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Official Title:

Spinal Cord Stimulation for Restoration of Arm and Hand Function in People with Subcortical Stroke

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Protection of Human Subjects

Study: Spinal Cord Stimulation for restoration of arm and hand function in people with subcortical stroke

Study Participants

Stroke is the leading cause of arm paralysis, and among the heterogeneous lesion types, those involving damage of the corticospinal tract at the level of the white matter and internal capsule induce permanent and severe motor deficits in survivors. These cases constitute a large portion of the stroke patient population (up to 25%). Interruption of the cortico-spinal tract isolates the spinal circuits located within the cervical segments from descending cortical inputs leading to permanent arm and hand paralysis. Additionally, lack of descending modulation of the spinal reflexes causes spasticity and poor limb control. People with this type of stroke typically have little to no functional limb use. We chose this study population for ethical reasons that include greater severity of impairment (i.e., a greater need for the proposed system), fewer alternate treatment options, and greater potential to benefit.

Currently the leading approved clinical therapy for stroke is physical rehabilitation which does not produce satisfactory recovery of motor function in this specific stroke population.

Inclusion criteria

In order to participate in the study, an individual must meet the following criteria at enrollment:

1) Participants must have a suffered a single, ischemic or hemorrhagic stroke more than 6 months prior to the time of enrollment with hemiparesis as a result.

2) There must be stroke-related damage, radiologically visible, in the deep white matter of the affected frontal lobe.

3) Participants must be between the ages of 21 and 70 years old. (Participants outside this age range may be at an increased medical risk and have an increased risk of fatigue during testing.)

4) Participants must have scores higher than 7 and lower than 45 on the Fugl-Meyer scale.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Participants must not have any serious disease or disorder (ex. neurological condition other than stroke, cancer, severe cardiac or respiratory disease, renal failure, etc.) or cognitive impairments that could affect their ability to participate in this study.

2) Female participants of child-bearing age must not be pregnant or breast feeding.

3) Participants must not be receiving anticoagulants.

4) Participants may not have any implanted medical devices that are not compatible with MRI

5) Severe claustrophobia.

6) Participants with spasticity scores higher than 2 on the Modified Ashworth Scale in any upper extremity muscle

7) Participants must not be on anti-spasticity or anti-epileptic medications for the duration of the study.

8) Participants who have been deemed inappropriate for participation based upon results from the Brief Symptoms Inventory (BSI-18) and discussions with the Principal Investigator and a study physician.

9) Evaluation to sign consent form score <12

Study Procedures, Materials, and Potential Risks

Only appropriately qualified physicians, researchers and/or clinical personnel will perform the procedures described below. All of the information gathered will be stored on a password-protected server, and available hard copies will be stored in a locked room inside a secured building.

The procedures involved in this study are as follows:

***Procedure* - 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. If a study physician believes there is a risk of renal insufficiency which could affect subject's ability to receive gadolinium-based contrast for the structural MRI, we will also perform blood urea nitrogen (BUN) and creatinine (Cr) tests to examine renal function.

Risk - The insertion of the needle to draw blood may cause temporary discomfort, bruising from where the needle enters the vein, or soreness. There is a slight risk of infection. Fainting may occur, but this risk is expected to be rare, or occur in less than 1% of people.

***Procedure* --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. This scan will be co-registered with a post-operative high-resolution CT scan of the neck so that we can accurately visualize the location of the leads with respect to neural tissue. We may use a neck brace during this MRI and the CT scan 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 brain and cervical spinal cord functional Magnetic Resonance at rest with eye closed to document the resting state functional connectivity of the brain before the start of the study. 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.

Risk - The magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. To ensure that the subject's neck is in the same position for the CT and MRI and to stabilize the spine for functional MRI imaging, we may ask the subject to wear a neck brace during these scans. Subjects may feel some discomfort as a result of wearing the brace. The subject may experience feelings of anxiety or claustrophobia during the MRI scan. There is also a risk of the MRI scanner attracting metal objects. There is a risk of loosening of ferromagnetic objects which are affixed to bone. There is a risk of tissue heating for metallic implants.

***Procedure* --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 vancomyin (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.

Risk - Allergic reaction, itching depending on each individual and their reported history. Seizure, fever, rash, itching, diarrhea C/Difficile (a bacteria), nausea, vomiting, increased liver enzymes, and abnormal blood urea nitrogen or serum creatinine levels, which are related to kidney function.

***Procedure* -- 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.

Risk - Increased pain at the injection site and local skin infection. Lightheadedness, dizziness, drowsiness, blurred vision, respiratory depression, and swelling, sore throat from the respiration tubes. Low blood pressure and irregular heartbeat.

***Procedure* -- Spinal lead placement procedure**

Between one and three percutaneous linear leads will be placed in the cervical epidural space near the spinal nerve roots and cervical dorsal root ganglia (Boston Sientific or Medtronic Leads). Clinical practice commonly includes placement of either a single paddle lead or alternatively two or three cylindrical linear leads into the epidural space of the cervical spine. All leads will be placed in the cervical epidural space by Dr. Peter C. Gerszten in the operating rooms at UPMC Presbyterian Hospital. Pre-operative antibiotics will be administered as is standard for such procedures.

The subject will be awake throughout the procedure, and 1% preservative-free lidocaine will be used for local anesthesia. 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 cervical 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 arm muscles ipsilateral to lead implantation. These will include: deltoid, biceps, triceps, extensors carpi radialis, flexor carpi radialis, extensor digitorum communis, flexor digitorum profundis, and abductor pollicis longus. However, they may include other muscles of the arm 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.

For each of the spinal leads, a 14 gauge epidural Tuohy needle will be advanced through the T1-T2 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. Either an 8- or 16-contact stimulator lead (Medtronic or Boston Scientific), which is designed to span 2-3 spinal segments, will then be advanced into the C5-T1 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.

During a brief volley of stimulation, the subject will be asked to report the region of their body over which they feel any evoked sensations. The lead placement will be iteratively adjusted based on subject feedback and EMG recorded responses until the evoked sensations and the EMG responses match the paretic muscles locations. The stylet will then be removed under live fluoroscopic guidance to ensure the lead does not move. Leads are secured to the fascia overlying the T3-T4 spinous processes using lead anchors (supplied within lead placement kit) and 2x 2-0 silk sutures. 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).

According to the clinical judgement of the neurosurgeon and anesthesiologist present during the implantation procedure, general anesthesia may be used instead of local.

Risk - According to the product performance report covering the Medtronic Spinal Cord Stimulation systems and leads, the most occurring adverse event were reported to be related to pain or discomfort near the area of the implant. The most likely technology related event was instead lead migration, which occurred 6.2% of patients. In the case of Boston Scientific Leads according to the PMA that covers the Boston Scientific spinal cord stimulator system, nearly all of the adverse events related to that device occur in less than 5% of cases. The exception to this is lead migration, which occurs in 16.6% of patients. Even in the case where lead migration occurs, the medical risk to the subject is low, with the more likely result being a change in the anatomical location of the perceived sensation. In the protocol described in this study, we intend to examine the stability of the neurophysiological response to stimulation over the course of the experimental session and the effects that stability may have on the perceived sensations. In the case of lead migration, we may replace the leads in a second procedure. We expect the risks associated with that procedure to be identical to the risks of the first placement procedure. The Medtronic Report rates complications based on data from the Medtronic Product Performance Report drawn from a multi-centric trial including 82 centers in North America studying adverse events registered in patients implanted with spinal cord stimulation systems. Placement of the stimulator leads needle could potentially result in nerve damage that can cause neurological dysfunction (1.7%). Among these, paresthesia was the most common. Paresthesia is a non-painful tingling sensation restricted to certain areas of the skin that correlate with the innervation of the dermatomes of the damaged sensory afferents. Very rarely, it is possible that a tear in the dura could occur during lead placement resulting in a spinal fluid leak (0.001%). A spinal fluid leak can cause headaches and may, in rare cases, require surgery. There is a low risk of infection as a result of lead placement, though the use of sterile technique during device placement makes this risk low (Risk: 3.1%). Placement of the Tuohy needle and spinal cord stimulator leads could potentially result in nerve damage that can cause neurological dysfunction. Additionally, it is possible that a tear in the dura could occur, resulting in a spinal fluid leak (Risk: 0.5%, Risk: 5.3%). A spinal fluid leak can cause headaches and may, in rare cases, require surgery. The placement of these devices is common clinical practice for treatment of intractable low back and limb pain, and complications are rare. There is a low risk of infection as a result of lead placement, though the use of sterile technique during device placement makes this risk low (Risk: 3.7%, Risk: 4%).

The lead placement procedure occurs under fluoroscopic guidance, which involves radiation exposure. The radiation exposure associated with this procedure is expected to be approximately 1.5 rems or less. If a lead replacement procedure is required, this radiation exposure will be doubled to approximately 3 rems or less. For reference, an annual radiation exposure of 20 rems is permitted to the most sensitive organs of radiation workers by federal regulation. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer.

***Procedure* --Post-operative antibiotics**

We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. Cefazolin (1g; IV) will be given every 8 hours for 5 days. 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.

Risk - Allergic reaction, itching depending on each individual and their reported history. Seizure, fever, rash, itching, diarrhea C/Difficile (a bacteria), nausea, vomiting, increased liver enzymes, and abnormal blood urea nitrogen or serum creatinine levels, which are related to kidney function.

***Procedure* -- 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. 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 with the affected arm relaxed in resting 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 affected arm, the external FDA approved stimulator Natus Medical Protektor32 will be connected to the SCS lead using Ad-Tech Medical Instrument Corporation interconnects that are used during routine clinical procedures to connect spinal and brain leads to the electrical stimulator.

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.

Stimulus parameters to vary include:

• Pulse amplitude (maximum of 12.7 mA per electrode; 20 mA for all electrodes simultaneously;)

• Pulse width (maximum of 1000 us;)

• Pulse frequency (maximum of 1200 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.

Risk - Uncomfortable sensations may be elicited as a result of stimulation. Involuntary movements which subside after several minutes may be elicited. It is possible for high levels of stimulation to cause damage to neural tissue.

***Procedure* --Post-operative High-Resolution CT to Document Lead location**

Within one week after lead placement, we may perform a high-resolution CT scan of the cervical spine to document the 3-dimensional location of the leads with respect to bony landmarks. This scan will be co-registered with the pre-operative high-resolution MRI to determine the location of the leads with respect to the spinal cord and spinal roots. We may use a neck brace during this CT and the MRI without contrast to ensure the subject's neck is in a similar position for both scans.

Risk - The maximum amount of radiation exposure that participants will receive from the high-res CT is 4 rem (a unit of radiation exposure). If the leads are placed twice, this exposure will double. In combination with x-rays and fluoroscopy during lead placement, the total exposure for a subject undergoing two lead placement procedures will be 13.4 rems, which is significantly less than the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from this CT is considered to be low.

***Procedure* -- Weekly X-Ray to Document Lead Migration**

Once every 2 weeks, two X-ray images (AP and lateral views) of the cervical 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.

Risk - The maximum amount of radiation exposure that participants will receive from each x-ray is 0.3 rem (a unit of radiation exposure). There will be two x-rays per week, for lateral and AP views of the cervical spine, for four weeks, totaling tro 2.4 rems. This is a small fraction of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from these additional x-ray exams is considered to be low and comparable to everyday risks.

***Procedure* -- EEG, EMG and transcutaneous muscle stimulation studies**

Non-invasive electroencephalography (EEG), electromyography (EMG) and transcutaneous muscle stimulation may be used during the study to measure neural and muscular responses to electrical stimulation. 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 forearm of the affected limb and electrical stimulation to stimulate forearm muscles will be delivered via FDA-cleared stimulation device (Natus Medical Protektor32).

Procedure - Three-dimensional Reaching/Simulated Activities of Daily Living (ADL) Task:
Periodically throughout the experimental sessions, we will ask each subject to perform a three-dimensional reaching/ simulated activities of daily living (ADL) task. Patients will be asked to reach towards custom built objects and grasp them. Each object will promote a particular type of grasp. For example, a large sphere will promote a power whole hand grasp, a cylinder will promote a cylindrical grasp while a flat shape object will promote a precision index-thumb pinch grasp. Objects may be placed in space by haptic robots that can measure grasping and interaction forces. Additionally, according to the level of motor-impairments patients might be supported in their movements by passive clinical arm support systems regularly used in rehabilitation protocols. Each ADL activity considered will be functionally based within five domains: homemaking, hygiene, feeding, dressing, and entertainment. Prior to testing, ADLs with which the participant has difficulty performing without treatment will be identified. A simulated environment will be presented to the participant including select props or objects commonly utilized while performing the ADL being tested. For example, a toothbrush and toothpaste bottle may be presented to evaluate the subject's ability to dispense the toothpaste onto the toothbrush by appropriately modulating their grip force; or a set of clothing presented to evaluate the subject's ability to fold clothes using the affected limb. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh.

During these trials EES will be provided to verify its effects on motor task execution. Superficial EMG electrodes and gyroscopes to measure limb movements will be placed on the affected arm, and external stimulators will be connected to the SCS lead. Bursts of stimulation derived from the tests previously described will be delivered through the EES 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 arm 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 reaching, grasping and pulling. Finally closed loop control of stimulation using kinematic or EMG inputs might be implemented to control force.

- 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.

- 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.

Procedure - Kinarm Center-out Task:
Periodically throughout the experimental sessions, we will ask each subject to perform an arm center out task in the Kinarm. Patients will be asked to reach towards targets shown on the kinarm system in a plane at different angles from center. Each target will promote a particular type of reach. For example reach in front, reach at 45 degrees on the right or reach towards the chest (effectively flexing the elbow). Target will be arranged in a standardized circular fashion at every 30 or 45 degrees (respectively 12 or 8 targets). The Kinarm facilitates reach execution by comfortably supporting the weight of the arm at the shoulder in a gravity neutral position. These tests will be performed in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh.

During these trials EES will be provided to verify its effects on motor task execution. Superficial EMG electrodes and gyroscopes to measure limb movements will be placed on the affected arm, and external stimulators will be connected to the SCS lead. Bursts of stimulation derived from the tests previously described will be delivered through the EES 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 arm 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 reaching and pulling.

***Procedure* -- 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 arm movement assessments in the KINARM system (Kinarm, Kingston, ON, Canada) at baseline, day 29 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) [5, 37]. 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.

***Procedure* -- Single Joint movement and torques**
To quantify the range of motion of arm joints (shoulder, elbow and wrist) and the joint torques produced with and without SCS we will use the clinical the clinical isokinetic testing system: HUMAC NORM by CSMi. This data will be captured at baseline, during the 29 days of the implantation period and at the follow up visit. The HUMAC NORM system is a clinical system used to assess isokinetic, isotonic and isometric joint movements and torques in patients. Hand strength/torques will instead be assessed with a standard hand-held

dynamometer and pinch gauge. Amy Boos will perform this testing. In these tests, a subject places their hand and fingers around a smooth bar or plate and applies force for 3 seconds before relaxing their muscles to release the bar/plate.

***Procedure* -- 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, the subject will be positioned prone on an examination table, and using sterile technique, the lead will be gently pulled until it is removed. 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 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. After this follow-up call, no further follow up will be required after device removal.

The Fugl-Meyer Upper Extremity Motor Performance Section Test and Modified Ashworth scale will be administered during the last week of the study. Self-report questionnaires about spasticity will be administered throughout the study and should take less than 30 minutes.

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 video recorded or photographed during any of the experimental procedures for research or educational purposes.

Adequacy of Protection Against Risks

Informed Consent and Assent

Consent will be obtained after initial screening procedures (i.e. phone screening, meeting with research team/PI, BSI-18 administration). The consent process will take place at the RNEL (Keystone Building) or at Dr. Gerszten's office (UPMC Presbyterian). The consent process will be supervised by Dr. Peter Gerszten in a joint meeting with the PI or other Co-PIs in order to ensure full availability to answer any technical or medical questions the patient may have. A licensed physician who is also a listed investigator will obtain consent.

Once a potential subject has been identified, the subject will be educated about the goals, tasks, and requirements of the study. Initial questions will be answered and they will be provided with a copy of the consent form. Initial contact may be made by any investigator but the participant will have an opportunity to talk to the one of the study physicians prior to providing consent. The potential participant will also be encouraged to discuss this study and the information provided in the consent form with her or his treating physician. After the subject has had time to review the consent, an investigator will meet with them to review any additional questions. Conversations with potential subjects about the study may occur via written or verbal communication or in a face-to-face meeting. Such meetings may take place in person or using face-to-face videoconferencing software, such as Skype or Facetime. Consent and study discussions will be documented. If the subject is interested in participating, the consent is completed. After completion of the consent, participation in the study is initiated. The subject may withdraw at any time. Possibility of coercion and undue influence are minimized by giving sufficient time to review the consent and multiple opportunities to ask questions or opt to decline. During the initial contacts and consent process, it will be made clear to the potential subject and/or family that their participation in this study is completely voluntary and whether or not they provide consent for participation in this study will have no effect on:
1) Their current or future relationship with the University of Pittsburgh;
2) Their current or future medical care at a UPMC hospital or affiliated health care providers;
3) Their current or future relationship with a health care insurance provider.

The study team, including the PI, will be available to the subject throughout the duration of the study to answer questions. The PI and the study team will encourage subjects to ask questions and voice any concerns they may have, as well as to inform subjects about any changes in study procedures or risks. Additionally, study physicians strongly emphasize during consent meetings that subjects may withdraw at any time.

We will only enroll individuals over the age of 21 to ensure that the subjects are mature enough to understand the tasks, as well as the risks, involved in this study. Subjects will be provided with a copy of the consent form to review prior to enrolling in the study, allowing ample time for questions. The consent form will be reviewed with the subject by a physician co-investigator, as well as the PI, at the time of consent so that it is fully understood.

Protection Against Risk for Vulnerable Subjects

There will be no inclusion of vulnerable participants and no inclusion of pregnant women, fetuses, neonates or children in this study. The inclusion criteria state all participants must be 21 years of age and over, and pregnancy tests are performed to ensure no pregnant women are enrolled. Participants that are pregnant or trying to become pregnant or breastfeeding will be excluded from the trial. If the participant is female and child-bearing is a possibility, the participant will be required to consent to a pregnancy test before commencing the research project, as well as immediately before the implantation procedure.

Incidental findings will be discussed with participants, and the Principal Investigator will, where necessary, refer the participant to an appropriate medical specialist. Additionally, information on the finding and action taken will be sent to the participant's primary care practitioner so that further treatment can be delivered promptly.

Potential Benefits of the Proposed Research to Research Participants and Others

There will be no clear benefit to the participant from partaking in this research. Their participation in this research will add to the knowledge of research currently being carried out in the field of biotechnology and may assist in the future use of assistive technologies in health care. Participants may benefit from interaction with healthcare care professionals on a regular basis. This may offer additional support to usual clinical care.

The potential benefits to the participant and the broader community are thought to outweigh the anticipated risks given the many risk mitigations and safeguards in place to monitor individual participants throughout the trial closely.

Importance of the Knowledge to be Gained

Over 5 million Americans currently live with a form of motor paralysis as a consequence of stroke, spinal cord injury and multiple sclerosis. Among all, paralysis of the arm severely impacts the quality of life of affected individuals. Recovery of arm functions could lead patients to the restoration of independent daily activities and therefore it is often listed as one of their top priorities. Moreover, life-time associated care costs for people living with arm paralysis tops 5 million dollars per patient. Stroke is the leading cause of arm paralysis, and among the heterogenous lesion types, those involving damages of the corticospinal tract at the level of the white matter and internal capsule induce permanent and severe motor deficits in survivors. These cases constitute a large portion of the stroke patient population (up to 25%). Interruption of the cortico-spinal tract isolates the spinal circuits located within the cervical segments from descending cortical inputs leading to permanent arm and hand paralysis. Additionally, lack of descending modulation of the spinal reflexes causes spasticity and poor limb control. Currently the leading approved clinical therapy for stroke is physical rehabilitation which does not produce satisfactory recovery of motor function in this specific stroke population.

The effects of SCS on people suffering from stroke has not yet been tested in clinical settings. We believe that accumulated scientific evidence justifies the hypothesis that the application of SCS could yield large muscle forces to sustain arm movements while simultaneously enabling fine finger control in people with subcortical stroke. Specifically, we believe there is significant evidence that electrical stimulation of the posterior spinal roots with spinal cord stimulator leads will produce selective muscle recruitment in the arm muscles.

We believe that our approach is necessary to design a clinical therapy involving the use of SCS in people with stroke. This approach will allow us to acquire critical clinical and neurophysiological evidences to justify surgical implantation of future dedicated spinal leads for a novel therapy in stroke rehabilitation.