Study Title: Spinal Epidural Electrode Array to Facilitate Standing and Stepping after Spinal Cord Injury

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Final protocol

A. Background, including a brief literature review:

Spinal cord epidural stimulation (SCES) has been applied alone in a number of individuals with clinically complete spinal cord injury (SCI), showing that some alternating stepping-like actions can be induced [1]. SCES has been used in combination with repetitive stepping on a treadmill for facilitation of walking-like movements after an incomplete lesion in two individuals showing stepping could be sustained for a longer period of time with less effort in the presence of SCES [2]. This report provides promising results of a combination of locomotor training and SCES. In contrast to our presently proposed studies on clinically complete SCI research participants, the previously reported studies included patients with incomplete injuries who already had some stepping ability before treatment [3]. Several recent findings suggest that a combination of SCES and locomotor training in individuals with clinically complete SCI could be very successful for the recovery of standing and walking. Locomotor-like patterns can be facilitated by SCES in complete spinally transected rats [4], cats [5], and humans with clinically complete SCI [6]. However, the long-term functional changes that occur in the spinal cord after clinically complete SCI have not been comprehensively examined, and it is likely to require more complex and adaptive stimulation protocols in order to achieve optimal results. A key to successful broad application of SCES to the majority of individuals with chronic SCI and other neurological disorders including multiple sclerosis, brain injury, stroke, and Parkinson's disease may be a functionally-adaptive site-specific stimulation. However, this capability will require a more advanced multi-electrode array technique which we are currently developing in preparation for the second phase of our long-term plans. The current proposal is a pilot study including 10 research participants with clinically complete SCI who will undergo epidural electrode implantation for spinal cord stimulation and locomotor training to improve standing and stepping with the combination of epidural stimulation and locomotor training; and to provide critical information for the development of more advanced electrodes.

There is substantial evidence that the mammalian spinal cord utilizes autonomous oscillating interneuronal circuits (central pattern generators, CPG) that respond to afferent input to generate locomotion [7-16]. The importance of afferent input in modulating and maintaining these neural locomotor patterns has been abundantly documented, and a completely spinal cord transected animal can relearn to hindlimb step and stand with task specific training that uses the critical sensory cues needed for each task [17-25]. Further, a myriad of reflexes are modulated in amplitude and even reversed by afferent input during different phases of the stepping cycle and CPG networks modulate these reflex pathways during locomotion [16, 26-42]. The human spinal networks use the sensory input during stepping to generate functionally relevant efferent output and, after minutes of manual assistance, can generate a series of independent steps. Also, brief standing with full weight bearing can be executed after weeks of stand training, again without SCES [43]. However, the independence of standing and stepping is not sustainable to allow a transition to walking overground [44].

We propose that daily locomotor training in the presence of SCES will enable the individual with clinically complete SCI to stand and step independently while bearing full weight. Non-patterned electrical stimulation of the lumbar spinal cord can induce patterned, locomotor-like activity in individuals with clinically complete SCI [1]. Modifying the frequency of stimulation can induce extensor patterns similar to that observed during standing [45]. In addition, when afferent information is also provided there is further modulation of these motor patterns elicited by epidural stimulation [46]. Individuals with a clinically complete spinal cord injury can execute independent steps using a body weight support system on a treadmill (BWST) using manual assistance without epidural stimulation. When combined with SCES, we anticipate the training will be even more successful, enabling prolonged periods of independent stepping and standing. Although there will not be a separate control group studied simultaneously, historical controls will consist of the best stepping and standing performance that have been observed previously in our laboratory in individuals that have a clinically complete SCI. Performance beyond this threshold by any individual treated with both epidural stimulation and training will be interpreted as a significantly better intervention than training alone.

Future studies will eventually focus on development and implementation of the more advanced multi-electrode array technique that will provide functionally-adaptive site-specific stimulation. The adaptive stimulation strategy proposed here takes advantage of capabilities of our new array design that are not possible using either conventional or commercially available electrode arrays. Our future arrays will provide two key benefits:

• Our electrode arrays cover a larger area than commercially available arrays, extending from the midthoracic to the sacral extents of the spinal cord. It is possible that the optimal stimulation sites for facilitating stepping versus standing may be spatially distinct on the spinal cord. If this is the case, conventional arrays are less likely to be able to recover both stepping and standing in the same patient.

• Numerous findings suggest that locomotor training may progressively change the state of the spinal networks that are responsible for stepping and standing. Therefore, the optimal sites for stimulating these motor tasks may migrate over the course of treatment. The adaptive algorithm that we propose will track the optimal sites for stimulation weekly and, using this information, we will select electrode(s) from our array that generates the most successful standing or stepping. An electrode array will allow us to precisely target the most effective stimulation sites.

A couple of recent studies have shown the ability to produce stepping following complete transactions in adult rats when stimulating at the S1 level [65, 66]. Therefore we propose the implantation of 2 stimulating electrodes to cover a broader area of the human spinal cord.

B. Objectives of the research

The overall aim is to assess whether task specific locomotor training and SCES can induce neural reorganization of the functionally isolated human spinal cord to improve standing and stepping in individuals with functionally complete SCI. We propose that locomotor training will result in generation of more effective standing and stepping efferent patterns by restoring phase dependent modulation of reflexes and reciprocal inhibition,

reducing clonus and mediating interlimb coordination. We propose that the SCES will optimize the physiological state of the spinal cord interneuronal circuitry compromised by compensating for loss of supraspinal input for the retraining of these tasks.

The proposed studies will allow us to gather critical information using commercially available electrodes to design the more advanced multi-electrode array technique that will be adaptive and conceivably be effective in a wider range of patient populations. The current electrodes used in this study will serve two objectives: 1) to improve standing and stepping with the combination of epidural stimulation and locomotor training in individuals with functionally complete SCI; and 2) to provide critical information for the development of more advanced electrodes.

C. Significance of the research

Locomotor training has been shown to improve overground walking in incomplete SCI research participants, however none have fully recovered [47-61]. Identifying the critical sensory cues that facilitate more effective motor output can provide knowledge that can further improve this rehabilitative approach for walking. Understanding the mechanisms of task specific training in relation to the potential for functional reorganization of the human spinal cord after injury can also have significant implications for rehabilitation strategies for the recovery of walking [62, 63]. Further, optimizing training strategies for functional recovery of spinal circuits after SCI will also be extremely important in combination with promising neural regeneration approaches that are continually emerging.

D. Thorough description of how human research participants will participate in the research

SCREENING: Evaluation Tests and Pre-Training (1st consent)

Dr. Maxwell Boakye, Dr. Camilo Castillo, and Susan Harkema, Ph.D., the principal investigators of this project, will perform the initial screening of the research participants. Dr. Joseph Neimat may perform the surgical implantation procedure. All eligible SCI research participants will be invited to the Human Locomotion Research Center to discuss the complete protocol and its risks and benefits with Dr. Harkema. The individual will view a video or a demonstration that exemplifies the stand and step training and the recording apparatus that will be used during testing. Dr. Harkema will verbally review all other testing that will occur and explain that the research participant can refuse any of the tests and discontinue their participation at any time without penalty. Dr. Harkema will answer any questions the research participant or family members may have in relationship to the research.

If the individual is potentially eligible for study and is interested in participation he/she will be seen by Dr. Camilo Castillo, for assessment of medical eligibility. Dr. Castillo will complete a medical history and neurological examination to determine medical eligibility for each SCI research participant. Dr. Castillo will discuss the risks and benefits with the potential research participant regarding the rehabilitative component. He will review all electrophysiological testing and training procedures that will be conducted during and explain to the potential research participant that s/he can refuse any of the procedures

and discontinue their participation at any time without penalty. Dr. Castillo will answer any questions with the potential research participant and/or family members who may have a relationship with them regarding the physical rehabilitative aspects of the research.

Dr. Boakye or Dr. Neimat will discuss the surgical protocols and the risks and benefits with the potential research participant. They will verbally review the surgical procedures and show the individual the stimulating and recording equipment that will be implanted. Dr. Boakye or Dr. Neimat will review all testing that will be conducted during the surgical procedures and explain to the potential research participant that s/he can refuse any of the procedures and discontinue their participation at any time without penalty Dr. Boakye or Dr. Neimat will answer any questions with the potential research participant and/or family members who may have a relationship with them regarding the surgical procedures and the research.

Dr. Harkema will determine study eligibility based on the inclusion and exclusion criteria and in accordance with the medical recommendation of Drs. Castillo, and Drs. Boakye or Neimat. Dr. Harkema will also encourage potential research participants to read the informed consent and take several days to discuss participation with friends and family before agreeing to enter the study. Drs. Harkema, Castillo, and Boakye will explain to the potential participant that the initial enrollment involves a series of pre-experiments and 80 step/stand training sessions and the results are necessary to determine if they are an appropriate candidate for the surgical component of the study. Participating in the initial portion of the study does not guarantee their eligibility for surgical implantation and epidural stimulation.

The screening informed consent will be written in at an 8th-grade language level and will contain information on all evaluations to be performed as well as contact information should the research participant or his/her associates have any further questions. The original signed informed consent and two copies will be kept in Dr. Harkema's office.

These individuals will not be concurrently enrolled in any other experimental studies unless approved by the principal investigator. Each research participant will be given a coded identification number to designate all evaluations. We will retain the data for reporting to granting agencies even when the individual is not eligible for the study. This data will be stored by the coded identification number without information identifying the individual.

We will evaluate the research participants for: 1) functional neurophysiological assessment (FNPA); 2) somatosensory evoked potentials (SEP); 3) sympathetic skin responses (SSR); 4) efferent motor activity during standing; 5) efferent motor activity during stepping; 6) reflexes during supine, prone, sitting and standing; 7) bladder function; and 8) cardiovascular function. Each of these measurements will take between 1 and 4 hours. The FNPA, SEP and SSR will be performed while the research participant is lying supine on a mat. The efferent motor assessments will be performed in the body weight support treadmill with the assistance of trainers at the hip and at each leg.

We will assess metabolic parameters, inflammatory markers, complete blood count, bone density and health markers, blood glucose control and drug toxicity panel. A trained

technician will draw a venous blood sample. Participants may undergo a 12-hour fast the night before, including no food or drink including alcohol or caffeine (water is permitted). A comprehensive drug screen by urinalysis will be done to assess the use of illicit drugs. These blood and urine analyses may be repeated periodically throughout the course of the study. A blood sample will be stored for batch processing at the end of the study (for participants that complete the screening process).

After completion of these evaluations, participants will undergo 80 sessions of step/stand training. We will repeat experiments after the completion of the 80 training sessions to quantify that no motor pattern changes are achievable with locomotor training alone. Drs. Harkema, Castillo and Boakye will meet to discuss the results of the preliminary testing and evaluate if the participant is eligible for surgical implantation for SCES.

FULL ENROLLMENT: Surgery + Epidural Stimulation + Training (2nd consent)

If after evaluating the results, the study investigators determine that the participant is an appropriate candidate for surgery and epidural stimulation, the participants will be asked to sign an additional consent form. The surgical and epidural stimulation informed consent will be written in at a 8th-grade language level and will contain information on the surgery and all experiments to be performed as well as contact information should the research participant or his/her associates have any further questions. The original signed informed consent and two copies will be kept in Dr. Harkema's office.

The surgery will be performed at University Hospital to insert the epidural stimulating electrodes. The lead wires will be tunneled subcutaneously to exit 5 centimeters from the incision site. The implantable neurostimulator will be internalized and the connecting wires for the implanted electrodes will be tunneled under the skin and connected with the battery generator that will be placed in the abdominal area. We will repeat the experiments beginning at least 10 days after the surgery both with and without stimulation for 10 – 14 days. During the first two weeks after the surgery, the research participants may be hospitalized at Frazier Rehab Institute to monitor the incision site. We will also identify appropriate stimulation parameters for inducing stepping and standing in combination with manual assistance using body weight support on a treadmill (BWST).

Following discharge from inpatient or recovering at home the individuals will be seen in our lab on a daily basis for testing and locomotor training. We will evaluate the combination of epidural stimulation with manual step/stand training. This stage will be conducted over six-eight months. During training, the patients will be provided with epidural stimulation using the parameters defined in Stage 1. Testing may be performed weekly. The blood samples for metabolic parameters may be repeated prior to and after each training period. A blood sample will be frozen and stored in the laboratory for batch analysis for inflammatory markers, metabolic parameters, and markers for bone density.

Locomotor Training: Every research participant will be slowly acclimated to the body weight support system to make him/her feel comfortable in an upright position. This may help the research participant avoid experiencing a lowered blood pressure or dizziness. However, if these conditions should occur, the research participant would immediately be

unhooked from the system, removed from an upright position, the legs elevated, and the blood pressure monitored. Stepping bouts are relatively short in duration, thus an increase in respiration as well as an increase in heart rate or blood pressure will generally last for only a couple of minutes. Each research participant will be closely monitored through each experiment and training session. Standing or stepping will immediately halt once the research participant feels tired or winded. Blood pressures and heart rates will be monitored by the physical therapist or trained staff regularly during each training session. Continuous blood pressure, breathing rate, and temperature may be monitored with sensors throughout the training sessions and experiments. Participants may be asked to train twice a day; they will train both to stand and step on the same day. The sessions will only be counted if the progression criteria is met, for example independence minutes or weight-bearing minutes.

In certain cases, the physician, Dr. Camilo Castillo, might recommend a specific training change or limit on sessions to mitigate risk for research participant. Any special considerations are specified in the addendum section.

Before and after every experiment and training session, a physical therapist or research staff member will examine the research participant's skin for irritations and abrasions. If skin irritations or abrasions are caused by the electrodes, harness position or hand placements of trainers, electrode, the harness and hand placement will be modified appropriately. Further, the physical therapist and research team will constantly monitor the research participant's skin and muscle for signs of muscle strain, joint sprain and skin irritation (e.g. temperature and redness).

Dr. Harkema and the research team will continually assess the appropriate BWS and continuously monitor manual assistance by trainers to avoid joint sprain and fracture. Body weight support will be kept above 50% for the initial sessions to allow bone and muscle to become stronger. Further, continuous monitoring of the research participant will be conducted by the staff for potential injuries. For example, signs of skin redness, swelling of joints, or spasticity can be indicators of injury when research participants have impaired sensation. Research participants will also be stretched by the physical therapist or trained staff member before and after each training session to prevent injury.

If any signs of risks or discomfort are noted, the experiment or training session will be immediately discontinued. If any complications arise, the stand or step training will immediately stop and Dr. Castillo will immediately be informed. In addition, the research participant's primary care provider will be notified as necessary. Dr. Castillo will be the medical advisor for the research participants throughout the locomotor training segment of this study. Dr. Boakye or Dr. Joseph Neimat will oversee all surgical related issues for the research participants.

Follow-up: After the training period has ended, patients will be followed up by Drs. Boakye/Castillo and Harkema every three-six months for a total of three years following surgery. After three years the patients will be followed up by Drs. Boakye/Castillo and Harkema every six months for continued long-term care until the device is explanted or the device is approved for stepping and standing in spinal cord injury. Follow-up neurological examination for the purpose of this study will be incorporated into each clinic

visit. The decision to continue to maintain the stimulators or remove them will be made during these follow-up visits.

Dr. Harkema and the research team might ask the participant to return for training in the laboratory for extended periods of 80-200 sessions post participation in the original sessions. Training (stand or step) will be designed to optimize parameters and built to improve on previous training. During this time participants might be asked to functional train with the combination of our adaptive epidural stimulation strategy with manual locomotor training. During training, the participants will be provided with ES using the parameters determined using the computation learning method which is developed during phase 2 described below.

E. How the study population is determined and how they will be equitably recruited

There are approximately 250,000 Americans with a SCI. Of this population, 82% are male. Fifty-six percent of the injuries occur in people between the ages of 16 and 30, and the average age of an individual who has sustained a SCI is thirty-one. Thirty-eight percent of the research participants studied will be derived from a population of minorities (African-American, American Indian or Alaskan Native, Asian, Hispanic or Latino, and Native Hawaiian or other Pacific Islander). Every effort will be made to recruit women, though only about 18% of SCI patients are female. Although many people after a SCI have secondary health issues such as spasticity and frequent urinary tract infections, they are otherwise healthy individuals. Standing and stepping is considered beneficial for people with SCI who are confined to a wheelchair, as immobilization can contribute to secondary pathologies such as osteoporosis, leg muscle contractures, decreased cardiovascular health, pressure sores and muscle atrophy. Children will not be studied. Pregnant women with SCI will not be studied because the risks to the fetus are unknown. No other vulnerable research participants will be included.

Research participants will be identified by Drs. Harkema, Castillo, and Boakye. Physicians and physical therapists at rehabilitation sites in the Louisville area will be provided with the purpose of research, selection criteria for referral, and flyers for advertisement. Further, we currently have a database of approximately 2000 potential SCI research participants matching the eligibility requirements who have expressed interest in participating in our research program (UofL IRB# 06.0647). The research aims and a summary of the criteria for eligibility will be posted on Dr. Harkema's website. We will also post flyers for advertisement to recruit individuals throughout the university. Flyers with a description of the study and a telephone number to call to express interest will be made available to potential research individuals.

F. Eligibility (inclusion) and exclusion requirements for research participants

In this pilot study, we will recruit ten research participants within a ten year period who have sustained a SCI to participate in this first phase of the study, i.e. using only conventional electrodes. Currently, there is no known treatment for patients with functionally complete spinal cord injury for the recovery of standing and walking. In this

study we hope to develop a treatment that will provide patients with the ability to stand and walk. Dr. Harkema's center routinely performs locomotor training that has shown to benefit some patients with spinal cord injury. Placement of a dorsal column stimulator in the lower thoracic- lumbar area of the spinal cord is well accepted and a commonly performed operation by neurosurgeons for treatment of chronic intractable pain in the low back and legs. Thus, both procedures combine standard treatment strategies, but this study investigates the potential expansion of both these therapies to more severely injured patient population. We are not aware of any other treatment that will provide such improvement in function. If this treatment is successful, it is anticipated that patients' locomotor function would improve to the point of the research participant being able to stand or walk with a walker or a cane. This study will evaluate potential gains in addition to those which occur following electrical spinal cord stimulation.

All research participants, irrespective of age or sex, will meet the following criteria: 1) stable medical condition without cardiopulmonary disease or dysautonomia that would contraindicate standing or stepping with BWST; 2) no painful musculoskeletal dysfunction, unhealed fracture, contracture, pressure sore, or urinary tract infection that might interfere with stand or step training; 3) no clinically significant depression or ongoing drug abuse; 4) no current anti-spasticity medication regimen; 5) non-progressive SCI above T10; 6) must not have received botox injections in the prior six months; 7) be unable to stand and step independently overground; 8) unable to voluntarily move all individual joints of the legs; 9) at least one-year post injury; and 10) must be at least 18 years of age. In addition, all subjects must satisfy each of the three conditions of the functional neurophysiological assessment described below.

Additionally, research participants with the following characteristics will not undergo any assessments using transcranial magnetic stimulation (TMS): 1) metal in head (except mouth) such as but not limited to cochlear implant, implanted brain stimulators, aneurysm clips; 2) increased intracranial pressure (which lowers seizure thresholds); 3) cardiac pacemakers; 4) implanted medication pumps; 5) intracardiac lines; 6) significant heart disease; 7) history of stroke or other brain lesions; 8) personal or family history of epilepsy; 9) receiving tricyclic antidepressants or neuroleptics (which lower seizure threshold); 10) heavy alcohol consumption within past 48 hours

Functional Neurophysiological Assessment (FNPA). We will use FNPA to screen potential research participants based on specific neurophysiological inclusion criteria. Participants must have no volitional control of movement below the level of the lesion, but must retain some brain influence on spinal reflexes. Our target population, which will be identified by FNPA, cannot be identified reliable using traditional assessments: hence individual subjects may be classified widely as Class A, B, or C on the ASIA SCI scale. We will include only subjects who fulfill the following three requirements:

1. There is no descending volitional control of movement below the lesion
2. Segmental reflexes remain functional below the lesion
3. Brain influence on spinal reflexes is retained

G. Design/methodology including all survey instruments, questionnaires, etc.

SCREENING CONSENT:
Stage 1A: Standing and stepping interventions
FULL ENROLLMENT CONSENT:
Stage 1B: Surgical Procedure
Stage 1C: Stimulation procedures and standing and stepping interventions
Stage 2A: Stimulation procedures and standing and stepping assessments
Stage 2B: Adaptive Multielectrode Epidural Stimulation and Locomotor Training

Stage 1A: Standing and stepping interventions

Prior to the initial surgery the participant will undergo 80 sessions of step/stand training (screening). We will evaluate the research participants with the following experiments: 1) functional neurophysiological assessment (FNPA); 2) somatosensory evoked potentials (SEP); 3) sympathetic skin responses (SSR); 4) efferent motor activity during standing; 5) efferent motor activity during stepping; 6) reflexes during supine, prone, sitting and standing before the initiation of training; 7) bladder function; 8) cardiovascular function; 9) MRI Scan; 10; Quality of life questionnaires. Each of these measurements will take between 1 and 4 hours. We will repeat these measurements at the end of the initial 80 training sessions. Participants will undergo laboratory tests to assess and reduce the risk of infectious diseases prior to surgery.

Protection against Infectious Diseases: Several lab tests (see table below) will be performed to assess the risk of infection prior to surgical implantation based on the recommendation from the Infection Prevention and Control Department (ULH) and Division of Infectious Diseases, Dept. of Medicine (UofL). Dr. Castillo will oversee treatment for any positive urine culture and infections in consultation with the Division of Infectious Diseases Department.

<table>
<tr><th>Test</th><th>Purpose</th><th>When</th></tr>
<tr><td>Nasal swab for MRSA</td><td>To determine if colonized to decolonize and use vancomycin as pre-operative antibiotics</td><td rowspan="2">Approximately 4 weeks prior to scheduled surgery to allow for time for treatment, re-test + treatment and final re-test.</td></tr>
<tr><td>Peri-rectal swab for MDRO Gram-negatives</td><td>To determine if colonized and, based on organism, consider decolonization and adjustment of pre-operative antibiotics</td></tr>
<tr><td>urinalysis</td><td rowspan="2">To identify infection for clearance prior to procedure</td><td rowspan="10">Within 30 days of scheduled surgery; may need to be repeated closer to surgery date</td></tr>
<tr><td>urine culture</td></tr>
<tr><td>C-reactive protein (CRP)</td><td rowspan="3">To obtain for baseline measure</td></tr>
<tr><td>Erythrocyte sedimentation rate (ESR)</td></tr>
<tr><td>Procalcitonin</td></tr>
<tr><td>Prealbumin/Transthyretin</td><td rowspan="6">To verify appropriate status for procedure</td></tr>
<tr><td>Albumin (included in CMP)</td></tr>
<tr><td>25-Hydroxy Vitamin D</td></tr>
<tr><td>CBC with differential</td></tr>
<tr><td>CMP</td></tr>
<tr><td>Pregnancy Test</td></tr>
</table>

If a patient tests positive for MRSA, de-colonization will be recommended and monitored by the infectious disease team in collaboration with Drs. Castillo and Boakye. Treatment plan includes the following to be administered for 7 days: chlorhexidine gluconate (2 or 4% solution) with daily washes or a disposable impregnated cloth; mupirocin ointment (2%) applied to the nares with a cotton-tipped applicator two to three times daily. Following initial treatment, the participant will be retested for MRSA. If the participant still tests positive then treatment will include repeated decolonization as well as the following: rifampin (600 mg PO daily) plus either doxycycline (100 mg twice daily) or trimethoprim/sulfamethoxazole (one double strength twice daily). The participant will be retested following this second treatment. If the participant still tests positive then they

should be excluded from the study. The physicians will manage the medical treatment for infections and for any immediate safety concerns.

Stage 1B: Surgical Procedure

One Medtronic Specify 5-6-5 or Specify 5-6-5 SureScan MRI (Minneapolis, MN) 16-electrode epidural arrays will be implanted intraoperatively using a single surgery procedure. The surgery will be conducted at University Hospital under a combined regional and general anesthesic. General anesthesia will be utilized for part of the surgery and mild sedation for the other part. We do not anticipate that the patients will experience any pain during this operation. However, if there is any discomfort, the patients will be administered analgesics by the anesthesiologist and/or the painful area will be infiltrated with local anesthetic. Patients will be placed in the prone position with an incision made in the thoracolumbar area of the spine. We will perform a partial laminectomy at the T11–T12 interspace providing a site for electrode insertion. The incision will be approximately 2.0 – 2.5 inches. One electrode will be threaded upwards to the T11-L1 segmental levels. If necessary the second electrode will be threaded downward to the S1-S2 segmental levels for placement over the group of spinal cord nuclei where activation of the muscles occurs. Fluoroscopy and neurophysiological parameters will be used to determine the optimal lead placement that will be determined by motor system monitoring.

Following the location of optimal lead(s) placement the participant will be rolled to the lateral decubitus position and the surgeon will proceed with the internalization of the implantable neurostimulator into the subcutaneous area of the abdomen. The wires of the implanted epidural electrodes will be tunneled under the skin and connected with the battery generator that will be placed in the abdominal area.

We do not anticipate any increased risks other than the well-recognized accepted risks of surgery (infection, bleeding, and anesthesia).

1) Infection: To minimize risks of infection participants will take a chlorhexidine bath one week prior to surgery at home, and the day of surgery in the hospital by a nurse. All neurophysiological equipment will be disinfected with PDI® Sani-cloth AF3 germicidal disposable wipes prior to entry in the OR. Access to the OR will be limited during the entire surgical procedure with restricted access through the sterile core. Only essential personnel will be permitted in the OR. Each participant will be administered intravenous antibiotics throughout the operation and for 48 hours postoperatively. Vancomycin powder will not be initially recommended, however we will use a TYRX™ Neuro Absorbable Antibacterial Envelope in the abdominal pouch site for the battery generator.

In the unlikely event of an infection, the patient may require prolonged intravenous antibiotics, reopening of the incision to irrigate and drain an abscess, or even removal of the epidural electrodes.

2) Hemorrhage: Scrupulous attention for hemostasis should prevent a postoperative hematoma from occurring. However, if a hematoma develops and is clinically significant, timely surgical evacuation of the clot will be performed.

3) Anesthesia: Patients will be induced by general anesthesia and once the incision if opened and epidural electrodes placed, the optimal placement of the electrodes will be confirmed with electrophysiological assessments by inducing monosynaptic reflexes and

monitoring their latency and amplitude from surface EMG electrodes from the quadriceps, hamstrings, adductor, gluteus maximus, tibialis anterior and triceps surae, bilaterally. Fine-wire EMG electrodes will also be used to monitor the Illio-psoas muscle. The patients will be closely monitored by the anesthesiologist for changes in blood pressure, pulse, and temperature with appropriate treatment will be instituted should alterations of these parameters be observed.

Stage 1C: Stimulation procedures and standing and stepping interventions

We may repeat experiments that were performed pre-surgery beginning 2 weeks after the surgery both with and without stimulation for 10 – 14 days. During the two weeks after the surgery, the research participants may be hospitalized at Frazier Rehab Institute to monitor the incision site.

Optimal configurations will also be tested for bladder and cardiovascular function. A specific stimulation parameter may be used to assess the influence of epidural stimulation on bladder function and/or cardiovascular function. In the case of bladder function, following its assessment with stimulation the bladder will be filled with saline solution a second time after a 5 minute break. The optimal stimulation configuration for bladder will be used and the pressure will be recorded. The individual will be asked to attempt to empty his/her bladder when the stimulation is ongoing. Pressure will also be recorded when the bladder is relived. This test will take approximately 60 minutes.
Similarly the cardiovascular function might be assessed without and with stimulation. The orthostatic stress test (sit up test) might be repeated with optimal stimulation for cardiovascular control. The butterfly catheter will remain in place from the initial non stimulation test and blood samples will be obtained to same time points to assess if any changes in

We will also identify appropriate stimulation parameters for inducing voluntary activity and stepping and standing in combination with manual assistance using body weight support on a treadmill (BWST) or overground. Each of the sixteen electrodes will be independently stimulated using subthreshold, tonic, non-patterned epidural stimulation applied at frequencies of 5-50 Hz, and amplitudes of 1-10 V. The specific stimulation parameters will be optimized for each individual to achieve the best motor performance for each task. We may monitor continuous blood pressure, breathing rate and temperature using external sensors pasted over the skins during training sessions or experiments.

Stage 2A: Stimulation procedures and standing and stepping assessments

Following post-surgery experiments, training will be conducted 5 times per week for 160 sessions on an outpatient basis. In Stage 2 the individuals will be seen in our laboratory on a daily basis for testing and training. After the initial 20 sessions of training, they might be asked to come train twice a day (stand and step on the same day) with a 2-4 hour resting period in between. We will evaluate the combination of epidural stimulation with manual step (locomotor) training. This stage will be conducted over four to eight months. Periodically, blood and urine samples may be collected, processed for testing as described above, and stored for batch testing at the end of the study period.

During training, the patients will be provided with epidural stimulation using the parameters defined in Stage 1.

In certain cases, the physician, Dr. Camilo Castillo, might recommend a specific training change or limit on sessions to mitigate risk for research participant. Any special considerations are specified in the addendum section.

The participants may be evaluated weekly for 1) efferent motor activity during standing and stepping and 2) reflexes during supine, prone, sitting and standing, as described above.

Home Training: Following the determination of optimal parameters for standing or voluntary activity, the participant might be given a Patient Programmer (Medtronic Model 37743) to translate weight bearing and stand training and/or voluntary movement with stimulation to the home environment and perform additional training. The programmer will be optimally programmed by the research team in such a way to restrict configuration changes by research participant. A pre-determined range of optimal voltages will be accessible by the research participants. A very specific protocol for stimulation and training will be given by the research team and the participant will be required to complete a training log. The research team will collect the home training log from the participant once a week and evaluate the need for changes to the home-based training protocol.

Stage 2B: Adaptive Multielectrode Epidural Stimulation and Locomotor Training

Stage 2 will evaluate the combination of our adaptive epidural stimulation strategy with manual step (locomotor) training. During training, the participants will be provided with ES using the parameters determined using the computation learning method in Phase 1.

Experimental materials.

We will acquire lower extremity and trunk muscles surface EMG activity and kinematics bilaterally during all experimental conditions. We will also use fine-wire EMG to acquire activity from the illio-psoas, extensor hallicus longus, extensor digitorum longus and other deep muscles muscle. We will also record individual limb loading and level of BWS during standing and stepping conditions. We may acquire continuous blood pressure with a finger cuff, breathing rate using an elastic band place loosely around their chest and temperature with 1-3 small sensors taped over their skin above and below their injury level.

Locomotor Training Intervention.

Individuals with SCI will participate in 80 sessions of weight bearing step-training (n=10) for approximately 16 - 20 weeks (60-90 minutes/session, 3-5 sessions/week) during which the individuals may be placed on the treadmill in an upright position and suspended by an overhead pulley (Innoventor, St. Louis, MO) in a harness (Robertson, Hendersen, NV). During stepping using BWST and manual assistance the maximum load will be used that avoids knee-buckling and trunk collapse [64]. A trainer positioned behind the research participant will aid in pelvis and trunk stabilization, as well as weight shifting and hip rotation, and trainers positioned at each limb will provide manual assistance using a customized technique that facilitates knee extension during stance (by manually

stimulating the patellar and Achilles' tendons) and knee flexion and toe clearance during swing (by manually stimulating the hamstrings and tibialis anterior tendons). Trainers provide assistance only when needed. Individuals will step at a normal walking speed for their height and age (0.89 m/s – 1.34 m/s) and at the maximum body weight allowed with minimal force needed by the trainers to assist during stance (4, 25). Body weight support will be continuously reduced over the course of the 80 sessions as the individuals increase their ability to bear weight on the legs during stepping. Step training sessions might progress to the overground environment when appropriate.

Participants may also stand train in a stand training device, based on optimal parameters acquired during the initial phase of training. The participant might be asked to follow a supine and/or stand training home program (in a standing frame or similar device) once independence is achieved with the stimulation. The home program will only be used as a complement to the daily outpatient training sessions, and will be closely monitored by the research team. The research participants will have to demonstrate independence and safe use of the patient programmer in the lab prior to initiation of the home program. Parameters loaded in the patient programmers will only include those that have been used safely and result in supine movements or independent standing by the research participant in the laboratory setting. In addition, family members and caregivers will be trained on appropriate techniques to provided assistance as needed during home-based training. Independent standing and availability of caregivers to provided assistance in the home environment will be key factors when developing the home program.

We will collect electromyography (EMG), joint angle, and footswitch data at 1000 Hz using a 24-channel hard-wired analog to digital board and a custom written Labview software acquisition program (National Instruments, Austin, TX) during stepping using BWST or overground and manual assistance. EMG data will be sampled from 0.1 to 1 kHz and AC coupled into a differential amplifier (Konigsberg Instruments, Pasadena, CA). Following standard skin preparation, bipolar surface EMG electrodes with a fixed distance between the electrodes will be placed on the soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, adductor, vastus lateralis, and rectus femoris bilaterally. Limb kinematics will be digitally acquired a passive marker high speed motion capture system (Motion Analysis, Santa Rosa, CA). Individual limb loads will be measured with shoe-insole pressure sensors (FSCAN, Tekscan, Boston). Data will be processed and synchronized using Labview software (National Instruments, Austin, TX) customized by our laboratory. EMG data will be full wave rectified and filtered using a 4th order bandpass Butterworth filter (40 Hz - 500 Hz). Mean EMG represents the relative number and frequencies of the motor units recruited per burst. Integrated EMG assesses the total EMG activity generated per step. EMG mean and integrated amplitudes from each muscle will be compared before and after locomotor training. Co-activation values of flexors and extensors will be calculated. The degree of coordination in the stepping-related oscillations of lower limb segments will be assessed through principal component analysis. Quantitative measurements and statistical testing have been described in detail in previous publications listed above.

Heart rate will be monitored using a digit pulse oximeter placed on the index finger of the research participant during training sessions and experiments.

Next analytical approaches will be utilized in these studies:
• EMG burst cycle analysis. EMG signals will be band pass filtered between 40-500 Hz to eliminate any transient signals and then rectified. A minimum threshold for EMG activity (3 standard deviations (SD) above mean baseline noise) will be selected for each channel. Onset of EMG bursts is detected as the location where the signal amplitude remains above the threshold for 50 continuous samples, and the end as the location where the signal amplitude remains below the threshold level for 150 continuous samples. Detected start and end points are displayed as marks on the data for verification. Mean EMG (MEMG) may be used to make interpretations about the relative number and firing frequencies of the motor units recruited per burst. Integrated EMG (IEMG) assesses the total EMG activity generated per step.
• Muscle co-activity and clonicity. We developed a method to quantify the clonicity of and coactivation among muscles during human locomotion based on a Bayesian approach to EMG analyses, using reversible jump Markov chain Monte Carlo (RJMCMC) simulation (Harkema et al. 1997). In Bayesian analyses, data are passed through a simulation algorithm multiple times (300,000), generating distributions of the quantities of interest. The Bayesian process yields an objective assessment of the mean and deviation of parameters of a signal (in this case co-activity and clonicity), thereby, minimizing research participative error. Further, the measures vary less than 0.5% after repeating the measures three times across five data sets. This approach allows for statistically valid inferences about these quantities and the differences between them.
• Linear envelopes. The high-pass filtered and rectified EMG data will be low-pass filtered at 5 Hz. EMG bursts may be averaged relative to the start of a burst in the muscle, the start of a burst in another muscle, or to a biomechanical event such as the rise or decline of force. Averages will be generated from data normalized to the duration of each burst or step cycle. Averaged waveforms are of interest because they may be assumed to represent the typical activity pattern. Coefficients of variation will be calculated to scale standard deviations to a mean value throughout the step cycle.
• Scatter plots. Scatter plots will be used to detect relationships among muscle EMG, limb loading, stepping velocity, and joint position. Scatter plots will be generated from individual steps and averaged waveforms. EMG amplitudes (5 Hz low pass filtered) of agonist and antagonist muscles will be plotted (triceps surae (TS), tibialis anterior (TA), hamstring (HM), quadriceps (Q), and adductor (ADD) to assess muscle coordination. This provides information about the phasing of a muscle activity relative to other muscles. The relationship between EMG activity and either phases of loading or joint position will also be plotted. Three-dimensional relationships incorporating two of the latter variables and muscle EMG will also be utilized.
• Voluntary response index. Voluntary motor task EMG from healthy individuals has been averaged across a five second window to generate response vectors (RVs). The prototype response vector (PRV) was generated by normalizing the RVs by the vector magnitude and then averaged. The PRV is comprised of 10 elements, one for each

muscle. A PRV is created for each phase of each movement in the voluntary motor task component of the BMCA protocol. A similarity index (SI) is then used for comparison of the data. The SI is a numerical expression of the similarity of the distribution of the EMG activity in the RV, computed as the normalized dot product between the two vectors (vector representing the distribution of activity generated by healthy research participants, and that representing the distribution of activity in the test research participant). A value of 1.0 for the SI represents an identical distribution.

• Kinematic and kinetic analysis. Joint kinematics will be analyzed using EVaRT and Orthotrak which provide instantaneous 3-D graphic displays and all kinematic parameters of the motion performed by a research participant. The force signals will be acquired from FSCAN at 50 Hz and interpolated to 1000 Hz and low-pass filtered (5 Hz). A minimum threshold (3 SD above baseline) will be calculated for each signal. BWS was acquired by Labview A/D and processed by customized software.

These results will reveal whether conventional electrodes can be used to facilitate stepping in clinically complete spinal cord injury patients. This study will clarify whether the optimal spinal cord sites for using epidural stimulation to induce stepping and standing migrate over the course of training in the human spinal cord. We expect that these data will provide further evidence of the plasticity of the injured spinal cord, and that training modifies the spinal networks for stepping. Stepping performance of the patients will be compared against historical controls that were given step training without epidural stimulation. The criteria for success of the combined treatment will be determined by the best outcomes that have been obtained for previous patients who were only trained.

h. Treatment regimen(s) (*for medically invasive research*)

i. Clinical information (when applicable) (*for medically invasive research*)

j. Statistical analysis of the collected data

No statistical analysis will be used for comparison of data. This study is designed as a proof of principle study without statistical power to demonstrate the feasibility of the methods.

k. Data and Safety Monitoring Plan

Entity responsible for monitoring is identified:

The study will be monitored by a Data Safety Monitoring Board consisting of: Dr. James Guest (Neurosurgeon), Dr. Steven Kirshblum (physiatrist); Dr. Steve

Schulman (cardiologist) and Dr. Thomas Kessler (Urologist) who are not associated with the study.

Policies and procedures for adverse event reporting are described:
If a subject develops an adverse event it will be reported to the DSMB, local IRB and Sponsor within 24 – 48 hours of being notified of the event.

Protocol Compliance:
Any deviations in the protocol will be documented and reported to the IRB.

Plans for measuring appropriate intervals between safety reviews and predetermined criteria for stopping the study:
Research participants will be continuously monitored for complications, adverse events and/or serious adverse events. If any complications arise during the course of the study the local Medical Advisor (Dr. Castillo) will be notified. All study procedures will be halted until the complication, adverse event and/or serious adverse event has been reviewed by the medical advisor and it has been determined that it is safe for the study participant to return to participating in study procedures.

If a serious adverse event occurs and is related to the study product all study procedures will stop. AE's and SAE's will be reported to the Medical Advisors, Medical Monitor, IRB and Sponsor.

Plans to ensure NIBIB/NIH is informed of actions taken by the IRB:
All correspondence with the IRB will be forwarded to the sponsor.

Reports of revisions or amendments to the Protocol:
All revisions and amendments to the Protocol will be sent to the sponsor and IRB. No study procedures will be conducted without IRB approval.

m. Investigator's Brochure for drugs or devices - The IRB is required to examine the Investigator's Drug Brochure and/or device guide in order to adequately assess the risk/benefit ratio for research participants participating in the research.

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Addendum 1

Recommendation for training interventions to mitigate risk of a research participant that has sustained a hip fracture:

Prior to a participant resuming step and stand training medical clearance will be obtained from their treating orthopedic surgeon.

Stand Training with stimulation will occur for the initial 40 sessions. No step training will occur during this time. Following the initial 40 sessions and clearance from study physician, the participant will resume study stand/step interventions with stimulation. Participant might be ask to complete an additional 160 sessions of combined training to reduce the variability at the assessment points. Assessments might be repeated after the initial 40 stand training sessions and then at various points following the initiation of standing and stepping. The research team will follow all procedures as specified in the protocol.

In regard to the evaluation of these results, in all publications the number of training sessions will be reported accurately. Given the high number of training sessions these individuals received, the variability in this research participant is not expected to significantly affect the outcome. However, this change in protocol will be considered in the interpretation of any results. In addition, additional assessments will provide information relevant to the interpretation.

STUDY TITLE: SPINAL EPIDURAL ELECTRODE ARRAY TO FACILITATE STANDING AND STEPPING IN SPINAL CORD INJURY

INFORMED CONSENT AND RESEARCH AUTHORIZATION

SPINAL EPIDURAL ELECTRODE ARRAY TO FACILITATE STANDING AND STEPPING IN SPINAL CORD INJURY

Industry Contracts number: 070943Y02; 080483 and 111096
Grants number: 1R01EB007615-01A1
Sponsor(s) name & address: National Institutes of Health
P.O. Box 5801, Bethesda, MD 20824

Christopher and Dana Reeve Foundation
636 Morris Avenue, Short Hills, NJ07078

Kessler Foundation
300 Executive Drive, Suite 70, West Orange, NJ 07052-3390

The Leona M. and Harry B. Helmsley Charitable Trust
230 Park Avenue, Suite 659, New York, NY 10169

Investigator(s) name, Degree, University Department, & address:

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Assistant Professor and Director of Spinal Cord Injury
Frazier Rehab Institute
220 Abraham Flexner Way
Louisville, KY 40202

Site(s) where study is to be conducted:

Neuroscience Collaborative Center
University of Louisville, KY
Department of Neurological Surgery, Louisville, KY
University of Louisville Hospital

Phone number for subjects to call for questions: (502) 581-8675

Introduction and Background Information

You are invited to take part in this research study because the results of the screening process have shown that you are eligible for participation. This study involves a non-indicated use of a FDA approved device and the manufacturer has not completed testing with the device as it will be used in this study. The study is being conducted by Dr. Susan Harkema, Dr. Camilo Castillo, Dr. Maxwell Boakye and Dr. Joseph Neimat. The study is sponsored by the National Institutes of Health, Christopher and Dana Reeve Foundation, Kessler Foundation, the Leona M. and Harry B. Helmsley Charitable Trust and the University of Louisville, Department of Neurological Surgery and will take place at the University of Louisville, University Hospital and the Frazier

Rehab Institute in Louisville. Approximately 10 individuals with spinal cord injury will be invited to participate in this study. Your participation in this study will last for approximately 3 years. After 3 years a decision will be made as to whether the spinal stimulator will be left in place or removed. If the stimulator is beneficial, it will be left in place. If ineffective, a decision will be made to keep the stimulator in place or remove it. Long term follow-up after 3 years will consist of visits to the clinic every 6 months at no cost to you until the device is removed or the device is approved by the FDA. If you are pregnant, anticipate pregnancy or are nursing you are not eligible to participate in this study.

Purpose

The purpose of this research study is to investigate the combined effects of stand and step (locomotor) training with electrical stimulation of the spinal cord in patients who have had a complete spinal cord injury. We hope to show that this treatment will increase the muscle strength in your extremities. It is known that patients with a severe spinal cord injury are able to be trained using locomotor training. Locomotor training is a process to develop activity in the nerves and muscles of patients with a spinal cord injury during standing and stepping with assistance from people. As well, electrical stimulation of the spinal cord following spinal cord injury in animals demonstrates a walking-like motion. The information learned in this study will be used to find the best conditions to assist patients to stand and walk using electrical spinal cord stimulation and locomotor training. The patient in a research study is called a subject.

Procedures

You will undergo locomotor training, a recognized method to enhance standing and walking following spinal cord injury, under the supervision of Dr. Harkema at the University of Louisville. In discussion with Drs. Boakye or Neimat, and Dr. Castillo, and Dr. Harkema, you have been considered to be eligible to enter this study.

1. Experiments

   We will test the activity of your leg muscles during resting conditions and while you are standing or stepping (overground or with body weight support) with the help of trainers who will be moving your legs. In all of these experiments, there will be sensors pasted to your skin to record the electrical activity of your arm and leg muscles. During the motor testing experiments we may use a needle to insert a fine wire in muscles in each leg to record the electrical activity. Other sensors pasted to the skin will record the position of your legs, and sensors placed inside your shoes will record the amount of weight on your legs. We may measure continuous blood pressure, breathing rate and temperature with different sensors during any of the experiments or training sessions. We will videotape how you stand and step. You will have the opportunity to rest at any time during any of these experiments. We will ask you to participate in these experiments throughout the study.

   a. Functional NeuroPhysiological Assessment
      i. In this test you will be lying down on your back and we will ask you to move your legs.
      ii. This test will take approximately 1 hour to perform.

   b. Somatosensory Evoked Potentials
      i. We will apply an electrical current over the on your wrists and ankles.
      ii. Devices maybe pasted to your skin to record the electrical activity of your muscles during the stimulation.
      iii. You will wear a cap with electrodes that will touch your scalp to record your brain activity.
      iv. This test will take approximately 1 to 2 hours to perform.

c. Sympathetic Skin Responses
   i. We will test the amount of sweat in your hands and feet after providing a low level of electrical stimulation over one of the nerves in your arm, leg and forehead.
   ii. This test will take approximately 1 hour to perform

d. Motor Testing
   i. You will be helped to stand or step on a treadmill while wearing a harness that is attached to an overhead suspension device which will support the weight of your body.
   ii. If standing or stepping overground, trainers will be there to assist you if you need it.
   iii. The testing will last from 2 to 4 hours.

e. Reflexes
   i. A low level of electrical stimulation will be used over one of the nerves of your legs, back, neck or arms to measure how your leg muscles respond to the stimulation during standing and also during resting conditions.
   ii. A pad will be pasted over the skin of your leg, neck or back and a small current will pass through it.
   iii. For some tests you will hear a loud sound, it might take you by surprise and we will measure how your leg muscles respond to your reaction to the sound.
   iv. For some tests, we will magnetically stimulate your brain and we will measure how your leg muscles respond to the stimulation of your brain.
   v. You will be provided earplugs during the magnetic stimulation test. You will be asked to inform the technician if an earplug loosens or becomes detached and the test will be stopped immediately to minimize the risk of permanent hearing loss.
   vi. We may use stimulation of your brain, neck or arms in combination with epidural stimulation and measure the responses on your legs.
   vii. Each test will take approximately 2-3 hours to perform.

f. Bladder Function
   i. You will be asked to rest on an exam table on your back.
   ii. A small tube will be inserted in your bladder. Your bladder will then be filled with water. The doctor or technician will measure the pressure in your bladder.
   iii. We may measure how your leg muscles respond to your bladder being filled and emptied.
   iv. We may repeat this test with stimulation following your surgery.
   v. This test will last approximately 30 minutes.

g. Cardiovascular Function
   i. We will measure your blood pressure, heart rate and breathing rate while you are lying down and also when you are moved to a seated position.
   ii. You will be asked to follow a diet excluding caffeine, alcohol, smoking, and foods that are high in fat on the evening prior to and the morning of study.
   iii. Devices will be pasted to your skin to record heart rate activity.
   iv. We will take a small blood sample (approximately 4 tablespoons) from your arm
   v. We may repeat this test with stimulation following your surgery and measure how your leg muscles respond to stimulation during this test.
   vi. This test will take approximately ninety (90) minutes to perform.

h. We will ask you to fill short questionnaire(s)

i. We will ask you questions about your injury and its impact of your everyday life, autonomic function and sexual function.
ii. You can refuse to answer any or all questions.

i. Blood tests
   i. You will be asked to have a 12-hour fast the night before, including no food or drink (no alcohol or caffeine; water is allowed).
   ii. A blood sample will be drawn to look at chemicals that provide information about your bone formation, bone loss, inflammatory status, blood glucose control and overall metabolism. Approximately 4 tablespoons of blood is needed.
   iii. A sample of your blood may be stored for testing at the end of the study.
   iv. All specimens obtained during this study that are not processed immediately will be stored in the Medical Dental Research Building at the University of Louisville. Samples will be stored for future analysis related to this study. Your samples will be stored until all data related to this study has been analyzed and at the end of this period your specimen(s) will be destroyed.
   v. This testing will take approximately 15 minutes.

j. Random Comprehensive Drug Screen
   i. You will be asked to provide a urine sample for random drug screening.
   ii. You may be asked to do this multiple times throughout your study participation.
   iii. Your results from this test may cause you to be withdrawn from the study.

Yes, you may keep my blood and urine samples:_____
Signature of Subject Date signed

NO, you may not keep my blood and urine samples: _____
Signature of Subject Date signed

2. Surgery
   a. You will be asked to complete several laboratory tests approximately 4 weeks before surgery. These tests are to assess and reduce your risk of infection. These may include nasal and rectal swabs, urine samples and blood samples. The study physicians may recommend treatment based on the results of these tests. You may be asked to repeat these tests.
   b. You will undergo spine surgery at University Hospital by Dr. Boakye or Dr. Neimat. You will also be asked to sign an additional surgical consent form required by University Hospital. This requires an operation on your lower back performed under sedation by intravenous medications injected into your body.
   c. A 4 to 6” cut will be made in your lower back and one electrode (device to produce electrical stimulation) measuring approximately ½ x 3” will be inserted in your spinal canal.
   d. During this 4-5 hour operation several electrical stimulations will be given to your spinal cord in order to determine the best place for the sensor.
   e. One 3” x 1/2” battery (generator) will be put under your skin through a cut placed in the lower abdomen (on each side). The subject and investigator will be able to adjust the electrical stimulator by an external device.
   f. Approximately half a cup of blood will be used during this operation, either from the surgical cuts or by the anesthesiologists who will draw blood to perform routine laboratory tests.
   g. The electrode and battery generator system will remain in place, but can be removed at your request.

h. You will be monitored following your operation in the recovery room at University Hospital for approximately 4-24 hours and then may be transferred to the Frazier Rehab Institute.
i. A second surgery will only be necessary in the rare case that the electrode wires become disconnected from the stimulator or the need to remove the electrode.

3. Mid-experiments
   a. You may remain at the Frazier Rehab Institute for approximately 2 weeks (only if necessary) and will undergo the same experiments you did before your surgery.
   b. During some of these experiments we will use the sensors we placed in your back and send a stimulus to your spinal cord. We will find the best stimulation settings to help you move your legs, stand and walk.

4. Locomotor Training
   a. The locomotor training program will take place approximately two weeks after your surgery.
   b. Each locomotor step/stand training session will last about 1-2 hours and will occur up to 5 times weekly for a total of 80 sessions each. After the initial 20 sessions, we may ask you to come train in the lab twice a day. A session will be counted if the progression criteria have been met. We will use different stimulation patterns to assist you stand or step.
   c. You will be helped to step on a treadmill while wearing a harness that is attached to an overhead suspension device that will support the weight of your body. There will be one person behind you and at your hips to help keep you stable. There will also be one person at each of your legs to assist you by helping you to put weight on your legs and to swing your legs.
   d. You will be helped to stand overground in a specially designed standing frame. There will be one person behind you and at your hips to help keep you stable. You will also be assisted to keep your knees extended and maintain good posture during standing.
   e. If you feel tired or need a break during the session you can take a break at any time.
   f. In the 80 sessions, the goal will be to reach your maximum comfortable walking speed on the treadmill with no assistance from the overhead suspension device that will support the weight of your body. We might train you to walk in the overground environment once you only need minimal assistance from the overhead suspension device.
   g. Throughout your 80 training sessions, we may repeat the experiments described above once a week.
   h. You might be asked to take a “Patient Programmer” device home, to practice additional standing with stimulation in a standing frame at home.
   i. We will only allow you to use the “Patient Programmer” at home if you have shown that you can perform leg movements in the supine position or stand independently in a standing device.
   j. The “Patient Programmer” will allow you to turn the stimulation on and off and up and down within the limits decided by the research team.
   k. If you are asked to do additional stand training at home you will be asked to keep a log of these sessions and bring it to the research team once a week.
   l. We might ask you to return to the laboratory for extended training (additional 80 - 200 sessions) during your follow up period. The training will be performed to optimize stand/step after a period of home training.

Potential Risks

This study may involve risks that are currently unforeseeable. The study may involve the following physical risks and/or discomforts:

Surgical Risks
- Mild Discomfort (likely)
- Bleeding (likely)
- Bruising (likely)
- Infection at the incision site (less likely)
- Complications from anesthesia
- Heart attack (rare)
- Pneumonia (rare)
- Blindness (rare)
- Excessive blood loss (rare)
- Death (rare)
- There may be mild discomfort during the two operations which will be treated with pain medications as required.
- If you have any of these difficulties from the surgeries, Dr. Castillo will be contacted immediately.

Psychological Risks
- It is unknown if there are psychological risk.
- There is a possibility of a psychological risk if the procedure does not work but they are unknown.

Electrode/Device Risks
- Jolting or shocking
- Erosion
- Undesirable change in stimulation
- Allergic response
- Hardware malfunctions or migration
- Breakage or failure resulting in further injury to the spinal cord

Locomotor Training Risks
- Dizziness with standing or stepping (likely)
- Skin irritation from the harness or hand placements of the trainers helping your legs (likely)
- Blood Pressure Changes (less likely)
- Shortness of Breath (less likely)
- Muscles & Joint Aches (rare)
- Joint Sprain (rare)
- Broken Bone (rare)
- If you have any of these difficulties during standing and stepping, we will stop the training session and Dr. Castillo will immediately be informed

Experiment Risks
- Muscle soreness (likely)
- Skin irritation from the sensors and/or wires (likely)
- Tingling feeling over the legs or back from the stimulation (likely)
- Changes in blood pressure and heart rate (likely)
- Dizziness (likely)
- Shortness of breath (less likely)
- Bleeding at site of needle insertion (rare)
- Burning or pressure when you urinate following the bladder test. (likely)
- Bleeding when you urinate following the bladder test (rare).
- Seizures from the magnetic brain stimulation (rare)
- Temporary or permanent hearing loss from magnetic brain stimulation (rare)

You will be excluded from any testing using magnetic brain stimulation if you have any of the following:
- metal in head, except mouth (i.e. cochlear implant, implanted brain stimulators, aneurysm clips)
- increased intracranial pressure
- cardiac pacemakers
- implanted medication pump
- intracardiac lines
- significant heart disease
- history of stroke or other brain lesions
- personal or family history of epilepsy
- you are receiving tricyclic antidepressants or neuroleptics
- have had heavy alcohol consumption less than 48 hours prior to the test.

Possible Pregnancy Risks

Pregnant women are excluded from this study, as the risk to the fetus is unknown. You should discuss pregnancy risks with your doctor before signing this consent form. Talk to your doctor about the best method of birth control to use while you are in this study. If you are pregnant or become pregnant, your unborn child may suffer harms that we have not seen before. It is important that you tell someone on the research team at 502-581-8675 right away if you become pregnant during the course of this study. If you become pregnant, you will be terminated from the study by the study doctor. If you become pregnant while in the study, the sponsor may ask to follow the outcome of the pregnancy. If you agree to allow the study doctor to follow your pregnancy, you will be asked to sign a separate consent form.

Benefits

We do not know the benefits of this study. Although there are no guarantees of benefits occurring during this experimental study, the information obtained from your participation in this study may help you and/or other patients who have/or will sustain spinal cord injuries in the future.

Alternatives

Instead of taking part in this study, you could choose to not participate. There are no alternatives to this study.

Research Related Injury

If you are injured by being in this research study, the study doctor will arrange for you to get medical treatment. Your study doctor has not set aside money to pay for treatment of any injury. You and your insurance will be billed for the treatment of these injuries. Before you agree to take part in this research study you should find out whether your insurance will cover an injury in this kind of research. You should talk to the study doctor or staff about this. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor, Camilo Castillo, M.D. at 502-899-3623.

Payment

You will not be paid for your time or inconvenience while you are in this study.
You will be paid by prepaid card for travel based on the federal mileage rate and parking fees up to $75 dollars per day while you are in the study. Because you will be paid to be in this study, the University of Louisville may collect your name, address, social security number, and keep records of how much you are paid. You may or may not be sent a Form 1099 by the University. This will only happen if you are paid $600 or more in one year by the University. This will not include payments you may receive as reimbursement for actual expenses based on receipts or actual miles traveled. We are required by the Internal Revenue Service to collect this information and you may need to report the payment as income on your taxes.
You can still be in the study even if you don't want to be paid.

Costs

There will be no additional costs to you for participating. However, you or your insurance company will be billed for all office visits and procedures that are part of routine medical care. It is your responsibility to find out what costs, if any, your insurance company will cover before taking part in the study. The cost of the operation(s)

that will take place at University Hospital will be covered by that institution. The cost of 14 days of hospitalization at Frazier Rehab Institute (if needed) will be covered by that institution. Radiology and anesthesia professional expenses will be covered by the radiology and anesthesiology PSCs at University Hospital. The epidural electrodes, leads, generator packs, and other expenses associated with the equipment for the operations will be also coved by the research project. Postoperative care provided by Drs. Boakye, Neimat and Castillo related to this study will be provided without charge for the duration of your participation in the study. Should any further procedures be required related to the epidural leads, and/or battery generator, the expenses incurred for those procedures will be covered by the participating institutions. If you are injured by the research, there may be additional cost to you for participating. Otherwise there will be no additional cost to you.

HIPAA Research Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides federal safeguards for your protected health information (PHI). Examples of PHI are your name, address, and birth date together with your health information. PHI may also include your medical history, results of health exams and lab tests, drugs taken and results of this research study. Your PHI may not be used or shared without your agreement, unless it meets one of the HIPAA exceptions.

State and federal privacy laws protect your health information. In most cases, health information that identifies you can be used or shared by the research team only if you give your permission by signing this form.

If you sign this form your health information will be used and shared to answer the research questions described in this document and to make sure that the research was done correctly. The time period when information can be used or shared ends when all activities related to this study are completed.

Your access to your health information will not be limited during this study. When the study is over, you will have the right to see your health information related to this research.

You do not have to sign this form. If you do not sign this form you may not participate in the study and health information that identifies you will not be shared with the research team.

Site(s) where health information about you will be used or shared for this research:

In our research, the research team will look at and may share information about you and your health. Federal law requires that health care providers and researchers protect the privacy and security of health information that identifies you. We may ask for your health information from the following:

Affiliated Sites:
University of Louisville
University of Louisville Hospital
Frazier Rehab Institute

Unaffiliated Sites: Any physician offices, clinics or medical facilities where you may seek treatment during this study.

Protected health information (PHI) that will be used or shared for research

Diaries and questionnaires
Discharge summaries
Records of your operation(s)
Medical Progress notes

STUDY TITLE: SPINAL EPIDURAL ELECTRODE ARRAY TO FACILITATE STANDING AND STEPPING IN SPINAL CORD INJURY

Healthcare provider orders
History and physical exams
Laboratory, x-ray and other tests
Photos, videotapes or digital or other image
Records about the study device

Revocation of Research Authorization

You may cancel the permission you have given to use and share your protected health information at any time. This means you can tell us to stop using and sharing your protected health information. If you cancel your permission:

- We will stop collecting information about you.
- You may not withdraw information that we had before you told us to stop.
  - We may already have used it or shared it.
  - We may need it to complete the research.
- Staff may ask your permission to follow-up with you if there is a medical reason to do so.

To cancel your permission, you will be requested to complete a written "Revocation of Research Authorization" form located at the end of this document. You may also obtain a copy from your study doctor, designated personnel or from the Human Subjects Protections Program Office website (https://louisville.edu/research/humansubjects/templates/biomedical-forms).

Information Available on ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Confidentiality

Total privacy cannot be guaranteed. We will protect your privacy to the extent permitted by law. If the results from this study are published, your name will not be made public. Once your information leaves our institution, we cannot promise that others will keep it private.

Your information may be shared with the following:

- The sponsor, The Leona M. and Harry B. Helmsley Charitable Trust and others hired by the sponsor to oversee the research
- Organizations that provide funding at any time for the conduct of the research.
- The University of Louisville Institutional Review Board, Human Subjects Protection Program Office, Privacy Office, others involved in research administration and compliance at the University, and others contracted by the University for ensuring human subjects safety or research compliance
- The University of California Los Angeles Institutional Review Board, Office for Protection of Research Subjects and others involved in the research program at the University.
- The local research team
- Researchers at other sites participating in the study
- People who are responsible for research, compliance and HIPAA oversight at the institutions where the research is conducted, i.e. Frazier Rehab Institute and University Hospital
- Government agencies, such as:
  - Office for Human Research Protections

  - Office of Civil Rights
  - Food and Drug Administration
- People responsible for billing, sending and receiving payments related to your participation in the study
- Data Safety Monitoring Board
- Medtronic

Medtronic will keep your health information confidential in accordance with all applicable laws and regulations. Medtronic may use your health information for its business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and another business purposes. Any reports or publications about the study or any other research will not include your name or a description of you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

Security

Your data will be kept private by being stored in a locked cabinet behind closed door with limited access. Electronic data is stored on a password protected computer with limited access in a locked area.

Conflict of Interest

This research study utilizes a device that is licensed to Power NeuroRecovery. The person running this study (or member of this research team) has a relationship with Power NeuroRecovery. If you have any questions about this conflict of interest, please talk to Holly Symonds Clark at (502) 852-3853. She is a not a member of the study team and does not have a conflict of interest related to the study.

Voluntary Participation

Taking part in this study is completely voluntary. You may choose not to take part at all. If you decide not to be in this study, you won't be penalized or lose any benefits for which you qualify. If you decide to be in this study, you may change your mind and stop taking part at any time. If you decide to stop taking part, you won't be penalized or lose any benefits for which you qualify. If you would like the electrodes removed from your body they will be removed. If you decide to withdraw from the study and have the electrodes removed please contact Dr. Harkema at (502) 581-8675. You will be asked to meet with Drs. Harkema, and Boakye and/or Neimat determine an appropriate surgery date for the removal of the electrodes.

You will be told about any new information about the study that could affect your decision to continue in the study.

Termination

Your study doctor has the right to stop this study at any point. Your study doctor may take you out of this study with or without your okay. Reasons why this may occur include circumstances that arise which warrant doing so. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate. If the study doctor believes that the pain or discomfort might pose a risk to you, you will be terminated from the study. If you become pregnant you will be terminated from this study.

Participation in Other Research Studies

You may not take part in this study if you are currently in another research study. It is important to let your doctor know if you are in another research study.

Contact Persons

If you have any questions, concerns, or complaints about the research study, please contact Susan Harkema, Ph.D. at (502) 581-8675.
Once you are enrolled in this study, you will be given additional contact numbers that are answered 24/7 to reach a designated research staff member if you need immediate assistance.

Research Subject's Rights

If you have any questions about your rights as a research subject, you may call the Human Subjects Protection Program Office at (502) 852-5188. You may discuss any questions about your rights as a research subject, in private, with a member of the Institutional Review Board (IRB). You may also call this number if you have other questions about the research, and you cannot reach the study doctor, or want to talk to someone else. The IRB is an independent committee made up of people from the University community, staff of the institutions, as well as people from the community not connected with these institutions. The IRB has approved the participation of human subjects in this research study.

Concerns and Complaints

If you have concerns or complaints about the research or research staff and you do not wish to give your name, you may call the toll free number 1-877-852-1167. This is a 24 hour hot line answered by people who do not work at the University of Louisville.

STUDY TITLE: SPINAL EPIDURAL ELECTRODE ARRAY TO FACILITATE STANDING AND STEPPING IN SPINAL CORD INJURY

Acknowledgment and Signatures

This informed consent document is not a contract. This document tells you what will happen during the study if you choose to take part. Your signature indicates that this study has been explained to you, that your questions have been answered, and that you agree to take part in the study. You are not giving up any legal rights to which you are entitled by signing this informed consent document. You will be given a copy of this consent form to keep for your records.

Subject Name (Please Print)	Signature of Subject Date Signed
Printed Name of Legally Authorized Representative (if applicable)	Signature of Legally Authorized Representative Date Signed

Authority of Legally Authorized Representative to act on behalf of Subject

*Authority to act on behalf of another includes, but is not limited to parent, guardian, or durable power of attorney for health care.

Printed Name of Person Explaining Consent Form	Signature of Person Explaining Consent Form (if other than the Investigator) Date Signed
Printed Name of Investigator	Signature of Investigator Date Signed

List of Investigators:	Phone Numbers:
Susan Harkema, Ph.D.	(502) 581-8675
Maxwell Boakye, M.D.	(502) 540-3694
Camilo Castillo, M.D.	(502) 333-8155
Claudia Angeli, Ph.D.	(502) 581-8675
Joseph Neimat, M.D.	(502) 581-8675

STUDY TITLE: SPINAL EPIDURAL ELECTRODE ARRAY TO FACILITATE STANDING AND STEPPING IN SPINAL CORD INJURY

REVOCATION OF AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR HEALTH INFORMATION FOR RESEARCH

PI Address: 220 Abraham Flexner Way
Louisville, KY 40202
PI Phone: 502-581-8675

Return To:

OR

Institutional Review Board
MedCenter One, Suite 200
501 E. Broadway
Louisville, KY 40202

Do not sign this letter unless you are withdrawing from this research. You will be sent confirmation that this notice was received.

☐ **Main** ☐ **Blood Sample** ☐ **Urine Sample**

To Whom It May Concern:

I would like to discontinue my participation in the research study noted above. I understand that health information already collected will continue to be used as discussed in the Authorization I signed when joining the study.

Your options are (***choose one***):

☐ **Withdraw from Study & Discontinue Authorization:**
Discontinue my authorization for the future use and disclosure of protected health information. In some instances, the research team may need to use your information even after you discontinue your authorization, for example, to notify you or government agencies of any health or safety concerns that were identified as part of your study participation.

☐ **Withdraw from Study, but Continue Authorization:**
Allow the research team to continue collecting information from me and my personal health information. This would be done only as needed to support the goals of the study and would not be used for purposes other than those already described in the research authorization.

_____ _____
Printed Name and Signature of Subject Date Signed

_____ _____
Signature of Subject's Legal Representative (if subject is unable to sign) Date Signed

_____ _____
Printed Name of Subject's Legal Representative Birthdate of Subject

_____
Relationship of Legal Representative to Subject

_____ _____
Subject's Address Subject's Phone Number

Optional:
I am ending my participation in this study because: _____