SPINAL CORD STIMULATION FOR RESTORATION OF FUNCTION IN LOWER-LIMB AMPUTEES

90-Day

Abstract

The goals of this study are to provide sensory information to lower limb amputees and reduce their phantom limb pain via electrical stimulation of the lumbar spinal cord and spinal nerves using FDA-cleared spinal cord stimulator leads for up to 90 days.

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INVESTIGATIONAL DEVICE EXEMPTION (IDE) APPLICATION

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D Investigational Plan

1.0 Purpose of the Investigation

1.1 Name of investigational device

SCS for Lower-Limb Amputations (SCS-LLA)

1.2 Intended use of the investigational device

In the proposed study, we will investigate the efficacy of community use and safety of a neuroprosthetic system that uses spinal cord stimulation to restore sensory feedback after lower-limb amputation. The device will consist of an external data acquisition and stimulation system (Nomad Research System, Ripple LLC, Salt Lake City, UT) connected to 1-3 percutaneously inserted spinal cord stimulation (SCS) leads which have prior premarket clearance and approval (Abbott Medical Spinal Cord Stimulation (SCS) System, 510(k) K960728 and PMA P010032), see the attached Right of Reference letter, **Appendix A**) and a set of sensors mounted on the subject's prosthesis and limbs. Ongoing experiments in our lab have focused on the use of SCS to evoke sensations in the missing foot and shank after trans-tibial amputation. In those experiments, we used similar SCS leads to those that will be used in this study, percutaneously placed in the lateral lumbosacral epidural space for up to 29 days. All experiments to date have been deemed "Non-Significant Risk" by the University of Pittsburgh Institutional Review Board and performed under their approval. During those experiments, the external connector from the percutaneous leads is attached to an external stimulator during in-lab testing in our facilities at the University of Pittsburgh. Currently no stimulation is performed outside of the lab or clinic environment. During the proposed study, we will perform similar experiments over an extended 90-day period, and will also provide subjects with a portable stimulation and data acquisition system that can be used outside the lab environment for up to two weeks. During this two-week portion of the 90-day trial, subjects will transition from supervised use of the system to unsupervised use in the home and community. While ongoing lab-based experiments have been informative for our understanding of the ability to evoke and control the perception of sensations in the missing limb, ultimately, the goal of development of a somatosensory neuroprosthesis is for the system to be used in the community. Such community use will provide us with insight into the effects of daily and extended use of the system on function (e.g. balance control and gait stability) and changes in phantom limb pain. The extended duration of the experiments will also allow us to collect substantially more data and to prepare for the week-long trial of community use than can currently be achieved during the 29-day testing period.

1.3 Objectives of the clinical investigation

The proposed clinical investigation is a feasibility study directed toward the following aims:

Specific Aim 1: Demonstrate the safety of the SCS-LLA system over a period of up to 90 days. We will monitor adverse events throughout the study, and these results will provide supporting data for future studies with larger cohorts and a fully implanted SCS system.

Specific Aim 2: Characterize the sensations evoked by lumbar epidural spinal root stimulation in lower-limb amputees.

- **Specific Aim 2a**: Quantify the threshold (minimum charge and pulse rate) stimulus required to evoke sensory percepts and neurophysiological responses (e.g. reflexive EMG responses,) during SCS, and monitor changes in those percepts and responses over time. These results will provide insight into the design requirements for a future SCS system, as well as a point of comparison among subjects and with other studies in the scientific literature. Additionally, the stability of the responses will provide insight into the feasibility of long-term use of the device.
- **Specific Aim 2b**: Evaluate the relationship between stimulation parameters (e.g. pulse width, pulse amplitude, stimulus location, etc.) and the modality and naturalness of perceived sensations. Lumbar SCS can evoke paresthesia referred to the amputated limb, but our goal is to produce meaningful (non-paresthetic) sensations. As we expect the stimulation parameters to have significant effects on the evoked sensations, we will perform standardized psychophysical examinations to determine the relationship between stimulation parameters and perceived sensations. These tests will be repeated at multiple points throughout the study to observe any changes that occur over multiple days of use.
- **Specific Aim 2c**: Document the subjective perception of lower-limb amputees of lumbar SCS for restoration of sensation. To achieve widespread adoption of a sensory neuroprosthesis, it will be crucial for amputees to perceive significant value from the device. As such, we will ask each subject to provide subjective feedback on their perceived utility of the sensory feedback provided by the device.

Specific Aim 3: Characterize the effects of lumbar SCS on phantom limb sensations and phantom limb pain in lower-limb amputees. This aim is secondary to the primary study goals in Aims 1 and 2, and as such, we will not exclude individuals that do not experience phantom limb pain.

- **Specific Aim 3a**: Document changes in phantom limb sensation during and shortly after lumbar SCS in amputees. Before placement of the spinal cord stimulator leads, we will document the subject's description of their perceived phantom limb. We will ask them to update their perception of the limb periodically throughout each experimental session, as well as within a month after the device has been removed.
- **Specific Aim 3b**: Document changes in phantom limb pain during and shortly after lumbar SCS in amputees. Before placement of the SCS leads, we will ask subjects about their history of perceived phantom limb pain. We will ask them to update their pain level periodically throughout each experimental session, as well as within a month after the device has been removed.

Specific Aim 4: Characterize the patterns of reflexive muscle activity that are evoked by SCS. Reflexive muscle activity plays a crucial role in maintaining standing balance and transitioning between phases of the gait cycle. As such, restoration of sensation may play an important role in restoring these functions. Importantly, these reflexes are context-dependent, and may change with posture.

Specific Aim 5: Characterize changes in control of a prosthetic limb in the presence of sensory feedback. The long-term goal of this line of research is to provide sensory feedback that can be used in the control of a prosthesis. In this study, we will test the subject's ability to stand and walk with and without sensory feedback provided by SCS. Using either a virtual prosthetic limb or an instrumented prosthesis, SCS will be modulated based on signals recorded from the limb

such as pressure under the foot or joint angles. In both the presence and absence of stimulation, subjects will be asked to perform tasks such as standing quietly and walking. We will perform a battery of clinically validated balance and gait metrics to evaluate the effects of sensory feedback on control of the prosthesis.

Specific Aim 6: Explore how sensations, balance, gait, and pain change after subjects have used the system in the community for up to two weeks. While lab-based studies will provide insight into the types of sensations and reflexive responses that can be evoked by SCS, as well as the impact of those sensations on balance control and gait stability, subjects' exposure to the device will be limited to tens of hours over the duration of the study. This limited access will restrict subjects' ability to learn to use the device and to incorporate sensory feedback into activities of daily living. Additionally, the effects on PLP may require an extended presentation of stimulation. We will perform detailed evaluations of the effects of sensory restoration in these subjects, monitor any changes in PLP and evoked reflexive activity, and track the extent of their use of the device during up to two weeks of community use, including up to one week of unsupervised use.

1.4 Anticipated duration of the clinical investigation

Active participation will last no more than the 90 days after the leads are placed. However, as several pre-surgical and post-removal procedures are required (e.g. balance and gait testing, pain questionnaires, blood work, MRSA screening, EKG, MRI), total duration of the subject's participation in this study across all visits (including screening, experimental testing, and follow-up surveillance) may last up to 9 months.

2.0 Clinical protocol

2.1 Title of clinical protocol

"Spinal Cord Stimulation for Restoration of Function in Lower-Limb Amputees"

2.1.1 Protocol number

University of Pittsburgh, STUDY19010019

2.1.2 Version number and date

Modification Version: STUDY19010019
Approval Date: 8/2/2022
IRB Expiration Date: 8/1/2023

2.2 Study design

2.2.1 General study design

This study is a prospective, non-randomized, open-label, descriptive, interventional study.

2.2.2 Study design schematic

Figure 1 illustrates the proposed study design. Procedures are discussed in **Section 2.4**.

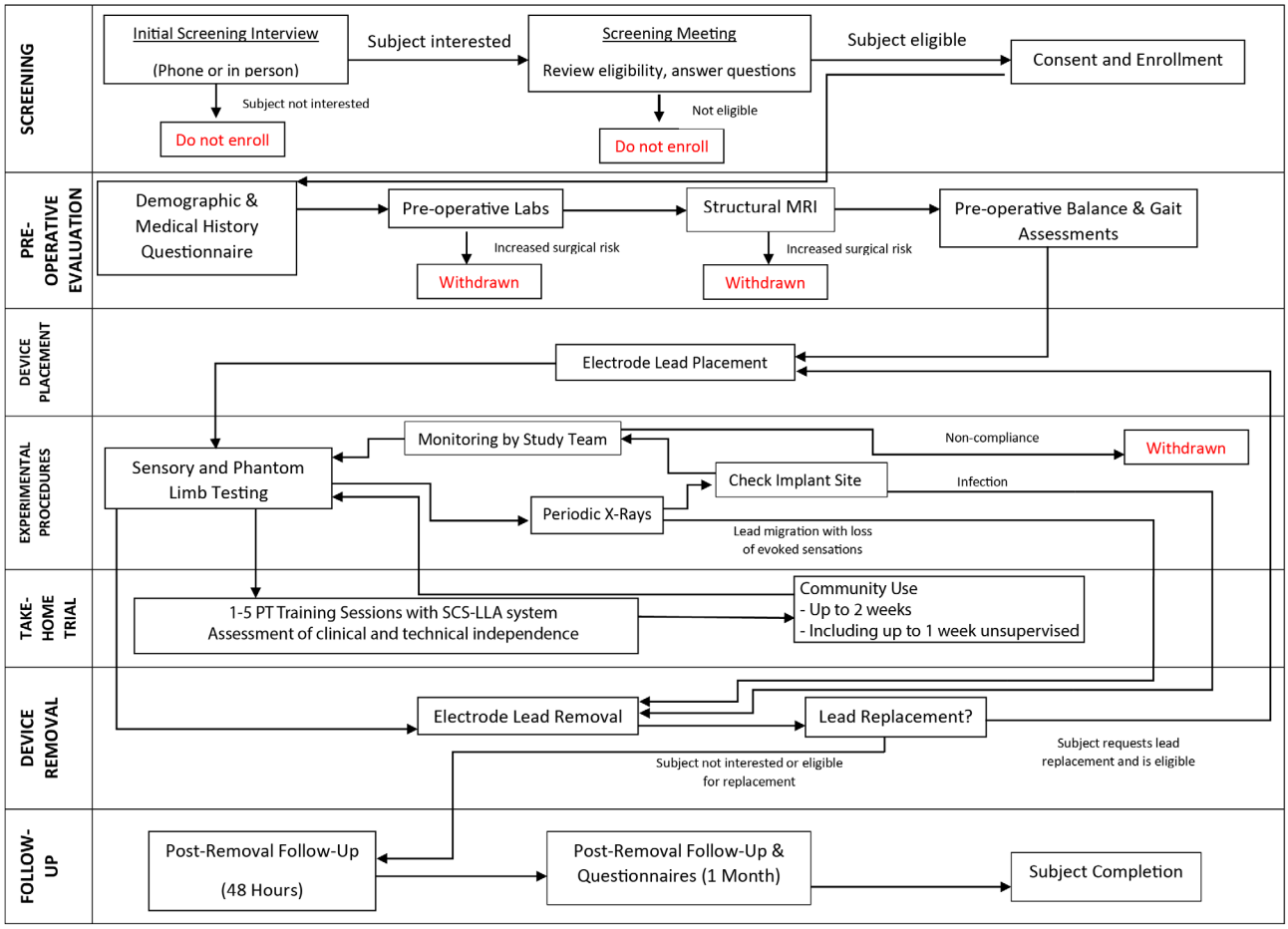

Figure 1. Study design schematic

2.3 Subject selection

2.3.1 General characteristics of the proposed subject population

The subjects for this study will be individuals between the ages of 22-70 with an amputation of one lower limb at a level between the ankle and knee joints. Subjects should be at least 6-month post-amputation at the time of study participation. To ensure their safety during participation, subjects will be screened to ensure that they have no serious diseases or disorders that could be complicated by participation. Due to the greater than minimal risk designation of the study, we will be using adult subjects to ensure that participants are mature enough to understand the tasks, as well as the risks, involved; further, we want to ensure that the central nervous system is fully developed prior to enrollment in this study.

2.3.2 Anticipated number of research subjects

Up to 15 total subjects may undergo research procedures, with the goal of completing all experiments with 10 subjects. Recruitment rates will be monitored by our DSMB. Because it is possible that a subject may enroll and then be determined to be ineligible, the

maximum number of subjects enrolled may exceed the number who undergo device placement. Subjects will be enrolled as necessary to maintain the target number of subjects. Recruitment will not begin until we have received all approvals.

2.3.3 Inclusion criteria

1) Subjects must have an amputation of one lower limb, at a level between the ankle and knee joints. Minor amputation of the contralateral limb (i.e. toes or partial foot) is not exclusionary.
2) Subjects must be over 6-month post-amputation at the time of lead placement.
3) Subjects must be between the ages of 22 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) Subjects must have used their current prosthesis for at least 6 months and achieved at least K-1 ambulator status at the time of lead placement, as determined by the Amputee Mobility Predictor.

2.3.4 Exclusion criteria

1) Subjects must not have any serious disease or disorder that could affect their ability to participate in this study.
2) Female subjects of childbearing age must not be pregnant or breast-feeding.
3) Subjects must not be receiving medications that affect blood coagulation.
4) Subjects must not have an allergy to contrast medium or renal failure that could be exacerbated by the contrast agent used in MRIs. For this study, renal insufficiency will be determined through blood work and defined as BUN of 30 mg/dl or more and Creatinine of 1.5 mg/dl or more.
5) Subjects may not have a hemoglobin A1c level above 8.0 mg/dl at time of implant.
6) Subjects may not have any implanted medical devices that are not cleared for MRI.
7) Subjects with a T-Score higher than 63 on the 18-question Brief Symptoms Inventory (BSI-18) who have undergone discussions with and been deemed unsuitable by the Principal Investigator, a study physician, and a psychologist
8) Subjects may not have a cardiac pacemaker.
9) Subjects may not have a cardioverter defibrillator.
10) Subjects may not be currently receiving diathermy therapy.
11) Subjects may not have an implanted infusion pump.
12) Subjects may not be immunosuppressed or currently receiving immunosuppressive medications.
13) Subjects may not have a profession (e.g. radiology technologist) or medical condition (e.g. remissory cancer involved regular follow-up x-rays) that would increase radiation exposure in the 12 months prior to starting or after ending participation in the study.

2.4 Study procedures

2.4.1 Screening procedures

We will recruit subjects from two University of Pittsburgh Institutional Review Board (IRB) approved registries developed by the Human Engineering Research Laboratories (Pitt IRB# PRO12080311) and the Department of Physical Medicine and Rehabilitation (Pitt IRB# PRO12030122). All members of the registry have agreed to participate in the registry, and have given permission to be contacted for future research. The IRB approved flyer for this study will be distributed to potential subjects according to the procedures established in the registry IRB approved protocols. The recruitment flyer will be accompanied by a letter from the registry PI/coordinator stating why they are receiving information about our study. In response to the recruitment flyer, potential subjects can directly contact the research team if interested in participating. We may also post the recruitment flyer, or other approved recruitment materials, on websites affiliated with our laboratory, the Physical Medicine & Rehabilitation Department, and the University of Pittsburgh. We may also recruit through organizations representing our subject population groups, such as assistive technology suppliers, adaptive sports organizations, amputee support groups, and amputation or other related clinics. The recruitment materials can also be made available in places such as hospitals, clinics or related events or promoted in social media or websites targeted towards individuals with amputation. Clinicians in the Department of Physical Medicine and Rehabilitation, Center for Assistive Technology, UPMC Centers for Rehab Services, and other departments at UPMC Presbyterian and UPMC Mercy who are knowledgeable about our study may distribute recruitment materials to their patients if they think they may be eligible. Clinicians or their administrative designees may also query their patient databases to find potentially eligible participants and contact these individuals directly. Individuals may contact our study team directly in response to the clinicaltrials.gov website, scientific publications, media, or other means besides our planned recruitment methods.

If an individual contacts us and is interested in this research study, we will provide that individual with information about the study (brochure, recruitment letter and/or consent form). We may conduct a phone screening to assess some of the inclusion and exclusion criteria. The initial screening can be conducted over the phone, in person, or using face-to-face video conference software, such as Skype or Facetime, for the individual's convenience. The purpose of this screening is to potentially eliminate the burden of travel on a potential participant who may not be eligible for the study. If any of the phone script screening questions indicate exclusion of that individual, the screening questions will stop at that point and the individual will be kindly told that they are not eligible for the study. If none of the phone script questions indicate exclusion from the study, then the individual will be asked to meet with the research team to further discuss study participation.

We will also use the Brief Symptom Inventory 18 (BSI-18) to screen all potential participants. Given the known increased prevalence of anxiety and depressed mood in individuals with amputation and chronic pain, it is our intent to use the BSI-18 to screen for mood symptoms as part of the consent process. The presence of symptoms, as reported on the BSI-18, will not exclude individuals from participating in the study – rather, responses given during the BSI-18 survey will be used as a tool to guide discussion

between the Principal Investigator, a study physician, and the potential subject. If an individual expresses severe depressed or anxious mood, resources will be provided to assist the individual in seeking appropriate mental health treatment. For those individuals with a BSI-18 T-score above 63, a meeting with a psychologist will be scheduled to assess their suitability for the study. Due to the sensitive nature of the questions on the BSI-18 survey, we will request that subjects complete the BSI-18 in person at the first screening visit, where appropriate clinical help, including a clinical psychologist, will be available.

Once a potential subject has been identified, the subject will be educated about the study, study goals, study tasks, and study requirements. 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 as this study requires a surgical procedure with the inherent risks of surgery, study physicians will be available to discuss any participant questions, either in-person or via teleconferencing software, such as Skype or Facetime, prior to 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 met with the study team, and agreed to participate in the study, they will be consented by a physician-investigator. If the individual is capable, they will sign the consent form.

Once written informed consent is obtained, the subject is enrolled in the study and is assigned a unique subject ID. A physician-investigator will verify the eligibility of the subject by assessing most of the eligibility criteria after consent via self-report. This will be documented on an "Eligibility Checklist" form.

After informed consent and after the participant's verbal self-report of eligibility criteria, an in-person clinical evaluation will be performed. Additionally, medical records will be accessed if additional information is required to perform pre-operative planning and review pertinent medical history, allergies, medications and radiology images.

2.4.1.1 MRI screening

Prior to undergoing an MRI for this study, a person will be asked about any implanted metal in their body. The screening covers items that would possibly exclude a participant from the study. In some cases, an x-ray may be requested by radiology prior to MRI to verify the shape and location of an implanted device. Female participants of childbearing potential will be screened for pregnancy prior to MRI using a urine pregnancy test. The completed MRI screens will be kept in a locked file cabinet located in a locked office to assure subject confidentiality.

2.4.2 Experimental procedures

Pre-surgical procedures and device placement will occur within 6 months after the subject undergoes screening procedures. We will work with each individual to determine the optimal testing schedule. The schedule will be designed to meet study goals and complete specific study tasks which will change over the duration of the study. The participant's engagement and training preferences will also be considered in this process. We will photograph or videotape portions of the experimental session. Appropriate permission will be obtained as needed for any photographs or videotaping of participants. Female participants will be encouraged to avoid getting pregnant throughout the duration of the research study. Experimental procedures are described below.

2.4.2.1 Demographic and medical history questionnaire

The subject will be asked to provide basic demographic information (age, weight, height, etc.) via self-report. We will also ask questions about their medical history including the date of amputation and their current level of function, prosthetic usage, as well as recent history and current status of phantom limb sensations and pain. We will also ask questions related to improvement of quality of life and neuroprosthetic technology.

2.4.2.2 Pre-operative physical and screening

Prior to the lead placement procedure, participants will undergo several screening procedures, including x-rays and clinical lab workups. For diabetic participants with elevated hemoglobin A1c levels (greater than 8.0 mg/dl), we may perform repeated blood draws within the 6 months following consent to ensure implant does not pose a risk of infection. If the participant's levels remain consistently above 8.0 mg/dl within the 6-month period following consent, we will not schedule lead placement, and will withdraw the participant from the study.

If the subject does not have an elevated A1c level, within two weeks prior to the lead placement procedure, we will perform: pre-operative chest x-ray; a routine urinalysis with microscopy; a complete blood count with differential and platelets; a prothrombin time and international normalized ratio; an activated partial thromboplastin time; iron, prealbumin, albumin, and hemoglobin A1c levels; a vitamin D 25-OH screen for deficiency/toxicity; urine pregnancy screen; and a MRSA screen. If study physicians suspect the subject may have renal insufficiency, which would prevent the use of gadolinium-based contrast agents, we may also perform blood urea nitrogen (BUN) and creatinine (Cr) testing. In the case of inconclusive test results and at the discretion of the study physicians, we may need to ask a participant for repeated sample collection. All lab work and repeated testing will be performed through UPMC.

2.4.2.3 Pre-operative structural MRI with contrast

We will perform a pre-operative MRI of the spine with contrast, to image the region where we will be placing the stimulator leads. If MR images of the region of interest already exist in the subject's medical record, these may be used instead. The MRI can be performed at any UPMC facility or at the Magnetic Resonance Research Center at UPMC Presbyterian.

2.4.2.4 Pre-operative or post-explant high resolution structural MRI without contrast

If scheduling permits, we will perform a second pre-operative or post-explant 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 spine (see **Section 2.4.2.13**) so that we can accurately visualize the location of the leads with respect to neural tissue. These MRI scans are not critical to our primary scientific questions, but will potentially provide interesting additional data for understanding the relationship between electrode location and the sensations evoked by spinal cord stimulation. Additionally, scheduling MRI scans can be highly challenging for studies with small sample sizes that do not have dedicated time slots. As such, we will attempt to schedule an MRI in the pre-operative or post-explant time windows, but may not collect

these scans if scheduling is impossible. High resolution structural MRI will be performed at the Magnetic Resonance Research Center at UPMC Presbyterian.

2.4.2.5 Pre-operative somatosensory function testing

Participants in this study may have impaired sensory function in the contralateral, intact limb. To account for those deficits when measuring functional control of the prosthesis (e.g. balance control), we may perform pre-operative measurements to quantify sensory function in the intact and residual limb. A variety of sensory function tests may be performed, such as tactile sensitivity testing, with Von Frey filaments or a mechanized tactor system, kinesthetic sensitivity testing, via manual or mechanized range of motion testing at the ankles and toes, and reaction time testing, in which a mechanical or electrical stimulus is applied to the limb and the subject must respond as quickly as possible (such as by clicking on a screen or pushing a button) to indicate detection of the stimulus. To reduce the burden on participants, we will not repeat testing on participants who are enrolled in another study where somatosensory data has already been collected. Additionally, transcutaneous stimulation pulses will be bi-phasic and charge balanced with frequency ≤ 1 kHz, pulse duration ≤ 1 ms, and amplitude ≤ 100 mA. We will start stimulation at a low amplitude (e.g. 1 mA) and slowly increase amplitude to avoid inducing pain. If we identify stimulation parameters that are painful, we will cease stimulation above that amplitude. The transcutaneous electrical stimulation will be delivered intermittently for the duration of testing, in a pattern of 5-10 seconds ‘ON’ for the pulses, followed by 30-50 seconds ‘OFF’.

2.4.2.6 Pre-operative 12-lead EKG

Up to 12 removable electrodes will be placed on the subject's chest and/or limbs. EKG wires will be attached to a monitor and the subject will be instructed to breathe normally during monitoring.

2.4.2.7 Decolonization for Surgical Site Infection Prevention

Participants will be instructed to shower each day for 5 days prior to surgery and the morning of surgery. An ointment will be provided to be used around the nose. These will help prevent bacteria on the body from causing an infection at the implant site. Decolonization will be performed before implantation and lead removal (as long as the removal procedure is not emergent). Also, we will provide participants with verbal and written instructions to care for their incision.

2.4.2.8 Prophylactic antibiotics

We will follow the standard clinical procedures to minimize the risks associated with percutaneous placement of electrodes. Prophylactic antibiotics will be administered intravenously 30 minutes before surgery and may be maintained as directed by a study physician and their clinical team. We will generally use cefazolin for this procedure; however, if the subject tests positive for or has a charted history of MRSA, intravenous vancomycin will also be administered. If the subject has a severe penicillin allergy, vancomycin will be administered without cefazolin. We have excluded pregnant females and those with renal failure (see **Section 2.3.4**) as they may be at an increased risk for complications resulting from administration of the antibiotics. Sterile silver dressings will

be applied to the insertion site, covering the protruding leads, to minimize the risk of infection. These procedures will greatly minimize the risk of infection and may vary based on the study physicians' clinical judgment and input from Infectious Disease experts.

2.4.2.9 Pre-operative sedation

The subject will see an anesthesiologist for procedural sedation to be used primarily during lead anchoring procedures. Small doses of Fentanyl and Versed may be administered intravenously. General anesthesia may also be used upon subject's request and anesthesiologist approval. Sedative administration may vary based on the anesthesiologist's clinical judgment.

2.4.2.10 Fluoroscopically guided lead placement procedure

Between one and three leads will be placed in the lumbosacral epidural space near the spinal cord. Clinical practice commonly includes placement of two or three of these leads in the epidural space. Leads will be placed by a physician with experience in spinal cord stimulation, at UPMC Mercy or UPMC Presbyterian using the following procedures, although, based on their professional judgment, they may make slight modifications to improve targeting and outcomes. The subject will be taken to a fluoroscopy suite or operating room, 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. The skin overlying the thoracolumbar area will be prepped and draped in aseptic fashion with Hibiclens and betadine. For local anesthesia, 1% lidocaine on a 22-gauge 3.5-inch spinal needle will be used in the skin and subcutaneous tissue. For each of the leads, a 14-gauge epidural Tuohy needle will be advanced through the L1-L2 space or a nearby intervertebral space to the posterior epidural space via loss-of-resistance technique. Needle location will be confirmed in anteroposterior (AP), lateral, and contralateral oblique fluoroscopy views. An 8-contact stimulator lead, which is designed to span 2-3 spinal segments, will then be advanced into the L3-S1 posterior epidural space and steered laterally using the accompanying catheter 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 P010032). The external portion of the lead will be connected to one of two external stimulators: 1) an Abbott External Pulse Generator included in PMA P010032 and 510(k) K960728, or 2) a current-controlled 32-channel neural stimulator (manufactured by Ripple, LLC, see **Section E** for more detail), a device which, according to the manufacturer "...meets safety standards for human research studies through IRB approval for both recording and stimulation." 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 until the evoked sensations are referred appropriately to the amputated limb.

2.4.2.11 Lead anchoring procedure

Once all of the percutaneous leads have been placed under fluoroscopic guidance, a neurosurgeon and study physician with extensive experience in spinal cord stimulation will secure the leads to the thoracolumbar fascia. Each 14-gauge epidural Tuohy needle will be kept in place until the removal at the end. We will apply a generous amount of 1%

preservative-free local anesthetic in the skin and subcutaneous tissues. The neurosurgeon will make a small incision with a scalpel at approximately 1 inch cranial and 1 inch caudal to each needle. The neurosurgeon will bluntly dissect around the approximate 2-inch opening with surgical tools in the subcutaneous tissue. The neurosurgeon will cauterize any subcutaneous bleeding vessels using monopolar and/or bipolar cautery devices. The dissection will then extend anteriorly to the thoracolumbar fascia. Once the thoracolumbar fascia is identified, the study physician will remove the epidural Tuohy needle under live fluoroscopic guidance to make sure there is no movement of the percutaneous lead at each level. Then an anchoring device will be deployed on top of the percutaneous lead and advanced to the most posterior aspect of the thoracolumbar fascia. The neurosurgeon and/or a neurosurgery resident will use the appropriate suture technique to secure the anchoring device in the thoracolumbar fascia at each level. We will use fluoroscopic imaging to make sure there is no lead migration during this process. Once each of the percutaneous leads have been secured in the thoracolumbar fascia, we will tunnel each of the percutaneous leads from the subcutaneous tissue out through the skin at a separate exit site. We may then utilize vancomycin powder and iodine solution at the needle entry site. The neurosurgeon and/or a neurosurgery resident will use suturing technique to close the subcutaneous tissues and skin. We will apply a sterile dressing to both the needle entry sites and the skin exit sites. The patient will be taken to a monitored bed in post-op for recovery. The entire procedure, including lead placement and anchoring, is expected to take approximately three to four hours.

Immediately following lead placement and up to 5 times per week for the following 90 days, experimental procedures will be performed. The day-to-day experimental procedures for each session will ultimately be decided by the PI, as they may depend on a variety of factors including progress towards our experimental goals, the current state of our technical setup (e.g. if hardware breaks and must be repaired), and the number of hours the subject is available on a given day. A typical day of testing might include psychophysical examination of sensations (e.g. receptive field mapping, measurement of threshold and just-noticeable difference) in the morning, followed by a lunch break, followed by x-rays and testing of the control of the prosthesis with sensory stimulation in the afternoon. Each testing session will be limited to no more than 8 hours, and will include breaks. Meals will also be provided. During experiments, SCS stimulation will either be delivered by an Abbott external stimulator or a current-controlled 32-channel neural stimulator (manufactured by Ripple, LLC; refer to **Section E** of this application for more detail).

2.4.2.12 Post-operative pain medication

If a subject is experiencing pain due to lead placement or removal, the study physician may choose to prescribe pain relief medication, such as Norco 5-325. Number of tablets prescribed will be at physician discretion.

2.4.2.13 Post-operative high resolution CT to document lead location

After lead placement, we will perform a high-resolution CT scan of the 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 or post-explant high resolution MRI, if performed, to determine the location of the leads with respect to the spinal cord and spinal roots. This scan can be performed at any UPMC facility.

2.4.2.14 Weekly x-ray to document lead migration

Once per week for the first four weeks' post-implant and once every two weeks for the remainder of the 90 days, multi-view x-rays (including AP and lateral views) of the thoracic and/or lumbosacral spine will be taken 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.

2.4.2.15 Weekly clinical exams and infection monitoring

Subjects will have clinical exams, in-person or via telemedicine visits, at least weekly following lead placement to monitor signs of infection. Physicians will verify that subjects do not have a fever, new redness at the incision site, or other signs indicative of infection. The physician will also ask if there have been any changes in medications. If local infection is suspected during a weekly exam, the examining physician will request drawn blood work (complete metabolic panel, C-reactive protein, erythrocyte sedimentation rate, complete blood count), swab the incision sites for culture, and schedule an additional clinical exam within 24 hours. A course of 5 to 7 day oral antibiotics will also be administered if superficial infection is suspected. Any signs of systemic infection (leukocytosis greater than $12x10^9$/L, fever, or positive blood cultures) or the presence of local infection with discharge suspicious for infection will result in immediate removal of leads at the infected site and administration of intravenous antibiotics recommended by Infectious Disease clinicians. Any local infections that do not show improvement with a course of antibiotics within 3 days will also result in lead removal. Infectious Disease will be consulted at all signs of infection and study physicians will follow all Infectious Disease directives.

2.4.2.16 Psychological evaluation

The subject will have opportunities to talk to a psychologist throughout the study, either over the phone, via telemedicine visits, or in person. These discussions can be scheduled regularly (at or shortly after the first screening visit and at approximately 1.5 months after implant) to discuss any concerns the subject may have. During each visit, the psychologist will assess the participant's mood, discuss the subject's expectations for the study, look for signs of discontent or frustration and discuss plans for after explant. The psychologist will provide written documentation of the assessments. By engaging in regular discussions, the psychologist will build a relationship with the participant that will help identify any changes in attitude or psychological status. The psychologist will also prepare the participant for life after the study. One follow-up visit will be scheduled approximately 3 weeks after explant. In addition, the principal investigator and physician co-investigators will be interacting with the subject on a regular basis and can refer the subject to a psychologist at their discretion. If the subject has severe problems or concerns, he or she may be withdrawn from the study.

2.4.2.17 Psychophysical testing

We will conduct a series of psychophysical tests to establish the relationship between SCS and sensory perception. During psychophysical stimulation trials, an external stimulator

will be connected to the SCS lead, a volley of stimulation will be performed, and the subject will be asked to respond to a set of standard psychophysical questions, as well as to provide any additional comments. Stimulus parameters to vary include the following: Pulse amplitude, pulse width, and pulse frequency limits are on Abbott Medical's PMA P010032 and/or a charge injection of 30 μC/cm^2, which is well below the generally accepted safe limit for stimulation through platinum/iridium macro-electrodes[1]. The values below were calculated for the surface area of an Abbott SCS electrode contact, which is a cylinder with 1.4 mm diameter and 3 mm length.

• Pulse amplitude (7.9 mA output maximum per electrode contact)

• Pulse width (maximum of 500 μs)

• Pulse frequency (maximum of 1,200 Hz)

• 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. rapidly adapting or slowly adapting neurons) or engineering patterns (e.g. sinusoidal modulation)

In clinical practice, the Abbott system is typically used for extended times throughout the day. 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.

Participants will be asked to identify where on their body any consciously perceived sensations were referred to, and will be asked to rate and describe various perceptual qualities of stimulation, such as naturalness, location, painfulness, and modality of sensation.

Participants will also be asked to compare two or more successive stimulus trains and describe or compare the effects of stimulation. Examples of the kinds of comparisons that participants may be asked to make include:

• Was the frequency of stimulus 1 higher or lower than stimulus 2?

• Did stimulus 2 feel stronger or weaker than stimulus 1?

• Which of stimuli 1, 2, or 3 felt like it came from the heel of the foot?

2.4.2.18 Mechanical and/or electrical stimulation

In order to provide a comparison between electrical stimulation and natural sensations, we will impart mechanical or electrical stimulation to either the residual limb or the contralateral limb, and ask subjects to document the perceived sensations.

Examples of stimulation include:

• Vibration of the skin using a mechanical tactor

• Skin indentation using von Frey hairs

• Passive movement of the limb

• Transcutaneous electrical stimulation of peripheral nerve or skin using adhesive gel electrodes

• Imagined or observed somatosensory stimulation

Responses from participants about sensations they may consciously experience during these peripheral stimuli will be recorded. Transcutaneous stimulation pulses will be bi-phasic and charge balanced with frequency ≤ 1 kHz, pulse duration ≤ 1 ms, and amplitude ≤ 100 mA. We will start stimulation at a low amplitude (e.g. 1 mA) and slowly increase amplitude to avoid inducing pain. If we identify stimulation parameters that are painful, we will cease stimulation above that amplitude. The transcutaneous electrical stimulation will be delivered intermittently for the duration of testing, in a pattern of 5-10 seconds 'ON' for the pulses, followed by 30-50 seconds 'OFF'.

2.4.2.19 EEG, EMG, and ultrasound studies

Non-invasive electroencephalography (EEG) and electromyography (EMG) will 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 residual and contralateral limbs and the trunk. Stimulation will be applied as described above. We may also utilize ultrasound imaging to confirm the identity of muscle responses. A portable ultrasound probe will be used to scan over electrodes detecting muscle activity of participant's limbs.

2.4.2.20 Effects on phantom limb sensation and pain

Periodically throughout the experimental sessions, we will ask each subject to rate their current phantom limb pain from 0-10 on a visual analog scale, and to describe any subjective effects of stimulation on their phantom limb sensations and pain. We will also administer the pain portion of the Trinity Amputation and Prosthesis Experience Scales and the McGill Pain Questionnaire before device placement, at least once during the 90-day testing portion of the study, and again within a month after device removal. Other similar questions may be developed to best capture the effect of stimulation.

2.4.2.21 Control of a prosthesis with somatosensory feedback

During some sessions, participants will be asked to utilize a prosthesis with and without sensory stimulation. The prosthesis may be their own device, for assessing balance and gait, or virtual reality limb or device provided by the lab, for assessing proprioception. Testing will be at PI discretion and will depend on experimental goals, technical set-up, and participant availability. When physical devices are used, they will be instrumented with sensors that measure signals such as pressure, force, and joint angle. Signals from those sensors will be used to modulate stimulation. Any sensors placed on the participant's prosthesis will be easily attached to the device and removed at the end of the session. To control the prosthetic or virtual limb, EMG signals will be recorded from the muscles in the residual limb using surface electrodes and/or limb motion of the intact and amputated limbs will be measured with an optical or magnetic motion tracking system and markers taped to the skin or clothing. Participants will be asked to perform tasks that test their ability to utilize sensory stimulation such as moving their limb to a specific point in space or applying a specified force through the limb.

2.4.2.22 Balance and gait assessment

To further evaluate the effects of sensory restoration on balance control and gait stability, we will also perform a battery of clinically validated balance and gait stability metrics.

Assessments include but are not limited to the Sensory Organization Test (SOT), Functional Gait Assessment (FGA), and the Amputee Mobility Predictor (AMP). Metrics will be performed with and without stimulation to determine the effects of sensory restoration on balance control.

In the SOT, study participants stand on a platform that can impart translational and rotational perturbations at the feet, and key elements of sensory feedback (e.g. visual feedback, ankle proprioception) will be manipulated. By providing sensory feedback that is either unreliable or incongruent with the actual perturbation, the test provides a method for isolating the influence of somatosensory, visual, and vestibular inputs on balance. This test has been used to investigate balance control in individuals with lower-limb amputation[2–5] and there is evidence that an amputee's ability to balance serves as a valid indicator of their fall risk[2] as well as their level of engagement in physical and social activities[6].

The impact of sensory stimulation on walking can be quantified using Functional Gait Assessment (FGA). The final score of this metric has been demonstrated to correlate with risk of falling[7]. The FGA includes ten modules that evaluate gait on level surfaces with variable speed, horizontal and vertical head turns, obstacles, pivots, with narrow base of support, with eyes closed, and while ambulating backwards[6]. Implementation of the assessment involves an expert reviewer who scores each task for levels of impairment, walking path deviations, changes in velocity, stumbles, and losses of balance[7].

The AMP can be used to the functional effects of sensory restoration[8]. The AMP encompasses many factors that contribute to an amputees' ability to ambulate with a prosthesis. The AMP is scored by an expert reviewer as the participant performs a number of activities including rising from a investigate chair, transferring between chairs, standing balance, single limb balance, standing reach, initiation of gait, and stepping over obstacles and stairs[8].

We will also perform posturography to quantify static standing balance[2]. During this assessment, subjects will stand quietly on an instrumented force-plate while we record center of pressure under the feet. By quantifying changes in the movement of center of pressure over time, we can assess changes in static stability with sensory stimulation.

We will also perform posture and gait analyses, in which subjects will stand or walk while wearing optical motion capture markers to measure the kinematics and kinetics during quiet standing and gait.

All balance and gait experiments will be performed either under the direct supervision of a physical therapist or with the use of a safety harness system. Balance and gait experiments may be performed prior to device placement and up to one month after device removal as well as throughout the implant duration of the study.

2.4.2.23 Electrode impedance

Periodically during experimental sessions, we will measure the impedance of the SCS leads as a means to ensure that the device is functioning properly. This functionality is included in the Abbott External Pulse Generator and the Ripple stimulator.

2.4.2.24 Clinic-based prosthetic training and assessment

Prior to each subject using the SCS-LLA system in the community outside the lab environment, one preliminary visit to the University of Pittsburgh's Physical Therapy Clinical and Translational Research Center (PT-CTRC) will be completed to determine the participant's baseline mobility, independence and function. This may include, but is not limited to, any relevant clinical evaluations of static and dynamic standing balance, gait and stairs. The participant's ability to perform transfers (sit to stand, stand to sit, etc.) may be assessed. These evaluations will not only serve as a baseline assessment of function, but will also determine the duration and type of training that will be required with the sensorized prosthesis.

Following SCS device placement and after stimulation parameters were selected for the SCS-LLA system, the participant will undergo 1-5 sessions of physical therapy and gait training with the SCS-LLA system and sensors attached to their prosthesis prior to the start of the community-use period. The duration of this training period will depend on the participant's baseline level of function and independence, their progression throughout the training, and the clinical judgement of an experienced physical therapist. During this period, the participant will perform tasks requiring varying levels of balance and dynamic stability in order to best prepare him or her for changes in environment during community use of the system. The primary purpose of this physical therapy assessment is to determine whether the participant can safely utilize the system independently.

In order to safely utilize the SCS-LLA system without assistance or supervision, the participant must be able to perform all necessary activities of daily living with modified independence (refer to checklist attached in **Appendix E**). Modified independence indicates that the participant is independent with the use of an assistive device. The participants must be able to safely maneuver curbs and thresholds. If the participant has stairs, either to enter or within their home, they should be able to ascend and descend steps independently, allowing the support of an assistive device or hand rail, if available in their home environment. Gait on uneven surfaces, over obstacles and up/down ramps will be tested and practiced, as well. The Amputee Mobility Predictor will also be used after training to determine K-level.

Assessment of functional independence and clinical judgement will be used to determine if the participant is safe to use the SCS-LLA system independently in the community. If the subject is determined to be a K-1 ambulator after training, they will be instructed to only use the SCS-LLA system within their home. K-2, -3, and -4 ambulators will be allowed to use the SCS-LLA both in the home and in the community. If, following 5 days of physical therapy, the participant is still not safe to use the system independently, in-laboratory testing with the SCS-LLA system will continue and the participant will not complete the week-long unsupervised portion of the community-use trial.

2.4.2.25 Technical training and assessment

Prior to each subject using the SCS-LLA system unsupervised in the community outside of the lab environment, they will undergo training with lab staff on the proper use of the system, including techniques for donning and doffing, proper operation, calibration, and approaches for responding to system errors. Subjects will be instructed on various operating techniques, including:

- Connecting each component of the system and managing cables to avoid tangling or snagging on environmental hazards.
- Charging external batteries and connecting them to the Nomad
- Turning the system on and off and switching between operating modes (e.g. standby, calibration mode, active/stimulation mode)
- (Optional) Operating the smartphone application and using it to understand system state information (e.g. battery status) and control system parameters (e.g. enter calibration state, adjust peak stimulation intensity)
- Calibrating the system
- Responding to various error states (e.g. low battery, no stimulation, unexpected stimulation)

Before subjects are cleared for unsupervised community use of the system, lab staff will evaluate their understanding of system operations and approaches for responding to system error states, using the checklist in **Appendix E**. Supervised technical training may occur in the lab environment as well as during the two-week community use trial; however subjects will not be cleared for unsupervised community use until they have successfully demonstrated understanding of safe operating principals of the system.

2.4.2.26 Community use of SCS-LLA system

Subjects may participate in up to two weeks of community use of the SCS-LLA system and sensors applied to the exterior of their own prosthetic limb, including up to one week of unsupervised community use. Initially, during a period lasting no more than two weeks, subjects will engage in supervised community use of the system to gain experience with its operation and understanding of how to don/doff the system and how to respond to error conditions. After successfully completing clinic-based prosthetics training and assessment (Section 2.4.2.23) and technical training and assessment (Section 2.4.2.24), subjects will be cleared to participate in up to one week of unsupervised community use of the system. The total duration of supervised and unsupervised community use will not last longer than two weeks. During community use of the SCS-LLA system, data will be automatically collected by the external system. These data may include, but are not limited to, time of use, system state and error information, button presses, all sensor signals recorded by the system, and the timing and amplitude of all stimulation pulses delivered by the system. All data will be stored in a password protected file system inside the portable stimulation system (See Section E for more information). During the community use trial, subjects may also participate in lab-based testing such as balance and gait assessment, measurement of phantom limb pain, or sensory psychophysics.

2.4.2.27 Removal of SCS leads

After completion of testing and no later than 90 days after device placement, the SCS leads will be removed. Within two weeks prior to removal, at physician discretion, we may do other bloodwork, such as a complete blood count with differential and platelets; a prothrombin time and international normalized ratio; an activated partial thromboplastin time; iron, prealbumin, albumin, and a vitamin D 25-OH screen for deficiency/toxicity pre

explant based on physician discretion. A MRSA screen will be also be done to determine what antibiotics will be used during the procedure.

The subject will be taken to the procedural room or operating room at UPMC Mercy and placed on their stomach. As with implantation, an anesthesiologist may administer a mild anesthetic or general anesthesia. Prophylactic antibiotics (cefazolin and/or vancomycin, depending on MRSA status) will be intravenously administered approximately 30 minutes before the procedure. The sterile dressings for both the lead exit site and needle entry sites will be removed. We will apply sterile prep and drape to both the lead exit site and the needle entry site. The study neurosurgeon will then use a scalpel to open each of the needle entry sites. He will use surgical equipment to bluntly dissect at each level to the thoracolumbar fascia. Each of the anchoring devices attached to the percutaneous leads will be removed. The percutaneous leads will be removed from the epidural space and skin exit site. A study physician will inspect each lead to ensure that it is intact and was completely removed from the body. If there are any concerns about incomplete removal, fluoroscopic imaging can be used intraoperatively to visualize the epidural space and guide decisions about next steps, which will be determined by the neurosurgeon (e.g. additional surgical dissection to remove the remaining portion of the leads). The neurosurgeon and/or a neurosurgery resident will suture each of the needle entry sites in the skin and subcutaneous tissues; a sterile dressing will be applied to the area. The patient will be taken to recovery. This procedure is commonly performed at the end of percutaneous SCS trials and has a low rate of complications.

2.4.2.28 Lead removal follow-up and monitoring

We will monitor participants following lead removal to ensure healing of the lead removal site and to track any remaining changes in sensation or pain. A research team member will contact the participant once within 48 hours and again within one month of electrode removal to discuss changes in sensations associated with phantom limb pain. Research staff will also ask the participant questions regarding general wellness and if they are experiencing any side effects associated with lead removal and infection, including bleeding, redness, swelling, or fever. Additionally, after the lead removal procedure and follow-up call, the participant will meet with a study physician. The timing of this visit is at the discretion of the physician but will be within three weeks after explantation. At this visit, the physician will remove any remaining sutures and examine the removal site for proper healing and signs of infection. Any cases of suspected of infection will be discussed with Infectious Disease and study physicians will follow all Infectious Disease directives. A neuropsychologist will also have a follow-up evaluation approximately 3-4 weeks after explant. A neuropsychologist will evaluate the participant's psychological state at this time to determine if a referral for further clinical help during the transition period following explant is necessary.

2.5 Study outcome evaluations

2.5.1 Study endpoints

The SCS leads will be removed no later than 90 days after implantation. The primary safety endpoint will be that there are no serious device-related adverse events. The secondary safety endpoint will be to determine the type and frequency of device-related

adverse events measured of the 90-day period following implantation. The primary efficacy endpoint for this study will be demonstration of the ability to evoke sensations localized to at least three focal regions of the missing foot and shank (e.g. lateral forefoot, medial forefoot, and heel). The secondary efficacy endpoints will be an improvement in balance control and gait stability and a reduction in phantom limb pain. Balance control and gait stability will be measured by a 10-point improvement in the Sensory Organization Test or a 6-point improvement in Functional Gait Assessment. A reduction in phantom limb pain will be measured by a 5-point improvement in the McGill Pain Questionnaire.

2.5.2 Study ending or halting due to safety

Subjects will be under medical supervision for the duration of this study and their health will be the top priority. Study physicians will be primarily responsible for evaluating a subject's medical condition. Study complications that may adversely affect a subject's health will consequently lead to the removal of the electrodes and ending of a subject's participation. Complications that could result in the removal of stimulation leads include:

- Lead migration that prevents the evocation of sensation in the missing limb
- Lead breakage
- Signs of systemic infection
- Unresolved local infection at the lead site
- Changes in subject's medical status that could affect eligibility
- Non-compliance with study procedures, including temperature monitoring, care of the implant sites, and attending testing sessions and clinical exams

We may halt the study and reevaluate our protocol and risk mitigation procedures due to the occurrence of multiple adverse events. Adverse events that could result in the halting of the study and re-evaluation of study protocol include:

- Two incidents of unresolved superficial infection resulting in lead removal
- One incident of deep infection
- One or more inpatient hospitalizations of subjects
- Two or more subjects who withdraw from the study due to worsening pain or intolerable dysesthesia
- One or more subjects who suffer a fracture due to falls related to the study interventions

2.5.3 Sample size determination

A maximum of 15 participants will be enrolled in order to achieve a maximum of 10 subjects undergoing study procedures. Because it is possible that a subject may enroll and then be determined to be ineligible for placement of the spinal cord stimulator leads, the maximum number of subjects enrolled may exceed the number of subjects who undergo lead placement.

This is one of the first studies to evaluate sensory perceptions during spinal cord stimulation in lower-limb amputees. Because this is a feasibility study, we feel that it is appropriate to begin with a small sample size in this initial investigation.

2.5.4 Outcome data and data analysis

The primary outcome measure of the study will be safety. We will track the rate of adverse events to monitor safety of the study. The primary efficacy outcome will be quantification and evaluation of the types of sensory percepts evoked by spinal root stimulation, as well as the anatomical locations to which those percepts are referred. Additionally, we will record any subjective changes in the perception of phantom limb sensations or phantom limb pain during and following spinal root stimulation. We will quantify differences in the ability to control a prosthetic limb with and without sensory stimulation. We will compare the balance and gait assessment scores of individuals using the SCS-LLA system and community-use of stimulation with the scores of subjects who underwent lab-only testing in our ongoing study to quantify the effects of extended access to the device.

New information will be learned with each participant, as this is a pilot study. Single-subject design statistical analyses will be used. Our main goals are to demonstrate device safety as well as the feasibility of using spinal root stimulation to evoke realistic sensory percepts referred to the foot and leg in individuals with lower-limb amputation, and to document any effects of that stimulation on phantom limb sensations and phantom limb pain. We will quantify the threshold for producing a just-noticeable sensory percept, as well as the relationships between stimulation parameters and evoked sensations when stimulating through individual electrodes or combinations of multiple electrodes.

To fulfill Specific Aim 1, we will document adverse events that occur during the study. We will report adverse events to the local Institutional Review Board and to the FDA in accordance with the respective reporting requirements. This documentation will serve as demonstration of the safety of the SCS-LLA system in this small sample.

To fulfill Specific Aim 2a, in which we quantify the threshold for evoking a sensory percept, we will use regression analysis to examine differences in stimulation thresholds related to a variety of factors. Examples of these factors include the anatomical location of each electrode (based on fluoroscopic imaging), level of amputation, time since amputation, level of pre-intervention phantom limb sensation and pain, and the thresholds of nearby electrodes.

With respect to Specific Aim 2b, the results will produce descriptive anatomical maps of the modalities and locations of sensory percepts evoked by spinal root stimulation. These maps will allow us to examine the specificity of stimulation through individual electrodes as well as the overall coverage of the evoked sensory percepts across the entire amputated limb. The results of Specific Aim 2c will be a set of purely descriptive statements made by the subjects that will provide additional insight into their experience with SCS and their preferences for this type of neuroprosthetic intervention.

The results of Specific Aims 3a and 3b will be a combination of descriptive statements on the subjective experience of SCS and its effects on phantom limb sensations and pain, as well as a data set including perceived pain ratings from a visual analog scale at multiple time points before and during the experimental study. These pain-rating results will be

compared within each subject and across subjects via regression analysis to determine if there is any effect of spinal root stimulation on phantom pain levels.

The results of Specific Aims 4 and 5 will be a data set including EMG, kinematics, and performance metrics that will allow us to quantify the subject's ability to control a prosthetic limb with and without sensory stimulation. Kinematic and performance metrics data will be compared within and across subjects using regression analysis to quantify changes in control with the addition of sensory stimulation.

With respect to Specific Aim 6, we will utilize analysis of variance to compare balance, gait, and pain scores before and after the trial of community use.

3.0 Risk Analysis

3.1 Anticipated risks

This study involves potentially serious risks. The risks of all experimental procedures are described below along with the steps that will be taken to minimize those risks.

Application of Anesthetic:

There is a risk of increased pain and/or local infection at the injection site. Additionally, because Lidocaine will be injected into the skin and the surrounding tissues prior to SCS lead placement, there is a low risk of adverse reactions including light headed-ness, dizziness, drowsiness, blurred vision, respiratory depression, edema, low blood pressure, and/or irregular heartbeat.

Steps taken to minimize these risks:

Subjects will be asked about any known allergies or previous reactions to lidocaine or similar anesthetics before the procedure. Further, the subject will be monitored throughout the device placement process and experimental procedures for adverse reactions to the anesthetic.

Application of General Anesthesia:

There are risks of side effects such as such as nausea, vomiting, chills, confusion for a few days, a sore throat caused by a breathing tube, breathing problems including pneumonia, and injury to the teeth.

Steps taken to minimize these risks:

General anesthesia will be only be used if the patient requests it and the anesthesiologist approves it. Subjects will be asked about any known allergies or previous reactions to general anesthesia before the procedure. Further, the subject will be monitored throughout the surgical procedure for adverse reactions to the anesthetic. The anesthesiologist will also be monitoring the participant’s vital functions and breathing.

Blood Draw for Pre-Operative Screening:

The insertion of the needle to draw blood may cause temporary discomfort, bruising at the insertion site, or soreness. There is a slight risk of infection. Fainting may occur but is expected to be rare, occurring in less than 1% of people.

Steps taken to minimize these risks:

Pre-operative screening will be performed in the Physical Medicine & Rehabilitation department at UPMC or another pre-operative screening facility within the UPMC system, which are experienced at and maintain the proper environments for these types of procedures.

EKG for Pre-Operative Monitoring:

There is a risk of skin irritation after removal of the electrodes used for EKG monitoring.

Steps taken to minimize these risks:

Sensors will be removed with caution and care to prevent discomfort.

Epidural Spinal Cord Stimulation:

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.

Steps taken to minimize these risks:

If a noxious or uncomfortable sensation is evoked in a participant as a result of stimulation, stimulation on that channel will cease. During stimulation trials, the stimulus charge will be increased slowly to allow self-reporting of any noxious sensations. If noxious sensations are evoked, the stimulus charged for that electrode will be limited to sub-noxious levels. To avoid tissue damage, stimulation parameters will stay at or below those described in the **Section 2.4.2.15**.

Interactions between the SCS-LLA system and prostheses:

There is a risk that electromagnetic or mechanical interactions between the SCS-LLA system and the prosthesis could cause malfunctions in either system. Examples of electromagnetic interactions include interference from an actively powered ankle joint on the wireless functionality of the Nomad or interference from the Nomad causing malfunctions in an actively powered prosthetic ankle. Examples of mechanical interactions include cabling from the SCS-LLA system wrapping around the ankle joint causing the cable to break or the ankle joint to seize.

Steps taken to minimize these risks:

Most prosthetic ankle joints are passive, do not have any electrical components, and will not generate electromagnetic signals that could interfere with the SCS-LLA system. The newest generation of actively powered or micro-controller controlled ankles, such as the Ottobock Empower or Ossur Proprio Foot have extensive documentation on their electromagnetic compatibility. If we identify that a subject has an actively powered prosthesis that could interfere with operation of the SCS-LLA system, we will consult the manufacturer documentation for recommendations about avoiding interference. For example, the Ossur Proprio Foot manual states “Portable RF communications equipment... should be no closer than 30 cm (12 inches) to any part of the device...” Based on these recommendations, we may, for example, use a wired pressure sensitive insole, rather than a wireless one. Further, during initial use of the SCS-LLA system during standing and walking, a study investigator will stand near the subject to provide support in case of a fall. To avoid mechanical

interference between the prosthesis and the SCS-LLA system, all cabling will be kept as short as possible and will be routed under clothing and secured with tape whenever possible. If cables from the SCS-LLA system do snag and break, stimulation will stop and the prosthesis will continue to operate as normal without sensory feedback.

Magnetic Resonance Imaging (MRI) with Contrast:

The magnet utilized for MRI will make intermittent loud knocking noises that could cause discomfort in some subjects. 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 that are affixed to bone. There is a risk of tissue heating for metallic implants. The contrast agent used during these MRI's, gadolinium, is FDA-approved and used routinely for MRI exams. The injection of contrast may cause discomfort, tingling, or warmth in the lips, metallic taste in the mouth, tingling in the arms, nausea, or headache. These symptoms occur in less than 1% of people and go away quickly. There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 individuals. Insertion of the needle to inject the gadolinium may cause minor pain, bruising, and/or infection at the injection site. People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching, and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung. NSF/NFD is a serious progressive disease and can result in death. If the subject has severe kidney failure and receives gadolinium, the risk of developing NSF/NFD is 1-5%. We may require a blood sample (about 1 tablespoon) to check kidney function before gadolinium contrast is utilized. There is evidence that repeated MRI scans with gadolinium can result is some accumulation of it in the brain. The significant of this and possible effect on health is not known.

Steps taken to minimize these risks:

Steps will be taken to minimize potential discomforts due to noise in the MRI, such as wearing earplugs and informing the subject beforehand about these discomforts. Two-way communication will be available throughout the scan in case the subject experiences feelings of anxiety or claustrophobia. The study team, as well as the staff at the MRI center(s), will administer standard screening procedures prior to the scan to ensure the subject's safety. Metallic implants, such as pacemakers or permanent piercings, are considered contraindications for MRI and may exclude potential participants. Any implanted metal will be investigated prior to MRI to determine its safety. Participants will be asked to notify a doctor, nurse, or technologist if they are allergic to gadolinium, if they have any kidney problems, or if they experience any other side effects. Individuals with renal failure or dysfunction will be excluded from study participation. A physician will be available during this procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of gadolinium should be stopped.

Mechanical and/or Electrical Stimulation of the Residual and Contralateral Limbs:

There are minor risks associated with the electrical and mechanical stimulation of the residual and contralateral limbs. These include uncomfortable sensations and irritation of the skin. As with EMG signal recording, sticky electrodes may be attached to the skin during electrical stimulation; these may cause skin irritation.

Steps taken to minimize these risks:

To avoid discomfort and skin irritation, we will ensure that the subject is aware that they may request to stop testing at any time. Further, we will work with the subject to ensure that we avoid repeating application of stimulation to the limbs that is excessively uncomfortable.

Observing a Virtual 3-D Environment:

Nausea or dizziness may result from wearing 3-D glasses in a virtual environment.

Steps taken to minimize these risks:

This risk will be mitigated by providing frequent breaks and adjusting task difficulty.

Two-Week Community-Use Trial:

There may be a risk of falling while walking/standing with the SCS-LLA system. There is a risk of system failure due to technical/software issues or power malfunction, which may cause distraction during walking, causing a fall. Falls may cause injuries ranging from minor (e.g. cuts, abrasions, bruises) to major (e.g. broken bones, head injury). The risks of interference between the SCS-LLA system and the subject's prosthesis are the same as those described in the section "Interactions between the SCS-LLA system and prostheses" above.

Steps taken to minimize these risks:

To avoid interference between the SCS-LLA system and the user's prosthesis, we will follow the mitigation procedures outlined in section "Interactions between the SCS-LLA system and prostheses" above. Prior to the unsupervised community-use portion of the trial, an engineer will train the subject on the technical aspects of the system, including device failure modes. An engineer will train subjects about the most likely types of failures and instruct them to contact us with any problems that may occur. Subjects will be shown how to turn the system on and off so that it can be powered off if it is not functioning properly. Once the system is off, whether due to powering off or battery failure, the subject's prosthesis will function as normal, greatly minimizing any negative effects resulting from technological issues. Additionally, we will provide between 1 and 5 training sessions with a physical therapist with expertise in lower-limb amputation, as well as evaluate the subjects' proficiency with the system, prior to completing the unsupervised community-use portion of the trial. While the subject is walking under the supervision of a physical therapist, we will intentionally turn the system off so they can experience this occurrence and how to properly respond. These safety precautions will minimize the risk of falling to no more than is expected during normal day-to-day activities.

Photographs and Audio/Video Recordings:

There is a risk of identity theft or breach of confidentiality.

Steps taken to minimize these risks:

We will take the necessary steps to protect personal identity and information. Photographs and videotapes will be stored digitally on our password-protected server; hard copies may be stored in a locked filing cabinet.

Placement of Spinal Cord Stimulator Leads:

According to the PMA that covers the Abbott Medical Spinal Cord Stimulation System, the most common adverse event is lead migration, which occurs in 13.6% 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 sensations. Other common risks include seroma and bruising at the placement site. The lead anchoring procedure performed by the study physician and neurosurgeon will minimize this migration. Additionally, 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. The tables included in the Abbott Medical Spinal Cord Stimulation System PMA (**Appendix C**) list the rates of complications. Placement of the Tuohy needle and spinal cord stimulator leads could potentially result in nerve damage that can cause neurological dysfunction, including paralysis. Additionally, it is possible that a tear in the dura could occur, resulting in a spinal fluid leak or hemorrhage (refer to **Appendix C;** risk: 0.5%). A spinal fluid leak can cause headaches and, in rare cases, may require surgery. The placement of these devices is common clinical practice for treatment of intractable lower back and limb pain, and complications are rare. There is a low risk of meningitis and infection at the electrode placement site as a result of lead placement, though the use of sterile technique during device placement makes this risk low (**Appendix C;** risk: 3.0%).

Steps taken to minimize these risks:

Placement of these devices is commonly done at UPMC Mercy by physician co-investigators. Decolonization procedures for minimization of surgical site infection will be provided to the participant prior to surgery. These procedures include showering each of the 5 days leading up to surgery, including the morning of surgery. Also, an ointment will be provided to use around the nose to minimize intake of bacteria into the body. After device placement and throughout the initial experimental session, the subject will be monitored for any adverse reactions to the device. At the time of discharge after implant and explant, the subject will be instructed on the signs and symptoms of nerve damage or spinal fluid leak and instructed to contact their physician if these symptoms occur. We will also follow up with the subject by phone within two days after lead removal to check for any symptoms of nerve damage or CSF leak. If surgery is required to correct a CSF leak, the costs will be covered through departmental funds from the Department of Physical Medicine & Rehabilitation. To minimize post-operative infection risk, IV cefazolin will be administered immediately before the lead placement procedure. If the subject is positive for MRSA via preoperative screening or has a history of MRSA, IV vancomycin will be used in addition to IV cefazolin. If the subject has a severe penicillin allergy, IV vancomycin will be used instead of IV cefazolin.

Post-Operative Pain Medication (Norco 5-325 or Similar):

Common risks associated with Norco 5-325 include drowsiness[9]. Infrequent risks include nausea, vomiting, constipation and/or diarrhea, pruritus, rash, dizziness, and confusion[9]. There is

also a risk of developing tolerance, physical dependency, and psychological dependency upon repeated and prolonged administration of narcotics.

Steps taken to minimize these risks:

Before the procedure, the subject will be asked about any known allergies or previous reactions to Norco 5-325 or similar pain medications. Pain medication will be prescribed for a short period of time and in limited doses to reduce the risk of developing tolerance or dependency. Prior to prescribing any narcotic pain medication, we will use the Screener and Opioid Assessment for Patients with Pain (SOAPP) questionnaire to evaluate risk of dependency. Subjects determined to be high risk will not be prescribed pain medication. The subject will be monitored during the first few weeks of the study following implant for signs of dependency and adverse drug reactions.

Using the results from the SOAPP questionnaire, the following steps would be taken.

SCORING: All 24 questions contained in the SOAPP®-R have been empirically identified as predicting aberrant medication-related behavior six months after initial testing. To score the SOAPP, add the ratings of all the questions. A score of 18 or higher is considered positive.

RESULTS: **If the score is less than 18,** opiate medication may be prescribed.

If the score is more than 18, the individual will be informed that opiate medication will not be used. Instead, Tylenol or a weaker opiate like Ultram (tramadol) may be prescribed. If the individual consents to this change, then the study and implantation of the device will continue.

If opiate medication is used for pain relief, then a study physician will follow up by asking every week after implant how the patient is doing in terms of how often they're using the medication, and counseling the individual on correct usage in terms of frequency.

Presence of Spinal Cord Stimulator Leads:

The risks associated with maintaining the sub-chronic placement of the spinal cord stimulator leads (for 90 days) are expected to be similar to those normally observed during clinical assessment of these devices for treatment of intractable low back or limb pain, although the risk of infection is likely higher because of the extended duration of the percutaneous implantation period. During normal clinical practice the devices are placed percutaneously near the spinal cord and maintained for approximately one week in the US[10], or multiple weeks in Europe[11], with good outcomes. Some of the risks associated with these procedures include, but are not limited to, pain at the electrode sites, allergic reaction in response to the implanted leads, CSF leak, lead migration resulting in undesirable changes in stimulation, lead breakage, tissue reaction, and spinal cord compression. Nerve damage causing neurological dysfunction and paralysis may also occur. The most common complications are lead migration, occurring in 13.6% of patients, and infection. Because of the extended duration of the percutaneous implantation period, the risk of infection is likely higher than that reported by Abbott, which reflects the traditional week-long trials performed in the US. Instead, the risk is likely to be similar to other procedures in which percutaneous catheters are maintained for extended durations. One meta-analysis reported that intrathecal catheters for cancer pain management have

an infection rate of 1.4% for deep infections and 2.3% for superficial infections. Another meta-analysis reported infection rates of 2% and 4% for deep and superficial infections, respectively. The outcome of infection may be serious and may lead to edema or other sequelae.

Steps taken to minimize these risks:

All device materials in contact with the body are known to be biocompatible materials. Because the leads protrude through the skin, there is a risk of infection throughout the study. The risk of infection is minimized by frequent checks of the site and a specific wound/skin care procedure designed to reduce the chance of infection. A sterile environment will be utilized during surgery, and individuals who may be at a high risk for infection (for example, those taking immunosuppressive drugs) will be excluded from the study. An antimicrobial silver dressing will be used and will be changed at least once every three days by a study physician, research staff member, or trained care-giver. We will provide detailed cleaning instructions to the participant and anyone who may assist with dressing changes. A study physician will complete a summary discharge document, of which the subject will receive a copy. During dressing changes, the subject or a caregiver will be instructed to inspect the site for redness or discharge. Participants will be asked to monitor their temperature at home, and temperature will be taken at each lab visit. A study physician shall be informed of a fever (>99.5 F). A physician will inspect the site at least once per week, or twice per week if vancomycin was the only antibiotic administered at the time of implant. If new redness is seen, blood work will be performed to look for possible signs of infection (e.g. CBC, CMP, CRP, ESR). If there is a suspected superficial infection and there are no signs of systemic infection (e.g. abnormal blood work, fever, chills), the incision sites will be swabbed and cultured and the subject will be prescribed a 5-7-day course of oral antibiotics. If the infection does not improve with three days of oral antibiotics, the lead(s) at the infected site will be removed. If any sign of systemic infection is detected or if there is a discharge at the incision site suspicious for infection (yellowish-white and/or viscous), the lead(s) will be removed. In any case of suspected infection, an expert in Infectious Disease at UPMC will be consulted by study physicians and IV antibiotics recommended by Infection Disease will be administered. If the devices migrate to a position where they are no longer functionally useful (i.e. they no longer produce sensations referred to the amputated limb), the devices will be removed and testing will cease. If lead breakage is suspected, the devices will be visually inspected during removal, and if necessary, fluoroscopic or x-ray images will be acquired to determine if complete removal occurred. At the neurosurgeon's discretion, additional surgical intervention may be required to remove lead fragments in the case of lead breakage.

Procedural Sedation:

Common risks of sedation with intravenous Fentanyl include nausea and vomiting, urinary retention, and pruritus[12]. Respiratory depression may occur, although literature reports indicate that most of these events are not significant[12]. Infrequent risks of Versed (midazolam) use include respiratory depression and temporary hypotension[13].

Steps taken to minimize these risks:

Before the procedure, the subject will be asked about any known allergies or previous reactions to Fentanyl and Versed. An anesthesiologist will be present to ensure subject safety.

Medical staff at UPMC Mercy will closely monitor subjects during and after the lead placement procedure.

Prophylactic Antibiotics (Cefazolin or Similar):

Allergic reactions, including itchiness, are possible depending on each individual and their reported history. Seizure, fever, rash, itching, diarrhea, C. difficile infection, nausea, vomiting, increased liver enzymes, and abnormal blood urea nitrogen or serum creatinine levels are considered infrequent risks.

Steps taken to minimize these risks:

Before the procedure, the subject will be asked about any known allergies or previous reactions to Cefazolin or similar antibiotics. The subject will be monitored for adverse reactions to the antibiotic.

Recording of Personal Information, text messaging and Bluetooth transmission from device:

There is a risk of breach of confidentiality since personal information will be obtained.

Steps taken to minimize these risks:

Identifiable data will be filed in locked areas immediately after collection. Study ID numbers will be used instead of the participant's name when recording study-related data. The information collected in this study, such as psychophysical data, will generally consist of numbers with little or no meaning to the casual observer. Electronic data is stored on password-protected network drives. Staff have been trained regarding the critical nature of participants' privacy, as well as about procedures for respecting their privacy and maintaining confidentiality.

Securing Electrodes and Leads to the Skin with Adhesive and/or Tape:

Removing tape from skin may cause discomfort. Adhesive and/or tape may pull hair from the skin and result in discomfort.

Steps taken to minimize these risks:

Tape will be used conservatively and will be removed with caution and care.

Spinal Cord Stimulation Electrodes Connected to Incorrect Stimulator Channels:

It is possible that a study investigator may incorrectly connect the percutaneous SCS leads to the wrong stimulation channels, resulting in stimulus pulses being delivered to the incorrect electrodes. This would cause aberrant feedback and could evoke painful sensations.

Steps taken to minimize these risks:

Each percutaneous lead will be clearly labeled with a unique identifier (e.g. a red, green, or yellow colored flag), which will be connected to a matching identifier on the stimulator connector. In the case that the connectors are swapped, stimulation will still always be delivered at levels within the 30 $\mu C/cm^2$ safety limit, so no tissue damage will occur. If a subject feels an unpleasant or unexpected sensation, they will be instructed to notify research staff.

Standing and Walking with Sensory Feedback Provided by Spinal Root Stimulation:

It is possible that subjects may find sensory feedback disorienting or distracting during standing and walking. Aberrant feedback may cause an inappropriate response to postural perturbations, a loss of balance, or falls.

Steps taken to minimize these risks:

During initial use of stimulation for sensory feedback during standing and walking, a study investigator will stand near the subject to provide support in case of a fall. During testing of postural stability and balance control, a physical therapist will stand near the subject or a harness will be used to protect against falls.

Structural MRI without Contrast:

The magnet will make intermittent loud knocking noises that may cause discomfort in some people. We may ask the subject to wear a neck brace during these scans to ensure that the spine is in the same position for both the CT and the MRI. Subjects may feel discomfort 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 ferromagnetic objects affixed to bone. There is a risk of tissue heating for metallic implants.

Steps taken to minimize these risks:

Steps will be taken to minimize potential discomforts due to noise in the MRI, such as wearing earplugs and informing the subject about the procedures. Two-way communication will be available throughout the scan in case the subject experiences feelings of anxiety or claustrophobia. The MRI scanner may attract metal objects. Some metallic implants, pacemakers, and other metallic substances are considered contraindications for MRI and therefore may exclude someone from participating in this study. Any implanted metal will be investigated to ensure that it is not unsafe for MRI. The MRI center will also perform their standard screening procedures prior to the scan to ensure the subject's safety.

Removal of SCS Leads/Lead breakage:

There is a risk of post-implantation infection of the skin where the electrodes were placed. Meningitis is also a rare but potentially serious risk. The risks of infection may increase the longer the electrodes remain implanted.

Steps taken to minimize these risks:

If lead breakage is suspected, the devices will be visually inspected during removal, and if necessary, fluoroscopic or x-ray images will be acquired to determine if complete removal occurred. At the study physician’s discretion, additional surgical intervention may be required to remove lead fragments in the case of lead breakage. Participants will meet with study physicians within three weeks following removal to check for signs of infection. Research staff will additionally follow-up with participants via phone call 48 hours and

within one month after removal to monitor recovery.

Please note that the following procedures utilize radiation. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from these procedures is below 50 mSv, which is the annual radiation exposure limit for radiation workers.

Fluoroscopy Guided Lead Placement and removal:

The lead placement procedure occurs under fluoroscopic guidance, which involves radiation exposure. The radiation exposure associated with this procedure is expected to be approximately 10 mSv. Although unlikely, fluoroscopy could also be used during lead removal if a lead breaks. In this case exposure is expected to be of a much shorter duration, with radiation exposure of approximately 1-2 mSv. For reference, federal regulations allow an annual radiation exposure of 50 mSv to the most sensitive organs of radiation workers. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer.

Steps taken to minimize these risks:

Imaging is required during placement of the spinal stimulator leads. The risk associated with the amount of radiation exposure that the subject will receive from this additional x-ray exam is below 50 mSv, which is the annual radiation exposure limit for radiation workers. At the end of the study, we will notify subjects of their effective radiation exposure dose during the study and will instruct them to notify their doctor of this dose prior to any additional imaging for 12 months following study participation.High Resolution CT Scan of the Lumbar Spine:

The maximum amount of radiation exposure that participants will receive from the high-res CT is 6 mSv which is less than the annual radiation exposure (50 mSv) permitted to the most sensitive organs of radiation workers by federal regulations.

Steps taken to minimize these risks:

The risk associated with the amount of radiation exposure that the subject will receive from the CT scan is below 50 mSv, which is the annual radiation exposure limit for radiation workers. At the end of the study, we will notify subjects of their effective radiation exposure dose during the study and will instruct them to notify their doctor of this dose prior to any additional imaging for 12 months following study participation.Optional X-Ray for MRI Clearance

The maximum amount of radiation exposure that participants will receive from this x-ray is 1 mSv. This is a fraction of the annual radiation exposure (50 mSv) 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 or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from these x-rays is considered to be low and comparable to everyday risks.

Steps taken to minimize these risks:

The risk associated with the amount of radiation exposure that the subject will receive from these x-rays is below 50 mSv, which is the annual radiation exposure limit for radiation workers. At the end of the study, we will notify subjects of their effective radiation exposure dose during the study and will instruct them to notify their doctor of this dose prior to any additional imaging for 12 months following study participation.Chest X-ray for Pre-Operative Screening:

The maximum amount of radiation exposure that participants will receive from 2 views of chest, x-ray is 0.01 mSv. This is lower than the annual radiation exposure (50 mSv) 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 x-ray exam is considered to be low and comparable to everyday risks.

Steps taken to minimize these risks:

The risk associated with the amount of radiation exposure that the subject will receive from these x-rays is below 50 mSv, which is the annual radiation exposure limit for radiation workers. At the end of the study, we will notify subjects of their effective radiation exposure dose during the study and will instruct them to notify their doctor of this dose prior to any additional imaging for 12 months following study participation..

<u>Thoracic and/or Lumbar X-Rays for Documentation of Lead Location and Migration:</u>

The maximum amount of radiation exposure that participants will receive from each multi-view x-ray of the thoracic spine is 1 mSv, and the lumbosacral spine is 1.5 mSv. Participants will receive multi-view x-rays for the first four weeks following implantation, and then multi-view x-rays biweekly for the remainder of the study, for a total of eight x-rays and a maximum exposure of 20 mSv. This is a fraction of the annual radiation exposure (50 mSv) 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 or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from these x-rays is considered to be low and comparable to everyday risks. To minimize radiation exposure, we will only collect both thoracic and lumbosacral x-rays if the leads cannot be visualized with only one of the two images.

Steps taken to minimize these risks:

Imaging studies are necessary to document any movement of the stimulator leads over the course of the study. The risk associated with the amount of radiation exposure that the subject will receive from these x-rays is below 50 mSv, which is the annual radiation exposure limit for radiation workers. At the end of the study, we will notify subjects of their effective radiation exposure dose during the study and will instruct them to notify their doctor of this dose prior to any additional imaging for 12 months following study participation.

3.2 Summary of risks and justification related to the use of spinal cord stimulation

The primary risk for a study of chronically placed electrodes is infection. However, current statistics show that this risk is quite low (6%). Infection risk is further minimized through the use of frequent checks by the physicians and study team, a specific wound/skin care procedure designed to reduce the chance of infection, and the administration of prophylactic antibiotics on the day of lead placement. The General Health Questionnaire mentioned previously also provides the study team with pertinent medical information, allowing us to exclude individuals who may be immunosuppressed and/or at a higher risk of infection.

There is also a risk of falling when performing tasks with the SCS-LLA system. This risk will be minimized by supervision of the subject by a physical therapist during in-lab testing and substantial training and assessment before unsupervised use of the system.

4.0 Description of the Device

4.1 Belt-worn stimulator and data acquisition system

Ripple has recently begun marketing a belt-worn system, called the Nomad Research System, that has undergone extensive safety and EMC testing, per IEC 60601-1 and 60601-2, and can be used in clinical trials under IRB approval to process and analyze sensor data and generate trains of stimulus pulses. A set of external sensors will be connected to the Nomad and stimulus encoding algorithms will run on a connected PC or on the Nomad's internal processor. Signals will be sampled by the Nomad's A/D board or will be transmitted wirelessly to the Nomad (e.g. via Bluetooth). A set of custom adapters will be used to connect the Nomad stimulation front-ends to the Abbott Spinal Cord Stimulator Leads. For more detail on the Nomad and its components, see **Section E**.

4.2 Spinal cord stimulator leads

Abbott Medical is currently marketing their Spinal Cord Stimulation system, a neurostimulation system that includes 8-contact leads designed for percutaneous and permanent implantation. The off-label approach used in this study is nearly identical to the FDA-cleared procedure (PMA P010032 and 510(k) K960728) in which these devices are placed in the epidural space for treatment of chronic intractable pain of the trunk and/or limbs. As in that procedure, the device will be tunneled percutaneously through the skin and secured in place, then removed at the end of the study. The devices will be placed during a fluoroscopically guided outpatient procedure, which typically takes 3-4 hours, and kept under the skin for no more than 90 days. The leads used in this study have been designed and tested for permanent implantation and contact with the body for >90 days. Removal will be accomplished by a physician during a visit to UPMC Mercy. We will target the appropriate regions of the spinal cord by using the catheter included with the device to steer it in the epidural space. The proposed study is intended to evaluate the safety of the integrated system, as well as to characterize the types of sensations that can be evoked by stimulation of the spinal cord. We will implement software limits to ensure that stimulus parameters remain within the limits described in the Abbott PMA and 510(k). Monitoring Procedures

4.3 University of Pittsburgh Education & Compliance Office – Human Subject Research

Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of Pittsburgh's Education and Compliance Office – Human Subject Research. The address is listed below. Monitoring procedures are listed on the office website at http://www.ecohsr.pitt.edu/ .

Education and Compliance Office – Human Subject Research

University of Pittsburgh, Office of Research Protections

Hieber Building, Suite 205

3500 Fifth Avenue, Pittsburgh, PA 15213

The sponsor-investigator and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

4.4 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) has been established to review this study. After this approval and at periodic intervals (to be determined by the board) during the course of the study, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents and plans for data and safety monitoring; Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;

2. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;

3. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;

4. Protect the safety of the study participants;

5. Report on the safety and progress of the study;

6. Make recommendations to the PI, IRB, concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;

7. Monitor the confidentiality of the study data and the results of monitoring;

8. Assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

4.4.1 Data Safety Monitoring Board Members

The DSMB will include experts from a variety of relevant fields such as physical medicine & rehabilitation, neurology, and regulatory science/clinical trials. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required. The research monitor has the authority to stop the research at any time, can remove individuals from the study, and take any steps necessary to protect the safety and well-being of participants until the IRB has time to assess the study. Contact information for the DSMB Chairperson is included below.

Dr. Ronald Glick, MD (Chairperson/Research Monitor)

Center for Integrative Medicine, Suite 310,

580 South Aiken Avenue, Pittsburgh, PA 15232

4.5 Monitoring by study team

The core members of this research team will meet at least monthly to discuss study recruitment, study goals and progress, adverse events, participant complaints, modifications, and confidentiality of ongoing studies. The investigators and study team will ensure that proper procedures are in place to ensure data integrity and participant safety. Data will be reviewed and any possible study design changes resulting from our experience or external studies/publications will be discussed. Our priority is to maintain participant safety and confidentiality while collecting data that accurately demonstrates the efficacy of this device. We will comply with the IRB's policy for the reporting of serious and unexpected adverse events as described in the Human Research Protection Office Policies and Procedures Manual. The outcomes of these meetings will be summarized and included in the annual continuing review. Minutes for these meetings will be kept on file.

Figure 2. Labeling for the SCS-LLA system, which will be affixed to the outside of the Nomad and the housing for the stimulation front-ends.

5.0 Labeling

Labeling (Figure 2 and **Appendix J**) will be affixed to the outside of the Ripple Nomad and the outside of a plastic box that will house the Ripple stimulation front-ends (**Section E, Sub-section 2.4**), passive circuitry to connect together up to five stimulation channels and connectors for the Abbott trial cables (**Section E, Sub-section 2.3**). A copy of the labeling for the device is included in **Appendix J**.

6.0 Consent Materials

Refer to **Section L** of this application.

7.0 IRB Information

University of Pittsburgh IRB & Human Research Protection Office (HRPO)

Hieber Building, Main Office, Suite 106

3500 Fifth Avenue, Pittsburgh, PA 15213

Chair: Margaret Hsieh, MD

8.0 Additional Records and Reports

8.1 Data handling and record-keeping

Case Report Forms (CRFs) will be completed for each subject enrolled into the clinical study. A full representation of CRFs are included in **Appendix E**. CRFs will be signed by the sponsor-investigator, a qualified sub-investigator, or a qualified member of the research team as indicated on each individual form. The sponsor-investigator will sign a Case Report Verification Form prior to lead placement and following lead removal to verify that they have reviewed all CRFs completed prior to the date of review. The sponsor-investigator's signature serves as attestation of the sponsor-investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic. Any data that is missed will be noted with an explanation and investigator initials. Protocol deviations will be reported to the IRB as required.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the *Source Documents*. Whenever possible, Source Data for clinical research procedures will be stored as a print out of the electronic medical record note. CRFs will be used to document the key outcome variables for each procedure and will also indicate that all original data was stored and backed up as appropriate.

Paper-based records will be kept in a secure location in locked file cabinets within each testing institution facilities. All researchers involved with the conduct of this research have been appropriately trained in the proper practices of research conduct. Each subject will be assigned a unique subject identification code and the link to that code will be stored on a restricted research server (described below). Whenever feasible, identifiers will be removed from study-related information and replaced by the subject identification code.

We may share somatosensory research data to prevent the burden of repeat testing on individuals enrolled in our other neuroprosthetic studies in which somatosensory data is collected. This data will be coded. No clinical information will be shared.

Photographing, videotaping, and/or voice-recording will be performed as part of this study and these data will be stored with study ID numbers in a locked office or on a password-protected research drive that can only be accessed by research staff.

Electronic storage of research study information will be on a restricted access, separate server used only by research faculty and staff. In order to maximize data security as well as our ability to analyze the data efficiently, we will utilize two research servers: (1) University of Pittsburgh Medical Center (UPMC) and (2) Rehabilitation and Neural Engineering Laboratory (RNEL) on the University of Pittsburgh network. All identifiable information (excluding photographs, videotapes, and voice recordings) will be stored on the UPMC server. The UPMC server is managed by an information security group, which is comprised of three main areas: threat and vulnerability management, identity management and account administration, and the technical team. Protection of information is maintained in a variety of ways including firewall, individual password accounts, and identity management.

Due to the large file size of the research data, we plan to store de-identified data locally on the RNEL laboratory server. This server is password protected and only research personnel affiliated with this project will be able to access study-related data. All original data will be stored in a 'read only' folder and will also be backed up at a separate location either on DVD in a locked file cabinet or on a separate password-protected backup server. The case report forms related to electronic data collection will also document that the data was stored and backed-up appropriately. All case report forms will be verified by the sponsor-investigator. Electronic systems used for data storage have not been certified as operating in full compliance with the FDA regulations at 21 CFR Part 11 due to the limited scope of this clinical investigation.

Our study team will conduct regular reviews of ongoing data analysis to ensure the accuracy and validity of these methods. In no way will any of the original data be altered through these procedures. All case report forms, log sheets, and data and safety monitoring minutes will be made available to FDA or IRB representatives as requested.

All data will be kept for a minimum of 7 years after the study ends in compliance with the University of Pittsburgh guidelines. Collaborating investigators may have access to study data after de-identification.

8.2 Record maintenance and retention

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

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted FDA Form 3500As, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;

- Curriculum vitae (sponsor-investigator and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor-investigator and listed sub-investigators;
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by sponsor-investigator;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of sponsor-investigator correspondence to sub-investigators, including notifications of adverse effect information;
- Subject screening and enrollment logs;
- Subject identification code list;
- Investigational device accountability records, including documentation of device disposal; and the
- Final clinical study report.

Identifiable data will be filed in locked areas immediately after collection. Study ID numbers will be used instead of the participant's name when recording study-related data. The information collected in this study, such as neural recordings, will generally consist of numbers with little or no meaning to the casual observer. Electronic data is stored on password-protected network drives. Staff has been trained regarding the critical nature of participants' privacy, and about the procedures for respecting their privacy and maintaining confidentiality. Subject names and other directly identifiable information will not appear on any reports, publications or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports for up to 7 years after investigations under the IDE have been discontinued and the FDA so notified.

SECTION D References

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