SPINAL CORD STIMULATION FOR THE TREATMENT OF MOTOR DEFICTS IN PEOPLE WITH SPINAL MUSCULAR ATROPHY

A SINGLE-CENTER, OPEN-LABEL, INESTIGATIONAL PILOT TRIAL TO EXPLORE POTENTIAL EFFECTS OF EPIDURAL SPINAL CORD STIMULATION ON LEG MUSCLE STRENGTH IN PATIENTS WITH TYPE 3 OR TYPE 4 SPINAL MUSCULAR ATROPHY.

STUDY AIMS

Spinal cord stimulation (SCS) has shown remarkable efficacy in restoring motor function in people with spinal cord injury by recruiting afferent input to enhance the responsiveness of spared neural circuits to residual cortical inputs. This pilot will test if SCS can show evidence to improve motor deficits in people with type 3 or 4 spinal muscular atrophy (SMA). We will enroll up to six subjects with Type 3 or 4 SMA aged 16 or older that show quantifiable motor deficits of the legs but are able to stand independently. We will then implant the subjects with percutaneous, bilateral, linear spinal leads near the lumbar spinal cord for a period of up to 29 days. Although these leads are not optimized for motor function but rather for their clinically approved indication of treating pain, we believe they provide a safe technology enabling our team to perform scientific measurement necessary to evaluate potential for effects of SCS in motor paralysis with SMA. After the end of the study, the leads will be explanted. The results of this pilot study will be used to refine the design of follow-up trials that will test the safety and efficacy of the long-term use of a fully implantable system tailored to SMA Type 3 or 4 patients.

HYPOTHESIS

Hypothesis 1: SCS immediately improves hip muscle weakness in subjects with SMA

Hypothesis 2: SCS immediately improves motor control in subjects with SMA

Hypothesis 3: SCS delivered over the course of 29 days induces measurable changes in spinal circuits and motoneuron recruitment properties

OBJECTIVES

The main goal for this pilot study is to assess Hypothesis 1 as well as verifying safety of the SCS procedure in SMA. For this we will measure variables that indicate an immediate improvement in selected motor control variables that are predictive of the potential efficacy of SCS to improve motor control in long-term efficacy studies. If no improvement is shown in these selected variables, then a conclusion can be made that SCS will not be effective in improving motor control in people with SMA. Selection of these variable is based on previous pre-clinical and clinical studies of SCS for motor control and tailored to the specific population of subject included in this study (see inclusion criteria). Additionally, we will evaluate safety of electrical stimulation. Please note that in this context safety does not refer to the specific devices, but to the delivery of electrical stimulation to the spinal cord in SMA.
Specifically we will evaluate:

- Muscle weakness - isometric torque: measure the isometric torque produced by the subject at the hip during hip-flexion.

● Safety of electrical stimulation: classify and report all adverse events, if any.

Secondary Goals:
Secondary goes in this pilot study are aiming at acquiring scientific evidence of the mechanisms that may allow an improvement of motor performances in subjects with Type 3 or 4 SMA by testing Hypothesis 2 and 3.

Test hypothesis 2: Quantify motor control performances during SCS

We will quantify motor control variables and performances when enrolled subjects are using SCS. The goal is to acquire as much information as possible to inform the design of a follow-on, long-term study that will couple SCS to physical exercise if this pilot study is successful. All measured variables are focused on locomotion and leg-motor control.

Test hypothesis 3: Quantify variables indicative of early signs of neural plasticity occurring in the central nervous system.
The following variables aim at identifying early signs of plasticity occurring in the central nervous system that could be associated to measured effects on motor control. These measurements will be critical to verify that potential improvement in motor function correlate with electrophysiological variables and not only with exercise and/or placebo.

Neurostimulation is a successful clinical solution in the treatment of degenerative conditions such as Parkinson's disease(Deep-Brain Stimulation for Parkinson's Disease Study Group 2001). Coupled to pharmacological interventions, electrical stimulation of the basal ganglia ameliorates symptoms and decelerates progressive worsening(Bronstein et al. 2011). In contrast, application of neurostimulation to motor deficits in consequence of neurodegenerative motor syndromes such as Spinal Muscular Atrophy, Amyotrophic Lateral Sclerosis and Muscular Dystrophies has not been successful(Fehlings et al. 2002). Reasons for this mostly lie in the lack of clear neural targets for the neurostimulation to ameliorate sensorimotor functions.

Here we posit that neurostimulation of the primary sensory afferents in the spinal cord can ameliorate motor deficits and improve quality of life in degenerative motor syndromes

Success of SCS in traumatic motor syndromes: Electrical stimulation of the spinal cord (SCS) combined with physical training has shown remarkable results in the ability to restore motor abilities in people with complete and incomplete traumatic spinal cord injuries (SCI)(Angeli et al. 2014, 2018; Gill et al. 2018; Harkema et al. 2011a; Wagner et al. 2018). More importantly, long-term use of SCS led to unprecedented neurological improvements in patients with chronic spinal cord injury(Angeli et al. 2018; Wagner et al. 2018). Our group is currently running a clinical trial exploring the use of SCS to restore motor control in subjects with chronic stroke (IRB: 19090210). Studies in rodents showed evidence that plastic changes occur in the proximity of the lesion as well as in the supraspinal centers (Asboth et al. 2018; van den Brand et al. 2012). This re-adaptation of the sensorimotor network triggered by the combined action of neurostimulation and physical training optimizes the use of spared neural resources. The injured system reshapes existing connections to use SCS excitatory inputs for the production of movement. Key to this mechanism is the right target of stimulation (Capogrosso et al. 2013, 2018).

Identification of neural targets for motor control: In a series of studies combining computer models, animal studies and human studies, our group identified the large primary afferents in the dorsal roots of the cervical and lumbosacral spinal enlargements as the optimal neural target for SCS in sensori-motor applications (Barra et al. 2020; Capogrosso et al. 2013, 2016a, 2018; Greiner et al. 2021; Wagner et al. 2018). Electrodes in the epidural space artificially recruit primary dorsal root afferents and convey mono and poly-synaptic excitatory neural activity to the motoneurons(Formento et al. 2018; Moraud et al. 2016). Unlike other types of neurostimulation technologies, excitation of the motoneurons via these pre-synaptic sensory pathways allows a natural recruitment of the motoneurons thus producing fatigue-resistant large forces and reinforcing spinal circuit activity by augmenting feedback inputs.

Motor deficits in Spinal Muscular Atrophy: A variant in the survival motor neuron 1 (SMN1) gene results in progressive degeneration and death of the spinal motoneurons causing the clinical syndromes of spinal muscular atrophy (SMA)(Arnold et al. 2015). Type I SMA presents with a severe phenotype at or shortly after birth. The milder presentation of Type II and Type III SMA comprises progressive muscle weakness that impairs quality of life through the deleterious effects on motor skills such as standing and walking. Type II SMA results in premature death. Physical therapy and strength training are interventions that can preserve and improve strength, ameliorate motor deficits and delay muscle atrophy. However, similar to the experience with physical interventions for SCI, trials testing efficacy of physical therapy for SMA have shown low quality evidences of efficacy(Bartels et al. 2019). Surprisingly, no study has attempted to complement physical training by artificially sustaining muscle tone and neural circuit activity with neurostimulation. It is important to note that anatomical evidences show that mouse models of SMA demonstrate reduced synaptic connectivity between sensory afferents and motoneurons. While the reasons for these deficits are unclear, they demonstrate that SMA also affects spinal circuitry organization leading to severe motor deficits. Our technology directly targets primary afferents and reinforces precisely these disrupted connections. Therefore, SCS offers a tool to selectively and directly target the affected spinal circuit infrastructure that is responsible for the motor deficits in SMA.

Systematic literature analysis on SCS and SMA
We performed a systematic literature search on May 7th 2020 to search for clinical works exploring the use of Spinal Cord Stimulation (SCS) or Functional Electrical Stimulation (FES) in people with Spinal Muscular Atrophy (SMA). We searched the dabase PubMed for keywords without time span limits and looking for all references of which full text was available (Table 1).

Only 13 entries (excluding 1 duplicate) were found that contained the selected keywords. We then performed a weighting analysis of these 13 papers based on inspection of the abstracts to identify only those that concern human studies (no in vitro) and that explored the effects of electrical stimulation for therapeutic use. Only 3 papers passed the criteria none of which concerned the use of SCS.

Paper 1 (Fehlings et al. 2002)
Evaluation of therapeutic electrical stimulation to improve muscle strength and function in children with types II/III spinal muscular atrophy
This study tested whether low-intensity direct electrical stimulation of muscles delivered overnight would increase muscle mass and strength in children with Type II/III SMA. The authors recruited 13 subjects (of which 9 completed the study) of 9.9 yo average age. The study was a placebo-controlled, randomized prospective study. The authors evaluated upper arm muscle mass and strength over a period of 12 Months against placebo group. The therapy consisted in the delivery of low-intensity electrical stimulation overnight.

There was no statistical difference between the tested group and the placebo group in either strength or muscle mass, hence the authors concluded that muscle stimulation alone is not effective to improve the quality of life of children with SMA.

Paper 2 (Norton et al. 2013)
Preservation of motor evoked potentials under anesthesia in children with spinal muscular atrophy type II undergoing spinal deformity surgery.
This study does not concern directly the application of electrical stimulation to therapeutic treatment. However, it constitutes an important evidence of the survival of cortico-spinal excitability. The authors measured motor evoked potentials induced by transcranial electrical stimulation during neuromonitoring procedures for spine surgery in patients with svere paralysis in consequence of SMA. They showed that the aplitued of motor evoked potentials was comparable with control group, demonstrating that cortico-spinal tracts are intact in SMA. This is an important conclusion as spared cortico-spinal connectivity is critical to the efficacy of SCS.

Paper 3 (Gobbo et al. 2019)
Exercise Combined with Electrotherapy Enhances Motor Function in an Adolescent with Spinal Muscular Atrophy Type III
This is a single case study. The authors analyzed the combined effect of motor training and FES on an adolescent with type III SMA. As opposed to Fehlings 2002, FES in combination with training significantly improved both muscle mass and motor performances even increasing subject's independence in daily-like activities such as stair climbing. This anecdotical study shows that the combination of electrical stimulation with physical activity can improve motor performances in people with SMA.

Given the lack of works related to the use of SCS in SMA we included here a report of the latest clinical results that report on the use of SCS in humans with motor paralysis in consequence of spinal cord injury. The results of our own stroke study currently ongoing at the University of Pittsburgh are excluded as they are not yet published.

PRIOR ART OF SCS IN TRAUMATIC SPINAL CORD INJURIES
The efficacy of spinal cord stimulation (SCS) to improve motor deficits in people with SMA has never been tested (see document SCS-SMA-Literature). However, recent clinical studies showed unprecedented results in patients with complete and incomplete spinal cord injury (Angeli et al. 2014, 2018; Gill et al. 2018; Harkema et al. 2011b; Wagner et al. 2018). These studies reported that 100% of patients immediately regained the ability to produce voluntary muscle activity in previously fully paralyzed muscles immediately after surgical implantation of the leads. Then, after long-term rehabilitation protocol combined with SCS, patients improved their ability to stand, move and walk, with and without SCS

All studies achieved similar clinical outcomes albeit with different timings that can be attributable to the efficiency of parameter optimization and optimal stimulation protocols (Angeli/Wagner). However, in terms of clinical and scientific outcomes the results are remarkably consistent.
All studies reported on the efficacy of SCS as a prosthetic intervention to enable movements of previously paralyzed joints since day 1 after implant. Second, when subject initiated physical training focused on walking and standing, subjects progressively acquired abilities of increasing complexity. At week 1 the ability

to stand with SCS on was reported in all subjects, starting from the second week, studies started reporting on the ability of subject to walk or move the legs over while using a treadmill. And After 20 weeks of training, 5/8 subjects were able to walk overground with only minimal level of support. The three subjects that did not achieve this goal were classified as ASI A. More importantly, for the first time, partial regain of function was reported in subjects even when stimulation was OFF by the end of the trial. Specifically 4/8 subjects (AIS B and C) could now activate muscles that were previously completely paralyzed even without SCS. 2/8 subjects (AIS C) were instead capable of performing single joint movements and even standing without stimulation or support.

RATIONALE FOR STUDY DESIGN AND SUCCESS CRITERIA
Clinical data in SCI shows that SCS has 2 effects:
1 an immediate effect: increase in the ability of subjects to move limb joints and produce forces
2 a long -erm effect: when physical exercise is combined with SCS over several weeks, functional improvements in motor control are observed, with and without SCS.

Our pilot study will focus on demonstrating immediate effects. Given previous results in SCI if, immediate effects are shown also in people with SMA, then a follow up study involving long-term implantation of spinal cord stimulation devices combined with targeted rehabilitation has chances of success.
Alternatively, if these immediate effects are not observed in this pilot study, then chances that a rehabilitation protocol would work are limited.

In consequence the success criteria of this study are focused on the immediate effects:
Increase in strength with SCS-on

HYPOTHESES
Hypothesis 1: SCS immediately improves muscle weakness in subjects with SMA

Hypothesis 2: SCS immediately improves motor control in subjects with SMA

Hypothesis 3: SCS delivered over the course of 29 days induces measurable changes in spinal circuits and motoneuron recruitment properties

SUMMARY AND RATIONALE FOR THE USE OF SCS IN SMA

Rationale for Hypothesis 1 and 2: Immediate improvements of motor ability
The first and most important goal of SCS therapy for SMA is to be a supportive treatment to improve the quality of life of people with SMA by a large, significant, and immediate reduction of motor and respiratory deficits resulting from SMA. This is similar to DBS for Parkinson's Disease.

In order to achieve this goal, SCS must be able to show immediate improvement in motor performances. Albeit no study has assessed the efficacy of SCS for SMA, we do know that motor deficits in SMA result from a combination of motoneuron degeneration, progression of the disease, and finally secondary cascade effects created by immobilization or poor use of muscles (Arnold et al. 2015).

What is the evidence that SCS can enhance motor performance in individuals with severe motor deficits? Three groundbreaking clinical trials in Louisville (Angeli et al. 2018), the Mayo Clinic (Gill et al. 2018) and EPFL

in Switzerland (Wagner et al. 2018) independently demonstrated that SCS can immediately restore voluntary control of legs in people with complete paralysis as a result of damage to the spinal cord (i.e. spinal cord injury). When the stimulation is turned on, every patient tested could immediately control paralyzed legs and even walk over ground with some supportive device.

How does SCS work and why will it work in SMA?
We discovered that SCS engages motoneurons through the recruitment of primary sensory afferents (Capogrosso et al. 2013, 2016b, 2018). In turn, this conveys excitatory inputs to spared motoneurons increasing their sensitivity to spared cortico-spinal projections (Formento et al. 2018; Harkema et al. 2011b; Moraud et al. 2016). Therefore, SCS is a neuromodulation technology that artificially enhances the neural activity of surviving motoneurons by making them more sensitive to descending controls and sensory feedback. In SMA types II and III, part of the spinal motoneurons degenerate (Arnold et al. 2015), thus the brain is not able to excite enough muscle fibers, thereby leading to motor deficits and paralysis. This also affects involuntary activity such as respiration because spinal respiratory reflexes as well cannot excite enough spared motoneurons. However, different from in the setting of SCI, spinal interneurons and cortico-spinal pathways are fully preserved (Norton et al. 2013).
Therefore, SCS in SMA will artificially enhance the activity of spared motor units to artificially higher levels, thus increasing muscle strength and motor output (Capogrosso et al. 2016b; Lu et al. 2016). In parallel, fully preserved cortico-spinal connectivity in SMA will enable subjects to gain full control over hyperexcitable muscles. Indeed, we demonstrated that SCS even enhances motor output in completely intact monkeys (Capogrosso et al. 2016b) (Video 2). Moreover, compared to a non-specific excitatory drug, SCS will target only the sensory-motor circuits, and it can be continuously and daily tuned in intensity and even turned off (for example during sleep) to immediately reduce circuit excitability.

Rationale for Hypothesis 3: Long term effects
The third and equally important outcome is whether SCS will have any effect on the rate of degeneration of the disease. While there is no direct evidence that SCS can enhance the survival of motoneurons, certainly similar supportive therapies increase life span and long-term life quality in people with neurodegenerative disorders such as Parkinson's Disease. The key to success is the identification of the right target for the stimulation.

Our hypothesis is that in SMA, the spinal motoneurons are affected, hence neurostimulation should be directed at supporting residual motoneuron activity. This support must occur through engagement of input pathways that can increase the responsiveness and general excitability of the cell without driving it completely, thus enabling voluntary motor control.

Sensori-motor circuits in SMA and the target of SCS
We know that SMA affects the primary afferents-to-motoneuron connectivity, likely as the result of immobility (Mentis et al. 2011). Abnormal sensory-to-motoneuron synaptic activity further alters an already compromised system leading to faster degradation of motor abilities and other spontaneous functions (such as respiration) that rely on spinal reflexes. Since SCS directly targets this compromised system (Capogrosso et al. 2013), we have strong scientific support for the hypothesis that SCS will strengthen this compromised system, thereby resulting in long term improvements effects.

Combined neurostimulation and physical therapy in SMA
Additionally, anecdotical findings in SMA suggest that the use of Functional Electrical Stimulation

(FES)(which we know is less effective than SCS in sustain motor function) in combination with physical therapy enhanced motor abilities and independence in an adolescent with SMA type III (Gobbo et al. 2019). In patients with a Spinal Cord Injury, when SCS was combined with physical therapy, all treated patients not only regained immediately their motor control, but they showed long term neurological improvements that lead to increased motor abilities even when the stimulation was turned off!! (Angeli et al. 2018; Gill et al. 2018; Wagner et al. 2018).
Despite studies in rodents demonstrating a potential key role of spared descending inputs to explain these long-term recovery effects (Asboth et al. 2018; van den Brand et al. 2012; Takeoka et al. 2014), direct evidence in humans is still lacking. However, since patients with SMA have a full sparing of cortico-spinal connectivity (Norton et al. 2013), we can argue that similar long-terms effect should also occur in patient with SMA.

Therefore, the second goal of our pilot study is to quantify the long-term effects of the use of SCS in patients with SMA as well as studying why these may occur.

RESEARCH ACTIVITIES

Both patients with SMA and healthy volunteers will be enrolled in this study. Healthy volunteers will be considered a control group and will not complete all sections of the protocol. Activities documented below will reflect healthy volunteer participation.

DEVICES:
In this study we are proposing the quantification of potential effects on motor control of spinal cord stimulation in people with spinal muscular atrophy. All the following research activities are geared towards the acquisition of this pilot scientific evidence and they involve motor tests and recordings of muscles activity during the delivery of electrical stimulation to the lumbosacral spinal cord.

To stimulate the lumbosacral spinal cord we will utilize FDA-appoved percutaneous spinal cord stimulation leads that are indicated for use to treat syndromes of refractory pain. The percutaneous leads will be connected to external stimulators that are either FDA-approved for use in humans, or human-grade research stimulator with strict safety features.

Below we describe the devices chosen for this study. Annexed documents provide further descriptions of these devices and their FDA approvals.

Percutaneous Spinal Cord Electrodes:
We will use 2 to 4, octopolar Medtronic leads (see documents in annexes) temporarily implanted in the epidural space of the T12 to L2 spinal vertebra. These devices have an extensive history of use in humans with minimal adverse effects. During the study, two to four FDA-approved spinal cord stimulator leads (Medtronic Vectris Leads) will be placed in the lumbar epidural space of participants and steered laterally towards the dorsal spinal roots under fluoroscopic guidance. This approach is identical to the FDA-approved procedure in which these devices are placed in the epidural space for treatment of trunk, back and limb pain. As in that procedure, the device will be tunneled percutaneously through the skin and secured in place with

tape. Therefore, in this trial we will implant the electrodes in the same region of their clinical indication and we will also externalize them for a maximum duration of 29 days. Which is also consistent with clinical practice. Surgical procedures are described below in specific paragraphs.

External stimulators:
During research activities the leads will be connected to an external stimulator. The Natus Medical Protektor32 IOM is FDA-approved under 510k Number K093304 (attached). This stimulator is commonly used for intra-operative neurostimulation and monitoring during neurological and neurosurgery procedures involving the recording of multiple neurophysiological signals as well as the delivery of electrical stimulation to the central nervous system.
Alternatively, the stimulation will be delivered through the Digitimer DS8.
The DS8 is an external isolated stimulator system for human research use. The DS8 is not a medical device but its safety specifications comply to standard for clinical devices utilized for transcutaneous electrical stimulation of human peripheral nerves. The device is non-invasive, non-toxic, and interaction with other componentry is unlikely and therefore it is rare to harm a patient. It is not intended as an implant nor does it present a potential for serious risk to the health, safety, or welfare of a subject. It is not purported or represented to be for use supporting or sustaining human life. It is not potentially for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health.

During the study, we will use the Syde device from Sysnav which records high precision motion data and has been previously used in clinical trials. The side device consist in an elastic ankle band similar to a modern "Apple Watch" device that can be wore at the ankle. We will use this data to assess changes in gait quality during the study. Participants will wear two devices, one in each ankle, during the entire day. To pre-process data, the Syde sends fully anonymized, encrypted raw kinematic data to the Sysnav data center via web transfer for preprocessing purposes after which it will be sent back to us for analysis. No identifiable information is included in these data transfers, and Sysnav will not have access to any patient information. The data will be transferred encrypted using https with protocol TLS 1.2. At night, participants will charge the devices in a charging station. If participants have access to internet connection, data collected during the day will be sent to Sysnav from the charging station. Otherwise, we will send the data weekly or at the end of the experimental sessions. There is no risk associated with the device, as only raw data is transmitted and analyzed.

In all sessions with spinal cord stimulation, the participant and the Syde device wearable monitors on the ankles are isolated from the stimulation. The participant and Syde device are isolated from the stimulator and electrical circuitry so that the stimulation is isolated to the leads to the implanted electrode array and back to the stimulator machine [termed: uninterrupted circuit].

For the research activities that do not require the synchronization of the stimulation with other variables, we will use the external wireless stimulator of the Intellis system from Medtronic. The Medtronic external trial stimulator is an FDA-approved medical device (PMA: P840001/S344) and routinely used for the stimulation of the same leads we use in this study via the same type of percutaneous connections and with the same parameters. Since this stimulator is wireless, it is more comfortable and convenient for patients when performing certain motor tasks such as locomotion.

STIMULATION PARAMETERS:
FDA approved parameters for the Medtronic stimulation electrodes for use in humans are:
Stimulation amplitude for each pulse should be lower than 25.5 mA
Pulse frequency should be lower than 1200 Hz
Pulse width should be comprised between 60 and 1200 μs
These parameters can be found in the Medtronic stimulation IFUs in the annexed

In our protocol we will never exceed the following ranges
Stimulation amplitudes will be comprised between 0.2 and 10 mA
Stimulation frequency will be comprised between 0.1 and 500 Hz
Pulse width will be comprised between 100 and 400 μs

Therefore, our stimulation parameter ranges are well within the FDA approved stimulation limits for the electrodes used and in no case will exceed the clinically approved maximum values for any of the three parameters. To ensure this condition we defined standard operating procedures that are summarized in the stimulation system checklist and stimulation reporting protocols attached in the annexes. These documents were reviewed and approved by the DSMB for the STUDY19090210: sIRB SCS for Stroke

Below we describe all the research activities that we will perform as part of this protocol:

-SCREENING (after consent, prior to surgical procedures):
Once written informed consent is obtained, the subject is enrolled in the study and is assigned a unique subject ID. A physician-investigator/sub-investigator will verify the eligibility of the subject by assessing most of the eligibility criteria after consent via self- report. This will be documented on an "Eligibility Checklist" form, included in this protocol.
After informed consent and after the participant's verbal self-report of eligibility criteria, an in person clinical evaluation will be performed, including a detailed history and physical examination, and a detailed musculoskeletal and neurologic examination. A history form will be completed to detail the dynamic and onset of their SMA. The The Physical Activity Disability Survey (PADS) will be administered. The Revised Hammersmith Functional Scale (RHS) and the 6 Minute Walk test will be performed as well as an evaluation of the ability of the subject to stand independently for at least 3 seconds. Moreover, also the other primary and secondary outcomes will be evaluated. Additional medical records may be accessed if more information is required to perform pre-operative planning and review pertinent medical history, allergies, medications and radiology images. Both healthy volunteers and individuals with SMA will be required to successfully complete screening procedures. Pre-surgical procedures and device placement for participants with SMA will occur within 6 months after the subject undergoes screening procedures. We will work with each individual to determine the optimal testing schedule. The schedule will be designed to meet study goals, and complete specific study tasks which will change over the duration of the study. The participants' engagement, and training preferences will also be considered in this process. We will photograph or videotape portions of the experimental session. Appropriate UPMC permission will be obtained as needed for any photographs or videotaping of participants. For participants who will need to travel a significant distance, any screening procedures that can be done prior to any travel will be done to decrease burden placed upon the participants who may not be eligible. Experimental procedures are described below.

-MRI screening:

All individuals with SMA, and some healthy participants, will be required to undergo MRI. Prior to undergoing an MRI for this study, a person will be asked about any implanted metal in their body and will undergo a MRI safety screening. We have attached a 3 page screen at the end of this. The screen covers items that would possible exclude a participant from the study. This screen has been used in previous MRI studies. The completed MRI screens will be kept in a locked file cabinet which will be located in a locked office to assure subject confidentiality.

- Demographic and Medical History Questionnaire:
The subject will be asked to provide basic demographic information (age, weight, height, etc.) via self-report. We will also ask questions about their medical history and their current level of motor and sensory abilities, as well as recent history. We will also ask questions related to improvement of quality of life. A complete copy of the questionnaire is included. Both healthy volunteers and individuals with SMA will be required to successfully complete demographic and medical history questionnaires.

- Pre-operative labs and screening:
We will obtain pre-operative complete blood count with differential, prothrombin time and international normalized ratio (PT/INR), and partial thromboplastin time (PTT) within two weeks prior to the device placement procedure. Pre-operative screening may also include a MRSA test, electrocardiogram, x-rays, and/or additional labs and tests as required by the neurosurgery team to determine safety of the surgical procedure. These preoperative procedures will apply to participants with SMA only.

-Pre-operative high-resolution MRIs:
We will perform a pre-operative MRI of the spine without contrast, to generate a high resolution scan of the spinal cord and spinal roots in patients with SMA. This MRI will be performed at the Magnetic Resonance Research Center at UPMC Presby or at the BRIDGE Center. We may use a neck brace during this MRI to ensure the subject's neck is in a similar position for both scans.
We will additionally perform high-resolution structural images of the brain. Specifically, we will acquire: high-resolution T1 weighted images, high-resolution T2 weighted images and Diffusion Tensor Imaging (DTI). The same brain images will be acquired also at the end of the study to document possible structural changes in fiber tracts that might correlate with brain plasticity and motor recovery.
Finally, we will perform a spinal cord functional Magnetic Resonance at rest and during muscles contractions. The same images will be acquired also at the end of the study to document possible changes in functional connectivity of the brain and spinal cord that might correlate with plasticity and motor recovery.
The total duration of the MRI session should not exceed the 2 hours.

-Passive Mobilization and Tendon Vibration:
Subjects will be asked to perform a task in the MRI scanner. Muscle spindle afferents from specific leg muscles will be recruited by stretching the muscles in which they are embedded (the limb is mobilized by a physiotherapist, aided with audio cues), and in separate runs by applying muscle tendon vibration using MR-compatible pneumatic vibrators (synchronized with MRI triggers). We will target the gastrocnemius medialis/ soleus, tibialis anterior, quadriceps, iliopsoas, gluteus and
biceps femoris muscles of only the right leg. Two runs are required for each pair of agonist/antagonist muscles per joint per muscle recruitment method. In each run, passive mobilization or tendon vibration, the flexor muscle and the extensor muscle are alternatively activated in blocks of 15 seconds followed by a block of rest for 10 to 15 seconds with a run lasting 7 minutes in total. To avoid any bias, the order of the runs are

randomized. Both healthy participants completing the MRI and those with SMA will be completing this activity. These activities will be done pre-implantation and post-explantation. Several scans may be repeated post-explant at the investigator's discretion for participants with SMA.

-MRI Scan for Characterization of Brain and Spinal Networks:
SMA and healthy subjects without contraindications for MRI may undergo MRI, at PI discretion, depending on the number of subject MRIs needed for a complete dataset. Depending on facility and subject availability, the MRI scan will take place at the Magnetic Resonance Research Center, which is part of the University of Pittsburgh, main campus, and is located on the 8th floor of UPMC Presbyterian Hospital, or the CMU-Pitt BRIDGE Center, located at Carnegie Mellon University. MRI data will be acquired in a 3T Prisma System (Siemens, Erlangen, Germany). A 64-channel coil will be used with a head stabilizer to limit head motion. For spine scans we will use a spine coil. We will acquire the following sequences:
- T1-weighted structural scan of the brain
- T2-weighted structural scan of the lower thoracic/lumbar area of the spinal cord
- DWI scan of the brain
- Functional MRI of the brain and of the lower thoracic/lumbar area of the spinal cord both at rest and while performing the same runs described in the “Passive mobilization and tendon vibration session”.
T1-weighted structural scan of the brain will be used to pre-process the fMRI data and the DWI data.
T2- structural scan of the spinal cord will be used to pre-process the fMRI data.
We will extract resting-state and task networks of the brain and of the spinal cord for patients and healthy subjects separately. We will compare the spatial and temporal organization of these networks between the two population groups. This type of analysis will allow to understand whether there are measurable changes in spinal circuits and motoneuron recruitment properties induced by SCS. This MRI will take approximately 3 hours to complete and will occur during a separate visit than other testing. This 3 hours can be split over two sessions if the 3 hours is too long to complete in one session for the patient. These activities will occur pre-implantation and post-explantation. Post-explant fMRIs may be repeated multiple times at the investigator's discretion.

-Measurements of active proprioception capacity:
Since SCS recruits proprioceptive afferents in the dorsal roots, it is important to assess the ability of each subjects to consciously and unconsciously process proprioceptive feedback. We (Dr. Pirondini) will assess subject’s capacity by performing leg movement assessments in the Humac Norm system at baseline, during the 29 day trial and follow up visits. The HUMAC NORM system is a clinical system used to assess isokinetic, isotonic and isometric joint movements and torques in patients. The participant will be seated in a chair with their legs supported by specific braces that are different for each of the tested joints (e.g. hip, knee, ankle). The participant will be asked to actively perform isometric movements as well as isokinetic and passive movements with and without visual aid to reach a specific target of force. This will allow us to measure the ability of a subject to assess the level of force applied at a joint or movement and velocities. Surface EMG from the main leg muscles will be recorded. We will assess the capacity of the subjects to assess limb position and joint movements. We will also assess subject’s capacity by performing arm movement assessments in the KINARM system (Kinarm, Kingston, ON, Canada) at baseline and follow up visits. The KINARM is a human research intended system used to evaluate motor performances in subjects with stroke. The participant will be seated in a chair with their arms supported against gravity. The participant will be asked to actively perform isotonic elbow extension and flexion, e.g. movements, against an opposing constant force of 0%, 10%, 20%, and 30% of the maximum voluntary surface electromyogram (EMG). Surface EMG from the main arm muscles will be recorded. Throughout the experiment the participant’s arm and hand

will be occluded from vision with a protective screen built in in the KINARM system. We will assess the capacity of the subjects to assess limb position and joint movement. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will be asked to perform these activities.

-Single Joint movement and torques:
To quantify the range of motion of leg joints and the joint torques produced with and without SCS we will use the clinical isokinetic testing system: HUMAC NORM by CSMi. This data may be captured at baseline, during the 29 days of the implantation period, and at the follow up visit. Both healthy subjects and participants with SMA will be asked to perform these activities.

-Pre-operative antibiotics:
We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. For example, antibiotic prophylaxis administration is usually initiated for the patient approximately 1 hour before the surgery and will be maintained as directed by the study physiatrist and their clinical team. Thirty minutes prior to the procedure, the patient will be given dose appropriate cefazolin (1-2g; IV), or vancomycin (1g; IV) if there is an allergy to cefazolin (anaphylaxis or airway swelling). We have excluded pregnant females and those with renal failure as they may be at an increased risk for complications resulting from administration of the antibiotics. Complications or side effects usually result from prolonged dosing, rather than the single dosing that will be administered in this study. Antibiotic ointment and sterile dressings will be applied to the implantation site to minimize the risk of infection. Standard sterile surgical techniques will be followed for this study. These procedures will greatly minimize the risk of infection. This activity applies to participants with SMA only.

- Pre-operative Sedation:
The subject will see an anesthesiologist for the eventual administration of very minimal procedural sedation. Traditionally, very small doses of Fentanyl and Versed will be administered intravenously. Please note that this may vary based on the anesthesiologist's clinical judgement. This activity applies to participants with SMA only.

- Intraoperative lead placement protocol:
Between two and four percutaneous linear leads will be placed in the lumbosacral epidural space near the spinal nerve roots (Medtronic Leads). Clinical practice commonly includes placement of either a single paddle lead or alternatively multiple cylindrical linear leads into the epidural space of the lumbar spine. All leads will be placed in the lumbar epidural space by Dr. Peter C. Gerszten in the operating rooms at UPMC Presbyterian Hospital. The procedure will be performed as described below. However, based on the surgeon’s professional judgement, he may make slight modifications to the surgical procedure in order to improve targeting and outcomes.
Preferentially, the subject will be awake throughout the procedure, and 1% preservative-free lidocaine will be used for local anesthesia but according to surgeon evaluation and medical records of the subjects the subjects may be fully anesthetized. The subject will be taken to the operating room and placed in a prone position with a pillow under the abdomen to decrease the normal lumbar lordosis. Each staff member involved in the procedure will sterilely scrub in with sterile gowns and gloves using standard surgical technique. The skin overlying the lumbar area will be prepped and draped in aseptic fashion with either Hibiclens or betadine solution. 1% lidocaine on a 22-gauge 3.5 inch spinal needle will be used in the skin and subcutaneous tissue for local anesthesia.

Percutaneous sterile needles or surface electrodes will be acutely placed on the principal leg muscles bilaterally. These will include: iliopsoas, rectus femoris, semitendinosus muscles, gastrocnemius medals, soleus and tibialis anterior. However, they may include other muscles of the leg and back if necessary. EMG leads will be connected to a standard clinical electrophysiology monitoring system. This monitoring is part of routine clinical practice as performed at UPMC Presbyterian Hospital (Protektor32).
A small incision will be performed on the skin and for each of the spinal leads, a 14 gauge epidural Tuohy needle will be advanced through the L1-L2 space or a nearby intervertebral space to the epidural space via loss-of-resistance technique. Needle location will be confirmed in anteroposterior (AP), lateral, and contralateral oblique fluoroscopy views. An 8 contacts stimulator lead (Medtronic see device section), which is designed to span 2-3 spinal segments, will then be advanced into the T11-L1 posterior epidural space and steered laterally using the accompanying stylet under live fluoroscopic guidance in the AP, lateral, and contralateral oblique fluoroscopy views. The lead may be connected to an additional extension lead that is included in the approved epidural stimulation system (under PMA P030017). The external portion of the lead will be connected to one an external electrophysiology monitoring machine. The machine, which is routinely used during clinical practice at UPMC is the Natus Medical Protektor32, which is an FDA approved neurological programmable intra-operative monitoring system able to deliver up to 16 channels of neural stimulation, and up to 32 channels of continuous monitoring including EEG and EMG signals. Connection to the Protektor32 will be performed using clinical connecting systems provided by Ad-Tech Medical Instrument Corporation, as also routinely used during clinical neuromonitoring and neurostimulation procedures (see Document Lead Connectors Example).
We will then iteratively stimulate at frequencies of 1, 2, 5, 10 or 20 Hz, pulsewidth of 200 or 400 μs, and current amplitudes between 100μA and 7 mA. These are common stimulation parameters normally used in similar mapping procedures and fully within the FDA-approved stimulation parameters range for spinal cord stimulation leads (currents up to 20 mA, frequencies up to 500Hz, puslewidth up to 2 ms).
The lead placement will be iteratively adjusted based on EMG recorded responses until evoked EMG responses occur in the hip as well as ankle muscles. The stylet will then be removed under live fluoroscopic guidance to ensure the lead does not move. The procedure will be repeated for the other side and other leg. Leads are then secured to the fascia overlying the L2-L3 spinous processes using lead anchors (supplied within lead placement kit) and 2x2-0 silk sutures (FIGURE 1). A subdermal pocket lateral to the insertion and anchoring site is created, and the strain-relief loop is placed within the said pocket. The incision will be closed with interrupted sutures. The leads may be connected to an additional extension lead that is included in the approved epidural stimulation system (under PMA P030017).The entire procedure is expected to take approximately two hours.
According to the clinical judgement of the neurosurgeon and anesthesiologist present during the implantation procedure, general anesthesia may be used instead of local. After the procedure, the subject will be kept for up to 23 hours in the hospital to minimize the infection risk. This activity applies to participants with SMA only.

-Post-operative antibiotics:
We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. Cefazolin will be given every 8 hours for 24 hours. Patients are sometimes treated with antibiotics for the duration of the time that the leads are implanted. These procedures should greatly minimize the risk of infection. This activity applies to participants with SMA only.

POST IMPLANT PROCEDURES
Immediately following lead placement and up to 5 times a week for the following 29 days, the following

experimental procedures will be performed. Each testing session will be limited to no more than 8 hours and will include breaks. Meals will also be provided to the subjects. Stimulation is performed with external stimulator (with the devices described in this protocol) using clinically approved interconnects. In normal clinical practice when the trial period is over the surgeon decide whether to implant the "battery or implantable stimulator" or to remove the lead. In our case we will remove the leads as per protocol. This is entirely identical to our other IRB protocol in STUDY1909021 and the studies STUDY19100220 and STUDY19100220 that use similar devices. Consistently with those protocols, the access point is monitored and cleaned weekly by Dr. Gerszten and his team. For the duration of the study the leads come out of the skin from the back about 10 to 20 cm away from the main incision point on the left or right side. For all procedures described below, stimulation parameters (pulsewidth, frequency and amplitude) will never exceed the FDA-approved parameter ranges for the spinal leads utilized in this protocol. This activity applies to participants with SMA only.

- Electrophysiology testing with spinal cord stimulation:
We will conduct a series of electrophysiology tests to establish the relationship between epidural spinal cord stimulation and motor responses in participants with SMA. All experiments will occur either in a patient examination room at UPMC Presbyterian, or in the testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh. During these tests the patients will be resting laying down on a bed or sitting in a relaxed position, and they will be asked to be as still as possible during the delivery of stimulation in order to make sure that recorded muscle activity is only coming from the stimulation.
During electrophysiological stimulation trials, superficial EMG electrodes and gyroscopes to measure limb movements will be placed on the legs, the external digitimer stimulator will be connected to the SCS lead using interconnects that are used during routine clinical procedures to connect spinal and brain leads to an electrical stimulator with standard clinical connections (TouchProof).
EMG responses and joint kinematics will be recorded in response to stimulation trains and the subject will be asked to respond to a set of standard psychophysical questions to assess possible levels of discomfort, as well as to provide any additional comments. In order to ensure quality signals are recorded, as well as to decrease any discomfort when removing the electrodes, some leg hair may be shaved. All precautions to avoid irritation/any cuts will be taken.
Stimulus parameters to vary include:
• Pulse amplitude (maximum of 10 mA per electrode)
• Pulse width (maximum of 400 us;)
• Pulse frequency (maximum of 500 pulses per second;)
• Spatial effects: groups of electrodes will be stimulated simultaneously to investigate the effects of spatial summation
• Temporal effects: the pattern of stimulus pulses will be varied to model naturally occurring neural patterns (e.g. muscle spindle changes to muscle stretches) or engineering patterns (e.g. sinusoidal modulation)
In clinical practice, these devices are typically used throughout the day, with the exception of while driving or sleeping. As such, we do not expect that we will need to impose any upper limits on the total duration of stimulation applied throughout any experimental session or the entire study. As subjects will not be provided with a take-home stimulator, there is no risk that subjects will drive or sleep during stimulation.
Participants may be asked to compare two or more successive stimulus trains and describe or compare the effects of stimulation. Examples of the kinds of comparisons that participants may be asked to make include:
• Was the stimulus 1 more comfortable than stimulus 2?
• Did stimulus 2 feel stronger or weaker than stimulus 1?

• Which of stimuli 1, 2, or 3 felt like it came from the foot?
• Did you prefer stimulus 1, 2, or 3 in terms of ability to move your limb?
These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation.

- Initial Stimulation Parameters:
When stimulation commences on an electrode that has not been previously used, stimulation parameters will be set conservatively in order to minimize the chance for eliciting an undesired response. Stimulation frequency will be set to 0.5 to 2 Hz maximum and pulse amplitude will be slowly increased until muscle responses are recorded. The patient will be continuously asked whether the stimulation is comfortable and amplitude increase will be limited to what the patient deems a comfortable range. If the patients think that a specific amplitude is uncomfortable we will immediately stop and limit the amplitude to comfortable level boundaries. Stimulation frequency will then be adjusted for the amplitude that elicits the most effective motor responses. Frequency will be increased starting from 10Hz and verifying that the sensation is comfortable at all time similarly to amplitude parameter search. These activities apply to participants with SMA after their implantation only.

- X-Ray to Document Lead Migration:
Every other week for a maximum of 2 X-ray sessions during the 4 weeks of the study, four total X-ray images (AP and lateral views) of the lumbar and thoracic spine will be captured to document the location of the leads and any movement that may have occurred. We will attempt to correlate movement of the electrodes with any documented changes in stimulation thresholds or the types of sensory percepts that are evoked by stimulation. These activities apply to participants with SMA only.

-Single Joint movement and torques:
To quantify the range of motion of leg joints and the joint torques produced with and without SCS we will use the clinical isokinetic testing system: HUMAC NORM by CSMi. This data may be captured at baseline, during the 29 days of the implantation period, and at the follow up visit. Both healthy subjects and participants with SMA will be asked to perform these activities.

- EEG, EMG and transcutaneous muscle stimulation studies:
Non-invasive electroencephalography (EEG), electromyography (EMG) and transcutaneous muscle stimulation may be used during the study (pre and post implant) to measure neural and muscular responses to electrical stimulation in participants with SMA. For EEG studies, electrodes will be placed on the surface of the scalp and, for EMG studies, electrodes will be placed on the surface of the skin on both the affected and contralateral limbs. Stimulation will be applied as described above. For Transcutaneous muscle stimulation studies, electrodes will be placed on the surface of the skin of the leg of the affected limb and electrical stimulation to stimulate hip and leg muscles will be delivered via Digitimer Stimulator. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in EEG and EMG activities.

- TMS measurements:
Non-invasive transcranial magnetic stimulation (TMS) of the motor cortex may be used during the study (pre and post implant) to assess the residual motoneuronal function of each participant and the interaction between corticospinal axons and spinal cord stimulation. Subjects will be positioned in the HUMAC NORM machine configured for the leg joint to be examined. The robot will then execute passive single joint

movements spanning flexion/extension of the joint within a range of motion that will be adjusted to each subject according to specific biomechanics and comfort. The speed of movement will be set to slow rates (less or equal 0.5 Hz) that are comfortable for each subject. During movement TMS will be delivered by random and infrequent (<0.2 Hz) triggering so that pulses will occur at multiple joint-angles and evoked potentials in the leg and feet muscles will be measured. This will allow us to have a joint-angle dependent analysis of motor evoked potentials (MEP). This experiment will be performed prior to implant, during the course of spinal cord stimulation through the implant, and after explantation.
During the period during which a participant is implanted, TMS will be delivered using the same method but while SCS is simultaneously delivered using parameters from the behavioral experimental sessions (see below). This will allow us to study the interaction between cortico-spinal inputs and SCS to test the hypothesis that SCS increases spinal responses to cortico-spinal neurons, thus enhancing voluntary motor control. We expect to see higher peak-to-peak MEP in legs and feet muscles and higher torques in the HUMANC NORM when TMS is delivered in conjunction with SCS.
During this experiment, TMS intensity will be adjusted from initial low values (e.g. 10% maximum output) and progressively increased until MEP threshold is found, in case the threshold is lowered by SCS and to avoid potential side effects of simultaneous stimulation. Paired TMS and peripheral stimulation is a commonly used procedure to study cortico-spinal excitability (see for example Sunday, Urbin and Perez, Brain Stimulation, 2018). Here we will use an established experimental protocol to pair TMS with SCS which recruits sensory afferents from the posterior roots. Both healthy subjects and participants with SMA will partake in TMS activities.

- Sit to stand transitions and standing:
Periodically throughout the experimental sessions, we will ask each subject to stand up from a sitting position. During these trials SCS will be provided to verify its effects on motor task execution. Under constant supervision of Physical/Occupational Therapist, the subjects will attempt to stand from sitting position and hold the standing position for as long as they can while they are receiving SCS or in control trials without stimulation. EMGs of the legs will be recorded during these tests. Subjects will utilize standing supports and walkers to ensure safety and stabilization. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in these activities.

-Overground locomotion:
Periodically throughout the experimental sessions, we will ask each subject to walk a few steps over multiple occasions while kinematic and EMG data from their leg is recorded. During these trials SCS will be provided to verify its effects on motor task execution. Under constant supervision of a Physical/Occupational Therapist, the subjects will walk at their preferred pace while they are receiving SCS or in control trials without stimulation. We will utilize special extension cables to enable sufficient cable slack for the subject to execute a few steps. In the case that subjects cannot safely move according to judgment of the study PT, we will use a walking aide or remove the activity to ensure the safety of all subjects involved. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in overground locomotion activities.

-Treadmill locomotion:

Periodically throughout the experimental sessions, we will ask each subject to walk on the AlterG Via, an antigravity treadmill, for as long as they can. The antigravity treadmill is a piece of rehabilitation equipment that uses air pressure to offset a percentage of body weight, relieving the user of some physical burden. Under the constant supervision of the study PT, we will adjust the percentage of body weight such that subjects can safely walk on the treadmill. During these trials SCS will be provided to verify its effects on motor task execution. Under constant supervision of a Physical/Occupational Therapist, the subjects will walk at their preferred belt-speed while they are receiving SCS or in control trials without stimulation. Superficial EMG electrodes and gyroscopes to measure limb movements will be placed on the legs, and external stimulators will be connected to the SCS lead. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in treadmill locomotion activities.

-Balance testing:
Study participants will stand on a platform that can impart translational and rotational perturbations at the feet, and key elements of sensory feedback (e.g. visual feedback, ankle proprioception) will be manipulated. By providing sensory feedback that is either unreliable or incongruent with the actual perturbation, the test provides a method for isolating the influence of somatosensory, visual, and vestibular inputs on balance. We will test whether SCS improves balance and proprioception of subjects with SMA. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in balance testing activities.

-Recumbent bike:
Periodically during the experimental session, we will ask participants to ride a Motomed recumbent bike for as long as they can while they are seated in a chair. During these trials SCS will be provided to verify its effects on motor task execution. Under constant supervision of a Physical/Occupational Therapist, subjects will ride at their preferred speed and resistance while they are receiving SCS or in control trials without stimulation. We will measure any possible torque asymmetries between legs, the time, distance and velocity that they are able to ride and the superficial EMG electrode. We will test whether SCS improves motor deficits of subjects with SMA. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh. These exercises may be done pre-implantation, during implantation, and in the follow-up phase of trial participation. Both healthy subjects and participants with SMA will partake in recumbent bike activities.

-Stimulation parameters during sit-to-stand, overground and treadmill locomotions and balance test:
Bursts of stimulation or continuous stimulation will be delivered through the SCS leads. Bursts will occur at various moments during the execution of attempted movement in order to study effects of different stimulation patterns on movement execution. Stimulation parameters will be restricted to those found to be more selective from the previously described procedures. Electrical stimulation will be either controlled manually by triggering pre-determined bursts or automatically. Automatic control will be based on residual EMG activity from leg muscles or gyroscopes as input signals. An attempted movement will trigger pre-defined stimulation patterns. Stimulation patterns might be also delivered in pattern for each movement phase by segmenting the movement in different parts such as swing and stance. Finally closed loop control of stimulation using kinematic or EMG inputs might be implemented to control force. This applies to SMA patients after implantation only, and will only be done during their 29 day testing period.

- Electrode Impedance:
Periodically during the experimental session, we may measure the impedance of the SCS leads as a means to ensure that the device is functioning properly. This functionality is included in the Protektor32 system.

- Removal of SCS Leads:
After completion of testing and no later than 29 days after device placement, the SCS leads will be removed at UPMC Presbyterian. To remove these devices, we will follow a similar procedure to the implant to minimize infections risks. In the operative room the subject will be positioned prone on the operating table, and using sterile technique, the lead will be gently pulled until it is removed after removing sutures. Similarly to the implant procedures, EMGs signals in response to test stimuli will be recorded for post-study controls. Visual inspection of the leads will confirm that they are intact and that no portion of the device remains under the skin. The skin will be sutured, cleaned with Hibiclens or betadine and dried with sterile 4x4 gauze dressings, and a sterile bandage will be placed on the site. A follow-up telephone call will be made to the patient within 48 hours of their discharge to make sure they are asymptomatic. A follow-up visit for suture removal will occur within 2 weeks after electrode removal.

-Replacement of Electrodes:
If, during the experiment, the electrodes move away from the target nerves, it may be necessary to remove the electrodes before the end of the 29-day
period. If deemed appropriate by study staff, participants may undergo the electrode placement procedure one additional time, followed by an additional 29-day testing period. In this case, we may repeat any of the screening and experimental procedures described above.

-Mid-study, post-study and follow up outcome measurements:
Primary outcomes related to muscle strength will be assessed pre-study, at week 2, week 4 and post-study follow up (at least 4 weeks after completion) safety will be assessed throughout the study.
Secondary outcomes will be assessed as follows:
1. MRI Imaging: will be assessed pre-study and post-study
2. Electrophysiology will be assessed, pre-study, throughout the study, and post-study
3. Pain will be assessed throughout the study
4. Motor function clinical scales will be assessed pre-study, at week 4 and post-study follow up

Prior to any procedure that may potentially involve risk to an unborn child, we will ask females of child-bearing potential to undergo a urine pregnancy test.

Subjects may be be video recorded or photographed during any of the experimental procedures for research or educational purposes. The study team will track subjects' choices for PHOTOGRAPH / VIDEO at the time of consent and follow subjects' choices on disposition of samples after use for this study in a document with appropriate confidentiality protections. The PI will oversee this process.

STATISTICAL ANALYSIS

This is a pilot proof of concept study. Because this is a pilot study, we feel that it is appropriate to begin with a small sample size in this initial investigation. Up to six participants will be enrolled in this proof-of-concept study. This pilot study is descriptive in nature and no formal statistical comparisons will be performed among groups instead, all data will be analyzed for all participants.

The study is considered successful if 70% of enrolled subjects (e.g. rounded at 4/6) achieve success criteria in primary outcomes