers will be maintained separately from the research data on a password protected server and only IRB-approved personnel will have access to the linking database.

14.0 Potential Benefit to Subjects or Others

This research is not expected to provide direct benefit to individual subjects, though it may lead to improvements in care for patients suffering from chronic pain in the future. A successful study outcome may contribute to this improvement and may be used in future subjects undergoing similar procedures.

15.0 Sharing of Results with Subjects

Due to the extensive amount of time needed for data processing, it will not be possible to disclose individual study results to subjects or their healthcare providers. Incidental findings and other results of diagnostic tests associated with routine care of subjects will be shared with the subject and their physician by phone, writing and/or electronic medical record communication by the PI.

16.0 Drugs or Devices

All of the following medical devices are to be used as they are FDA approved and marketed.

The LR10 (Tucker Davis Technologies, Alachua, FL), used for signal recording from SCS paddle during MEP and SSEP procedures is a non-diagnostic physiological signal amplification device. The device is exempt from Investigational device exemptions (IDE) regulation per 21 CFR 812.2 paragraph C (*exempted investigations*) subparagraph 3. (please see 21_CFR_812.2_Exempt_Devices.pdf)

The Biodex Pro System 4 (Biodex Medical Systems, Shirley, NY), used during the TTDPM testing, is an upgraded version of a previous Isokinetic dynamometer (Biodex System 3) that was also classified as a 510K/Pre-market notification device (K951770). Due to the similar nature and intent of use for the upgraded model, the Biodex Pro System 4 is exempt from 510K classification as per 21 CFR 890 Subpart A and 21 CFR 890 Subpart B 890.1925 *Isokinetic testing and evaluation system classification*. (please see 510(k)_Biodex System 3_Biodex Medical.pdf , 510(k)_PremarketExemption.pdf)

The MA300 EMG system (Motion Labs, Baton Rouge, LA), used during EMG module analysis, is a 510K/Pre-market notification device (K974385) as described in 21 CFR 807 Subpart E (please see 510(k)_MotionLabs_EMG.pdf)

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