# Transcutaneous Spinal Cord Stimulation for Chronic Spinal Cord Injury Recovery: A Multicenter Randomized Controlled Trial

**BIOST/STAT 524: Project Proposal**

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## *LIST OF ABBREVIATIONS AND ACRONYMS*

| | |
|---|---|
| ANOVA | Analysis of variance |
| ASI | American Spinal Injury Impairment |
| BWSTT | Body Weight Support Treadmill Training |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| DSMB | Data Safety Monitoring Board |
| ES | Electrical stimulation |
| FDA | Food & Drug Administration |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | International Classification of Functioning, Disability and Health |
| IRT | Item Response Theory |
| IRB | Institutional Review Board |
| MCID | Minimally clinically important difference |
| MRI | Magnetic resonance imaging |
| PI | Principle Investigator |
| PM&R | Physical Medicine & Rehabilitation |
| QOL | Quality of Life |
| REDCap | Research Electronica Data Capture |
| SCI | Spinal Cord Injury |
| SCI-QOL | Spinal Cord Injury Quality of Life Questionnaire |
| tSCS | Transcutaneous spinal cord stimulation |
| TUG | Timed Up and Go Test |
| 6MWT | 6-minute walk test |
| 10MWT | 10-meter walk test |

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**Sponsored by:**

National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)
U.S. National Institutes of Health (NIH)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the U.S. National Institutes of Health, unless otherwise specified by them. Publication of the results of this study will be governed by NIH public access policies. Any presentation, abstract, or manuscript will be made available by the investigators to the NIH Manuscript Review Committee for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Site Investigator of Record

_____ _____
Signature of Site Investigator of Record Date

***Transcutaneous Spinal Cord Stimulation for Chronic Spinal Cord Injury Recovery: A Multicenter Randomized Controlled Trial***

## SCHEMA

**Purpose:** To evaluate the efficacy of transcutaneous spinal cord spinal stimulation (tSCS) in recovering gait function in people with spinal cord injury when combined with gait training relative to gait training-only therapy.

**Design:** Randomized Double-Blind Controlled Study

**Study Population:** Chronic spinal cord injury

**Study Size:** 182

**Treatment Regimen:** All participants will receive 2 months of gait training-targeted physical therapy 3 times per week. Half of these participants will also receive tSCS during these sessions and the other half will receive a placebo spinal cord stimulation.

**Study Duration:** 6 years

**Primary Objectives:**

- To assess changes in walking speed using the 6MWT during tSCS combined with gait training compared to gait training alone in people with chronic spinal cord injury.

**Secondary Objectives:**

- To evaluate impact of tSCS combined with gait training on quality of life in people with chronic spinal cord injury compared to gait training alone using the SCI-QOL questionnaire.
- To evaluate impact of tSCS combined gait training on gait function compared to gait training alone in people with chronic spinal cord injury (TUG, 10MWT).
- To evaluate the long-term changes in walking speed using the 6MWT 6 months after tSCS combined with gait training on gait function compared to gait training alone.

**Study Sites:**

- University of Washington Medical Center
- Shirley Ryan AbilityLab
- Spaulding Rehabilitation Hospital
- Kessler Institute for Rehabilitation
- Mayo Clinic
- TIRR Memorial Herman
- Craig Hospital

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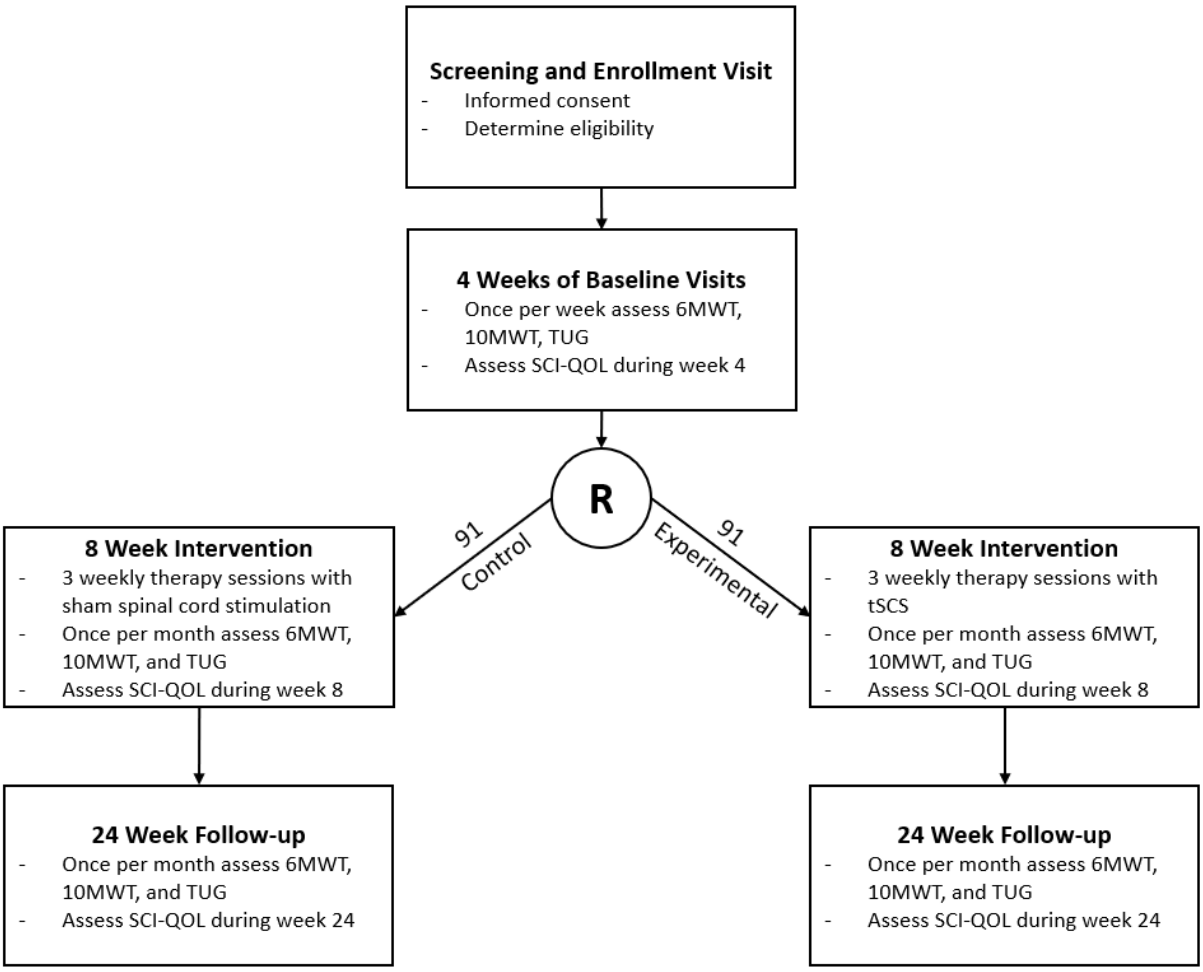
## OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



# 1 INTRODUCTION

## 1.1 Background and Prior Research

### 1.1.1 Epidemiology and Causes of Spinal Cord Injury

In the United States alone, over 17,000 people are affected by spinal cord injury (SCI) each year, and it is estimated that at least 291,000 people are currently living with SCI (Mehdar, Mahjri, Al Rashah, & Alyazidi2019, ; *Spinal Cord Injury Facts and Figures at a Glance Re-Hospitalization*, 2019). Road traffic accidents are the most recent leading cause of injury, closely followed by falls (Jakimovska, Biering-Sørensen, Lidal, & Kostovski, 2020). Acts of violence, especially gunshot wounds, and sports or recreation activities are also considered common causes of SCI (Mehdar et al., 2019; *Spinal Cord Injury Facts and Figures at a Glance Re-Hospitalization*, 2019). This type of injury to the spinal cord can result in negative life-changing consequences and chronic disability. This is because the spinal cord is an important part of the central nervous system that connects the brain to the rest of the body to transmit nerve impulses to and from the body to the brain (Dumont et al., 2001).

As life expectancy of people with SCI continues to increase, the burden on the healthcare system for short-term and long-term SCI management also increases (Wyndaele & Wyndaele, 2006). SCI, is perceived as a disorder that mostly affects the younger population as a result of high-velocity impacts (Harrop, Sharan, & Ratliff, 2006). But it remains a long-term health problem and affects people as they age (Widerström-Noga, Felipe-Cuervo, Broton, Duncan, & Yezierski, 1999). Men are known to be more affected than women (McKinley, Santos, Meade, & Brooke, 2007). The male to female ratio of SCI occurrence is 5:1 (Jakimovska et al., 2020). Injury of the spinal cord results in a malfunction in brain and body communication that further causes a loss of control over the neuromuscular system. Less than 1% of people with SCI have complete neurological recovery at the time of discharge from the hospital (*Spinal Cord Injury Facts and Figures at a Glance Re-Hospitalization*, 2019).

### 1.1.2 Diagnosis, Symptomology and Treatment

Diagnosis of spinal cord injury includes evaluation of the entire nervous system because mild traumatic injury accompanies many SCIs' due to the nature of its causes. The possibility of multi-level injury is always kept in mind while assessing people with SCI. Assessments include evaluation of mental status, cranial nerves, motor, sensory and autonomic systems, coordination, and gait function (Mcdonald & Sadowsky, 2002). The severity of injury is accurately conveyed by the simple five-level (A–E) American Spinal Injury Association (ASIA) impairment scale (Kirshblum et al., 2011). International standards for neurological and functional classifications of spinal-cord injury assesses motor function in ten muscle groups (arms, C5–T1; legs, L2–S1) and sensation (light touch and pinprick) in 28 dermatomes (C2–S4/5) on both sides of the body (Kirshblum et al., 2011). Apart from the ASIA exam, medical imaging serves as an important diagnostic tool including Magnetic resonance imaging (MRI), Computed tomography (CT), and radiography (Yokobori et al., 2015). Among all medical imaging techniques, MRI is the best method used to see the definition of neural tissue (Mcdonald & Sadowsky, 2002).

Anteroposterior, lateral, and special-view radiographs (odontoid, neural foramina views) can define integrity and alignment of bony structures. If a cervical fracture is suspected, a radiograph is essential to ensure that low cervical fracture or subluxation is not overlooked (Mcdonald & Sadowsky, 2002). CT helps to define bony structures and bone marrow density better than radiography and is used when radiographs suggest injury or include poorly visualized areas (Frey-Rindova, De Bruin, Stüssi, Dambacher, & Dietz, 2000; Kasimatis et al., 2008).

Individuals with SCI face significant emotional, social, and economic challenges in the years after injury (Whiteneck et al., 1992). About 39% people with SCI develop additional health complications and about 53% develop associated injuries (Dudley-Javoroski & Shields, 2006; Jakimovska et al., 2020). This has a detrimental effect on their physical functioning and further affects their participation in activities of daily living. Most common physical complications and injuries include leg spasms, muscle spasticity, stiffness, pain and problems with bowel and bladder function (Dudley-Javoroski & Shields, 2006). Pain is the most common issue that most individuals with SCI face. About 80% of individuals with SCI have reported experiencing pain to some extent following SCI (Siddall, McClelland, Rutkowski, & Cousins, 2003), and pain is ranked as one of the five major difficulties described by individuals with SCI (Widerström-Noga et al., 1999). Chronic pain could lead to other complications including depression, chronic fatigue and decreased quality of life (Ataoğlu et al., 2013; Craig et al., 2013).

A variety of pharmacological and non-pharmacological treatments can be used for pain relieving including antiepileptics, tricyclic antidepressants, opioids, transcranial direct electrical stimulation, or invasive surgical process (Hatch, Cushing, Carlson, & Chang, 2018). Since full recovery is not possible, people with SCI usually prioritize their functional recovery pertaining to their needs in daily life. There is a growing body of literature examining the activity preferences or values of individuals with SCI. Bowel/bladder function, upper and lower extremity function, and sexual function are perceived priorities for functional recovery over the general SCI population (Simpson, Eng, Hsieh, & Wolfe, 2012).

### 1.1.3 **Health Priorities**

SCI leads to secondary health conditions and imposes severe limitations on a person's independence, social participation, health, and quality of life (QOL) (Lo, Tran, Anderson, Craig, & Middleton, 2016). Rehabilitation, especially physical therapy interventions are targeted across all three functioning domains of the International Classification of Functioning, Disability and Health (ICF): body functions/structures, activities, and participation (Gómara-Toldrà, Sliwinski, & Dijkers, 2014). Given the wide nature of impairments, determining the priorities of individuals with an SCI can assist in choosing rehabilitation priorities that will ultimately improve people's quality of life (Simpson et al., 2012). With ambulation, or walking, being one of the main limitations in people who have had an SCI, developing, and evaluating training interventions to improve this recovery is instrumental. Lower extremity function is integral for ambulatory purpose and physical activity and thus enhances quality of life in people with SCI (Stevens, Caputo, Fuller, & Morgan, 2008). As a result, retraining the individual with SCI for ambulation, or walking, is one of the main goals of the rehabilitation program.

### 1.1.4 Current Standard of Care

Physical therapy for walking, which is also known as gait training, is the standard of care to improve walking function (Gómara-Toldrà et al., 2014; Harkema, Schmidt-Read, Lorenz, Edgerton, & Behrman, 2012; Lisa A. Harvey, 2016; Nas, Yazmalar, Şah, Aydin, & Öneş, 2015). Most individuals with SCI show some improvement in the walking ability, which is further correlated with functional and neurological recovery in individuals with SCI after the inpatient rehabilitation gait training (Menon, Gupta, Khanna, & Taly, 2015). In the field of rehabilitation, functional recovery means the individuals ability to partake in daily life tasks. However, this recovery is not long-term and the gains in function do not translate to long-term walking capacity. Moreover, continued walking or walking long distances and durations is still limited with conventional gait training. Even though improvements are observed in clinics in various capacities, an individual's performance in community is not positively affected. This restricts an individual's participation in various activities and therefore has a negative impact on their quality of life. (Hardin, Kobetic, & Triolo, 2013).

### 1.1.5 Electrical Stimulation

Regarding the neuroscience after an SCI, unharmed neurons and spinal circuits can reorganize themselves to restore sensory and motor function. This ability to reorganize is known as neural plasticity. Therapy induced gains following this reorganization mechanism are correlated with functional outcomes. However, the development in the structure and function of the spinal cord and brain is limited and cannot recover to the state before injury (Isa & Nishimura, 2014). Recent research has found that the functions of the neuromuscular system can be restored with electrical stimulation (ES) of the central nervous system. ES has proved to leverage the ability of neural circuits to reorganize and help facilitate this neural plasticity beyond what the body can do on its own (Dietz & Fouad, 2014; Edgerton & Roy, 2012). This has highlighted the fact that such stimulation can facilitate neural recovery more than therapy alone. This means that even the best physical therapy intervention may not be able to induce effects that electrical stimulation can.

Walking requires recruitment of neuronal circuits that can produce rhythmic motor patterns. These neuronal circuits, which are also known as the central pattern generators (CPG), are known to induce stepping patterns even without direct inputs from the brain (Takakusaki, 2013; Zehr, 2005). This framework has been the basis of gait training in people with SCI for many decades. Given the prior results, we know that recovery of walking can be more easily achieved with the combination of stimulating the central pattern generators, through the practice of walking, along with ES. Considering the theory of restoration with ES and neural plasticity, we can speculate achieving long-term walking function in these individuals.

With respect to electrical stimulation of the spinal cord, the literature has mainly explored invasive, epidural stimulation and its ability to enhance motor control in people with SCI (Barolat, Myklebust, & Wenninger, 1986; Carhart, He, Herman, D'Luzansky, & Willis, 2004; Sherwood, Sharkey, & Dimitrijevic, 1980). This technology has proved to improve people's overall motor function and has demonstrated positive changes in muscle activation and gait kinematics (Hofstoetter et al., 2015). Some studies have also shown that it can reduce spasticity and increase the activity of central pattern generators following SCI (Hofstoetter et al., 2015; Minassian et al., 2016). Even though there have been positive

changes associated with epidural, or invasive, stimulation, it is important to note that this type of stimulation requires a surgery wherein the stimulating device needs to be attached to the person's spinal cord. It is an invasive procedure, which has shown to have both neural and functional improvements in people with spinal cord injury (Barolat et al., 1986; Carhart et al., 2004; Sherwood et al., 1980).

Transcutaneous spinal cord stimulation (tSCS), however, is a non-invasive way to administer spinal cord stimulation that restores some functional movement in paralyzed individuals (Gerasimenko et al., 2015). Unlike epidural stimulation, this type of stimulation can be administered to the surface of the skin at higher energy levels that will not induce pain due to a special designed stimulation waveform (Gad et al., 2017; Gerasimenko et al., 2015; Inanici et al., 2018). Thus, tSCS may allow individuals with SCI to regain the ability to modulate their spinal functions without the need of an invasive surgery and a constant device on their spinal cords.

Several studies have examined the effects of tSCS of both upper and lower body function and mobility. These studies, however, are limited in their sample size and do not include randomization or comparison with a control group (Gad et al., 2017; Gerasimenko et al., 2015). Therefore, full cause of the effects of tSCS cannot be confirmed without a randomized controlled trial. These studies have induced tSCS along with a specific physical therapy regimen, which is indicative of the importance of task-specific training being integral to neurological recovery (Gerasimenko et al., 2015; Inanici et al., 2018). Keeping that in mind, a randomized, controlled, multi-site clinical trial will help to identify the effect of tSCS on walking function in individuals with SCI. Through this study, we plan to evaluate effects of tSCS by utilizing two types of stimulations: tSCS and a placebo that feels like tSCS but does not have any known effects on function. Since gait physical therapy is an integral aspect of neurological recovery of gait function, our aim is to evaluate the efficacy of tSCS combined with physical therapy in improving gait function (Gerasimenko et al., 2015; Inanici et al., 2018).

The proposed study is a critical incremental step in the science and application of non-invasive spinal cord stimulation for neurorehabilitation. If this study unveils the efficacy of tSCS combined with physical therapy over the administering of physical therapy alone, a phase 3 clinical trial can be induced. The outcomes of this research will lead to sustained neuro-recovery of gait in function in people with chronic SCI. In the long-term, this will reduce their healthcare and rehabilitation costs, leading to a reduced burden on the overall healthcare utility. The rehabilitation of people with SCI takes years and is resource intensive. The potential utilization of tSCS in clinics, in the future, will permit faster and greater recovery of SCI with lesser resources and thus promote more efficient healthcare delivery.

## 1.2 **Rationale**

Individuals with chronic SCI, even after pharmaceutical and rehabilitation management, remain unable to completely recover after their injury. The current standard of care is focused on treating the symptoms of a spinal cord injury such as chronic pain through medicines or invasive electrical stimulations. More focus is needed on finding a robust treatment that addresses the underlying mechanisms of spinal cord injury and induces neuroplasticity to promote functional recovery. Spinal cord stimulation is a

potential solution, as it applies electrical stimulation directly to the central nervous system to augment neural recovery that an individual with SCI is unable to do on their own. Non-invasive spinal stimulation, specifically, offers this possibility without the need for a high-risk surgery to implant electrodes. Early research has taken substantial strides in showing what neurorehabilitation improvements are possible when providing someone who has an SCI with tSCS during their physical therapy sessions yet does not have randomize trials and have limited sample size. A phase 2b, blinded clinical trial is an important next step to gaining a better understanding of the possibilities and effects of tSCS along with physical therapy on the gait function in SCI patients. If tSCS proves to be efficacious through clinical trials, it could one day be made available as a method for neurorehabilitation in the clinical setting.

# 2 STUDY OBJECTIVES AND DESIGN STATEMENT OF GOALS

## 2.1 Statement of Goals

The overarching goal of this research study is to evaluate the effects of transcutaneous spinal cord stimulation (tSCS) with standard physical therapy on the gait function in people with chronic SCI.

## 2.2 Primary Objective

- To assess changes in walking speed using the 6MWT during tSCS combined with gait training compared to gait training alone in people with chronic spinal cord injury.

## 2.3 Secondary Objectives

- To evaluate impact of tSCS combined with gait training on quality of life in people with chronic spinal cord injury compared to gait training alone using the SCI-QOL questionnaire.
- To evaluate impact of tSCS combined gait training on gait function compared to gait training alone in people with chronic spinal cord injury (TUG, 10MWT).
- To evaluate the long-term changes in walking speed using the 6MWT 6 months after tSCS combined with gait training on gait function compared to gait training alone.

## 2.4 Study Design

This is a Phase 2b, multi-site, blinded randomized control trial examining the effects of tSCS on gait function, mobility, and quality of life. We are seeking to recruit a total of 182 participants with SCI split up into two groups: an experimental group and a placebo group. Both groups will go through three phases of the study: baseline, intervention, and follow-up (See the design figure on page ix). The baseline phase will last a total of 4 weeks, with the outcome measures assessed each week and averaged to ensure accurate baseline values. The intervention phase of the study with last a total of 8 weeks. The

outcome measures will be assessed at week 4 and week 8. During the randomized trial, both groups will be receiving intensive gait training 3 times/week. The experimental group will also be receiving transcutaneous spinal cord stimulation in two locations: around the site of injury, and the lower thoracic region of the spine. The placebo group will receive a sham spinal stimulation at the same locations so that it feels as if they are receiving tSCS, when they are not. The follow-up phase will be a 24-week period in which participants visit their corresponding site once per month to perform the outcome measures.

The primary outcome of this study is gait speed as evaluated by the 6-minute walk test (6MWT). This is a clinical functional test with low inter-rater variability, extensive validity in the SCI population, and few equipment needs. It is quick to administer with minimal training and does not impose burden. This makes it ideal for our multi-site study with individuals with SCI. The 6MWT involves participants walking around a 30-meter walkway for a total of 6 minutes. Participants can take breaks as needed, and at the end of the 6 minutes, their total distance is recorded, and the measured outcome is converted to speed in the unit of meters/second (m/s). Apart from the 6MWT, we will have several secondary outcome measures including the 10-meter walk test (10MWT), timed up and go test (TUG), and the Spinal Cord Injury Quality of Life (SCI-QOL) questionnaire. The 10MWT is another clinical, functional test that assesses participants speed over a shorter period. It is administered by having the participant walking down a 10-meter walkway at a self-selected pace while being timed and then converting the measurement into speed in the unit of meters/second (m/s). TUG examines participant mobility by timing the participant as they get up from a chair, walk around a cone at a set distance, and sit back down. The timing of this test is used to assess participant mobility when doing some activities other than walking, like sitting and standing. The SCI-QOL questionnaire will be used to qualitatively assess the impact of the intervention of the participants quality of life. The domains included in the SCI-QOL are emotional health, physical-medical health, social participation, and physical function (Tulsky, Kisala, Victorson, Tate, et al., 2015). These sections are targeted towards understanding the effect of the intervention on common challenges facing people with SCI.

There will be a total of 7 sites participating in this study, with each site enrolling around 26 participants (Table 1). These sites were selected based on their expertise in working with individuals with SCI, access to the space, research experience, and having the number personnel required to provide intense physical therapy 3 times per week. These are explained in detail in Section 4. Permuted-block randomization will be used to centrally organize and block participants at the individual center level. For each site, we will use random blocks of size 2 or 4 to avoid potential imbalance in the number of participants assigned to each treatment group. Participants, clinicians, testing physician/evaluators and researchers will all be blinded during the whole process of this trial.

Table 1. These sites will be partaking in this study.

| Institution | Location |
|---|---|
| University of Washington Medical Center | Seattle, WA |
| Shirley-Ryan AbilityLab | Chicago, IL |

| | |
|---|---|
| Spaulding rehabilitation network | Boston, MA |
| Kessler Institute for Rehabilitation | West Orange, NJ |
| Mayo Clinic | Rochester, MN |
| TIRR Memorial Hermann | Houston, TX |
| Craig Hospital | Denver, CO |

# 3 STUDY POPULATION

182 individuals with chronic spinal injury, with ASIA level C or D, will be included in this study. ASIA level C is defined as an incomplete spinal cord injury where motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3 (Kirshblum et al., 2011). ASIA level D is defined as an incomplete spinal cord injury where motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more (Kirshblum et al., 2011). Participants will be selected for the study according to the criteria in Section 3.1 and 3.2 and the guidelines in Section 3.4. They will be recruited, screened, and enrolled as described in Section 3.3 and assigned to a study treatment/product/intervention group as described in Section 7.4. Issues related to participant retention, adherence, and withdrawal from the study are described in Sections 3.5, 3.6 and 3.7 respectively.

## 3.1 Inclusion Criteria

Adults who meet all the following criteria are eligible for inclusion in this study:

- are at least 1 year post spinal cord injury
- have an incomplete spinal cord injury
- are 18 – 70 years old
- ASIA level C or D
- can stand independently but have difficulty walking in daily activities
- have stable medical condition without disease or frequent autonomic dysreflexia that would contraindicate participation in lower extremity rehabilitation or testing activities
- can perform simple cued motor tasks
- able to attend 3 physical therapy session each week for 2 months at one of our 7 locations
- cleared for gait training by a physician
- can read and speak English

We are requiring that all participants be at least 1-year post-injury because this is the time point to when they have reached the classification of chronic SCI. This means that the best standard of care at this time point is to target rehabilitation interventions to improve their function. Their injury must also be classified as incomplete, otherwise they would

likely not be able to partake in the physical therapy protocol. Participants must be at least 18 years of age so that they are able to consent themselves. They must be under 70 years of age, however, to prevent risk of further medical complications due to age. Because this study is focusing on lower limb recovery and includes intensive gait training, we are requiring that all participants can stand independently as a prerequisite, but have challenges walking on their own. This could be anyone classified by the American Spinal Injury Impairment (ASIA) Scale as Grade C or D. Participants must have a stable medical condition without any autonomic disorders, as this may impact one's ability to train and participate in the protocol. Physical therapy sessions may include the need to follow instructions given by the physical therapist to perform certain tasks. For this reason, all participants must be able to follow cued motor tasks to ensure maximum participation in the physical therapy protocol. This study is a large time commitment, so each participant must be able to attend up to three physical therapy sessions each week at one of our seven locations for the duration of the two-month stretch of the study. All participants must be cleared for gait training by a Physical Medicine and Rehabilitation (PM&R) physician to ensure that a combination of low risk, secondary health conditions does not put the participant at any additional risk by participating in the study. Finally, participants must be able to read and speak English so that they can communicate with the clinicians, read and understand the consent forms, and complete the questionnaire.

## 3.2 **Exclusion Criteria**

Individuals who meet any of the following criteria will be excluded from this study:

- have autoimmune etiology of spinal cord dysfunction/injury
- have history of additional neurologic disease, such as stroke, multiple sclerosis, traumatic brain injury, etc
- have peripheral neuropathies
- have rheumatic diseases
- have significant medical disease; including uncontrolled systemic hypertension with values above 170/100 mmHg; cardiac or pulmonary disease; uncorrected coagulation abnormalities or need for therapeutic anticoagulation
- have active cancer
- have cardiovascular or musculoskeletal disease or injury that would prevent full participation in physical therapy intervention
- have an unhealed fracture, contracture, pressure sore, or urinary tract infection or other illnesses that might interfere with lower extremity rehabilitation
- are pregnant
- have cognitive impairments or are unable to follow the instructions given as part of the study
- have established osteoporosis and taking medication for osteoporosis treatment.
- are dependent on ventilation support
- have an implanted stimulator (i.e. pacemaker, epidural stimulator, etc.)
- have depression or anxiety, or underlying alcohol or drug abuse.

- have any condition that would render the participant unable to safely cooperate with the study intervention or spinal cord stimulation, as judged by a screening physician
- Any allergens to the adhesives on the electrodes.

These exclusion criteria were selected based off discussions with physicians on why someone would not be cleared for gait training or spinal cord stimulation. These are specific secondary health conditions that put the participant at an additional unknown risk. Further research needs to be completed before these participants are included in a large-scale clinical trial. Additionally, little is known on the effect of spinal cord stimulation on someone who is pregnant, has a combination of neurologic diseases, with an autoimmune disorder, or has active cancer. Thus, individuals with any of these dualities will not be included in the current study. Due to the risk of falls and over-exertion during gait training, people with cardiovascular or musculoskeletal disease/injury, such as fractures, osteoporosis, or pressure sores with not be included in the study. Because of the time commitment of being in a rehabilitation clinical trial and the mental toll of rigorous physical therapy, we will refrain from including anyone with depression, anxiety, or alcohol/drug abuse. Participants can also not have any implanted stimulator, such as a pacemaker or epidural stimulator, as this could interfere with the transcutaneous spinal cord stimulation (tSCS). Before anyone is enrolled in the study, they must be cleared by a screening physician at one of our seven sites to determine that the risks of participating in the clinical trial for each participant is are minimal. This includes confirming that they do not have an allergy to the adhesives to be used on the electrodes.

## 3.3 **Recruitment Process**

Recruitment will happen at all seven participating institutions once they have completed the appropriate approval process through their respective Institutional Review Board (IRB). The participating institutions are described in Section 9.1. We will recruit for this study through our clinical contacts at each of the sites for the study. We will have an established research coordinator each site that will be responsible for setting up a calendar for entire recruitment period, keeping track of and disseminating information for recruitment, finding clinicians to work with on the study as well as evaluating the whole program. We suspect that each site will be able to recruit about 26 participants, and that this will take approximately 5 years. They will be expected to post IRB-approved flyers at their institutions and identify clinicians who can be a part of the study helping to recruit and be interventionists. This would include research physical therapists and Physical Medicine and Rehabilitation (PM&R) physicians that are trained and familiar in working with individuals with SCI. These clinicians will be trained on the study protocol, but also the specific inclusion and exclusion criteria for the study to assist with the recruitment.

Participants will be recruited via a flyer made available at each site. Clinicians recruiting for the study will also notify their current patients, as well as any previous patients who consented to being contacted about future research studies, who they think meet the necessary criteria. They will reach out via email, phone call or in-person meeting, as appropriate. Individuals who express interest will be given more information about the study including duration, required commitment, and the inclusion and exclusion criteria. If

individuals decide they would like to participate in the study, then they will proceed with the study procedures described in Section 5.

## 3.4 Co-Enrollment Guidelines

Participants cannot enroll in other research studies involving any form of electrical stimulation. This includes but is not limited to neuromuscular electrical stimulation and epidural spinal stimulation. Additionally, participants cannot participate in any drug-related research. Details on concomitant medications and physical therapy that are not part of another research study can be found in Section 4.8 and 4.9, respectively.

## 3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain him/her for the three months of the study and the six months of follow-up in order to minimize possible bias associated with loss-to-follow-up. *S*tudy site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit. This includes a strong emphasis on the frequent visits required during the intervention portion of the study. Participants will not be enrolled in the study if they do not have the resources to commit to three physical therapy sessions each week during that time

- Thorough explanation of the importance of both study treatment groups to the overall success of the study.

- Each site will have 1-2 social workers to set-up visits with participants and coordinate a ride to and from the study site as needed.

- Collection of detailed contact and locator information at the study screening and consent visits, and active review and updating of this information at each subsequent visit, especially during the follow-up phase of the study.

- Use of mapping techniques to establish the location of participant residences and other locator venues. Emphasis will be given to the ~9-month commitment to the study as well as a specific mention of the other sites of the study if another site would be a better fit.

- Use of appropriate and timely visit reminder mechanisms. Physical therapy sessions during the intervention phase of the study will be scheduled a week in advance to be flexible around the participant's schedule. During monthly follow-up visits, timing will be planned 1-month in advance with a follow-up

reminder via a phone call 1-week before the planned visit to ensure the planned time is still applicable, and if not, finding a new time.

- Immediate and multifaceted follow-up on missed visits as well as scheduling of replacement visits if possible.

- Regular communication with the study community at large to increase awareness about SCI and explain the purpose of SCI rehabilitation research and the importance of completing research study visits.
- We will provide travel support for our participants so that they can reach the research site conveniently, which would further promote retention.

## 3.6 **Participant Adherence**

Every effort will be made to maintain a high adherence rate for the three months of the study and the six months of follow-up. Our sample size was selected to account for a dropout rate of up to 10%. As an incentive to promote adherence, parking vouchers will be provided for each participant as appropriate and social workers will help coordinate rides to the study site for those who may require transportation. Participants will be compensated for their time and effort and will be compensated financially each week using checks at a rate of $20/visit. Throughout the study, physical therapists will strengthen participants fulfillment by emphasizing the positive contribution about the study adherence. During the intervention phase of the study, each physical therapist will pay attention to the participants symptoms, testing outcomes and report any signs or emotions that may lead to poor adherence. The research team will take every effort to keep the intervention schedule consistent with respect to days and times of the week per participant, so that it does not disrupt participants' weekly activities. The research team will be flexible in scheduling if a certain participant prefers a specific time or days of the week or needs to adjust their schedule during the study. The progression of gait training will be conducted in accordance with participants' endurance and willingness. In no circumstances will the training be forced on them. Rest breaks will be provided as needed throughout all intervention and assessment sessions. Each site will also have a social worker who will be responsible to look after participants' welfare. We will provide travel support for our participants so that they can reach the research site conveniently, which would further promote their adherence to the intervention protocol. Clear communication opportunities with the research team members will be available each time they visit and can be scheduled as needed. During the follow-up period, the assessment sessions will be scheduled in advance so that the participants can plan their other activities accordingly and adhere throughout the follow-up process.

### 3.7 Participant Withdrawal

#### 3.7.1 Rules for Withdrawing during the Intervention Phase:

- The participants will be allowed to withdrawal consent at any time during the study.
- If the participant experiences an adverse effect during intervention, such as sustained low or high blood pressure; arrhythmia (heart beats with an irregular or abnormal rhythm); chest pain; a muscle strain, joint sprain, or fracture from lower extremity physical therapy; severe allergic reactions, that cannot be treated with antihistaminic medication or thermal reaction to stimulation or recording electrodes, they will be withdrawn from the study.
- If the participant becomes ill and cannot continue, they will be withdrawn from the study.
- If the participant becomes unable or are unwilling to complete the study procedures, they will be given the option of withdrawing.
- If the participant becomes pregnant during the study, they will be withdrawn from the study.

#### 3.7.2 Rules for Withdrawing during the Follow-up Phase:

- The participants will be allowed to withdraw consent at any time during the follow-up period.
- If the participant experiences an adverse event and would no longer like to participate in the intervention, they will still be encouraged to complete the follow-up assessments.

## 4 STUDY TREATMENT/PRODUCT/INTERVENTION

### 4.1 Device Details

The stimulator to be used in this study is the alpha prototype of the 'External Spinal Cord Neuromodulator – Coulomb-3M & Multichannel 9CES' (NeuroRecovery Technologies, Inc., San Juan Capistrano, CA, USA). The stimulator device generates electrical pulse under safe circuitry and proprietary algorithms. This device is currently for experimental use only. Before any devices are used at one of our sites, they will be inspected, tested, and approved for use on human subjects by each institutes respective Health Sciences and Academic Services and Facilities Department. Additional details on the equipment used for spinal cord stimulation can be found in Section 9.3.1.

### 4.2 Intervention Regimen

Each intervention visit will last 2 hours with the duration of spinal cord stimulation to not exceed 90 minutes. The additional time will be used to set-up the device, place electrodes, prepare for the physical therapy session, and remove all equipment from the participant after the session. Each participant will receive spinal cord stimulation, either

transcutaneous spinal cord stimulation or sham spinal cord stimulation, along with gait training physical therapy. The parameters of the stimulator will be set by the site physician at the participants' first intervention visit. These parameters will be recorded and used by the physical therapist for all remaining session. Details on the administering of the spinal cord stimulation during each physical therapy session are described in Section 4.3.

During a 90-minute therapy session, participants will partake in several physical therapy activities with a licensed research physical therapist. Each participant will receive 45 minutes of over ground gait training and 45 minutes of body weight support treadmill training. The progression of gait training will be determined as per the tolerance of the participant. Adequate rest breaks during each session will be provided as per the needs of the participant.

The specific amount of time spent standing or walking will depend on each participant's level of exercise-induced fatigue. The physical therapists will start each intervention session with mild to moderate stretching exercises for up to 10 minutes (L. A. Harvey & Herbert, 2002). This will be followed by over ground gait training. Walking over ground will be practiced as feasible, with or without mobility devices, for an additional 45 minutes each session. Mobility devices for over ground walking have been kept optional as it will depends on participant to participant. Some participants might choose to use canes or walkers during initial phases of the study but may feel comfortable walking independently towards the end of the study. Over ground gait training will be followed by gait training on the treadmill using body weight system for 45 minutes in 3- to 10-minute increments. The increments will be progressed as the participants develop endurance and the fatigue levels reduce. Rest breaks will be provided for each training session as required. Vitals will be intermittently monitored for any changes. During the rest breaks, participants will sit down, and vitals will be monitored.

For body weight support treadmill training (BWSTT), participants will wear a climbing harness which will be attached to an overhead lift. Weight support and treadmill speed will be adjusted to enable training at speeds greater than 0.72 m/s with a goal of over 1.07 m/s (Dobkin et al., 2006). Walking practice with partial weight support will allow physical therapists to initiate gait training when full weight bearing becomes exhaustive. This will allow practice of reciprocal stepping at faster speeds with greater safety and less fear of falling.

Over ground gait training will primarily include mobility training. Participants who can bear full body weight will practice walking over ground with parallel bars or physical assistance from a physical therapist. Participants who can stand but do not have the motor control for stepping will be passively assisted by a physical therapist to facilitate their stepping patterns. Each participant will be made to wear a safety harness while over ground walking, to prevent them from falling.

## 4.3 **Device Administration**

The main treatment being evaluated in this study is transcutaneous spinal stimulation (tSCS). Because of the importance of activity dependent neuroplasticity as discussed in Section 1.1.5, this treatment is administered during intense physical therapy sessions several times a week. This study will compare the combination of tSCS with physical therapy to a control group receiving a placebo stimulation with physical therapy.

Transcutaneous spinal cord stimulation is administered on the surface of the skin at the back of the spinal cord in biphasic, rectangular waveforms, with 1 millisecond pulses at a frequency of 30 Hz with a carrier frequency of 10 Hz [37]. This allows the stimulation to be administered at a higher amplitude without inflicting pain. The intensity of tSCS safely vary from 30 to 200 milliamperes [30]. The intensity used in this study will vary depending on the individual person's tolerance and will be modulated based on each participant's muscle contraction level within each intervention session. For each participant, on the first day of spinal cord stimulation, the site physician will start the spinal cord stimulation as low as possible and reach an intensity that is 5-10% below the threshold for muscle contraction [30], [38]. Some of the effects of spinal cord stimulation are acute and therefore we will be able to monitor our participants' functionality right after the spinal cord stimulation. The optimal intensity of each participant can be different and will be determined on the first day of spinal cord stimulation.

In this study, four 2.5-cm round electrodes (Lead-Lok, Sandpoint, USA) will be used to deliver spinal cord stimulation. The four round electrodes will be place on the participants back to deliver the spinal cord stimulation (Figure 1). Two 3x4 $cm^2$ ground electrodes will be placed on the iliac crest as the anodes. The two larger electrodes will be placed at the location of the participant's injury, and two electrodes will be placed on the lower spine at T11-T12.

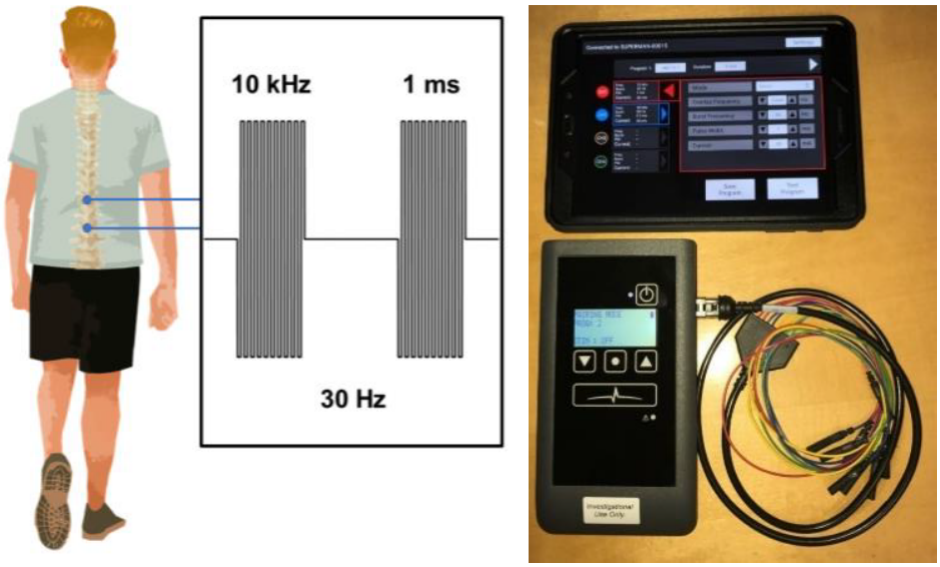



Figure 1. Spinal cord stimulation is delivered to the lower spine using the non-invasive stimulator shown on the right.

## 4.4 **Device Supply and Accountability**

The site research coordinator will maintain a detailed record of any malfunctions with the device. If a device is not working properly, the University of Washington principle investigator will be notified immediately to contact the company, NeuroRecovery Technologies, Inc. Spinal cord stimulation shall not be administered to any participants if the device shows any wear or previously malfunctioned without being resolved.

## 4.5 Adherence Assessment

Adherence to the study will be defined differently during each phase of the study. During the baseline portion of the study, when ideally there will be the collection for 4 baseline measurements, there must be no less than 2 baseline visits. During the intervention phase of the study, as long as participants attend a minimum of 3 2-hour sessions of physical therapy each week, they will have adhered to the study protocol. During the follow-up portion of the study, emphasis will be made on retaining participants for at least the final follow-up visit at the end of the 6$^{th}$ month. The participant may attend additional follow-up visits, even if they miss one. The Data Safety and Monitor Board (DSMB) will monitor all adherence assessments throughout the study.

## 4.6 Response to Unanticipated Adverse Device Effects

If any unanticipated adverse device effects are observed during a session, spinal cord stimulation and the physical therapy session will cease immediately. To this date, all unanticipated adverse device effects reported from non-invasive spinal cord stimulation cease once stimulation is stopped. The continuation of any unanticipated adverse device effects after spinal cord stimulation is turned off will be reported to the Data Safety Monitoring Board (DSMB) immediately for consideration of next steps. The research team will take the direction suggested by the DSMB when dealing with any unanticipated adverse device effects regarding any necessary modifications to the study protocol. If any changes are required, the study will be put on hold at each institution until their perspective IRB's approve the new study protocol, at which the study will continue. If any event becomes life-threatening, the appropriate emergency health care services will be contacted. Withdrawal from study treatment for a participant who experienced an unanticipated adverse device effects will be determined by the combined efforts of the DSMB, the participant's physician, and the participant themselves.

## 4.7 Clinical Management of Pregnancy

If a participant becomes pregnant during the study, they will immediately be withdrawn from the study. This is because the effects of spinal cord stimulation on a fetus are unknown currently. If desired, participants are encouraged to use any method of contraception they see fit during the study, as discussed with a physician.

## 4.8 Concomitant Medications

Use of the following concomitant medications is not be permitted by enrolled study participants:

- Botulinum toxin
- Diabetes medication
- Clonidine
- Tizanidine-antispasmodic

- Dantrolene

Participants may take the following medications under some restrictions:

- Benzodiazepine – only allowed if 5 mg at bedtime
- Baclofen – only allowed if less than 40 mg
- Gabapentin – only if between 1800-3600 mg
- Lyric-pregabalin – only if between 110-400 mg

All concomitant medications taken or received by participants within the 4 weeks prior to study enrollment will be reported on applicable study case report forms. In addition to prescribed and over-the-counter medications such as vitamins, herbal remedies, and other traditional preparations will be recorded. Alcohol and recreational or street drug use will be recorded in clinical progress notes if needed for interpretation/documentation of observed participant health status and may dictate withdraw from the study. Medications used for the treatment of unanticipated adverse device effects that occur during study participation also will be recorded on applicable study case report forms.

### 4.9 **Concomitant Physical Rehabilitation**

Participants may not participate in any other lower body physical therapy during the time of the study. They may, however, participate in upper body-only physical therapy and occupational therapy.

# 5 STUDY PROCEDURES

An overview of each study visits and procedure schedule is presented in Section 13. Presented below is a summary of information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in a study-specific procedures manual and distributed to all sites during initial training, described in Section 10.6. Data from each subject's visit will be recorded using the sample case report form (CRF) shown in Section 18, followed by electronic reporting in the Research Electronic Data Capture (REDCap) software. This study consists of four phases: enrollment/screening, baseline, intervention, and follow-up. Each of these visits are described in detail below.

### 5.1 **Enrollment/Screening Phase**

Before the enrollment/screening visit, participants will be interviewed via phone, to ensure that they meet all the inclusion criteria and none of the exclusion criteria outlined in sections 3.1 and 3.2. Details of the study will be discussed with each participant as our research coordinator requests them to sign the Health Insurance Portability and Accountability (HIPAA) authorization form. After they sign the HIPAA authorization form, our research team will reach out to the study spinal cord injury specialist to check their medical records. The physician on our research team will look at their medical records

and consult with a specialist, as needed, to determine if it is safe to include them in the study. If the specialist agrees and the medical records confirm that the individual does not violate the exclusion criteria, the research team will reach out to them again letting them know they are eligible for the study and set up a visit for the consent process. During this visit, the research coordinator will carefully explain to the participant the process of consent. Details of the study will be thoroughly discussed with each participant. During this time, they will be encouraged to ask any questions and take time to consider their commitment to the study to best ensure retention in the study. If they decide to participate in the study, then they must sign the consent form. Section 14.0 provides a sample consent form that will be used at the University of Washington Medical Center. If they decide not to participate in the study or do not satisfy the necessary inclusion and exclusion criteria, then they will be informed and no longer continue with the study.

## 5.2 Baseline Phase

The baseline phase will last a total of 4 weeks. Each week participant will have 2 visits each week to assess the outcome measures. Each functional outcome measure (6MWT, TUG, 10MWT) will be recorded each week and averaged to ensure accurate baseline values are collected. During this time, the participant does not receive any intervention treatments. The SCI-QOL questionnaire will be completed at the end of the baseline phase before intervention begins.

## 5.3 Intervention Phase

The intervention phase of the study will last a total of 8 weeks, with the functional outcome measures (6MWT, TUG, 10MWT) assessed at week 4 and week 8. The SCI-QOL questionnaire will be completed at the end of the intervention phase. During the intervention phase of the study, all participants will receive intensive gait training 3 times/week. The experimental group will also receive transcutaneous spinal cord stimulation in two locations: around the site of injury, and the lower thoracic region of the spine (details in Section 4.1 and 4.3). The control group will receive a sham spinal stimulation at the same locations so that it feels as if they are receiving tSCS, when they are not.

Physical therapy sessions during the intervention phase will be controlled so that all participants across institutions receive the same intervention. This will be done through training sessions with physical therapists at each institution. Each participant will receive 45 minutes of over ground gait training and 45 minutes of body weight support treadmill training during each intervention session. More details on the intervention regimen are provided in Section 4.2.

## 5.4 Follow-up Phase

The follow-up phase will be a 24-week period in which participants visit their corresponding site once every 4 weeks to perform the functional outcome measures (6MWT, TUG, 10MWT). During each of these visits, the outcome measures will be

reassessed. There will be no physical therapy or spinal stimulation administered during the follow-up phase. The SCI-QOL questionnaire will be completed once at the end of the follow-up phase.

# 6 DEVICE SAFETY MONITORING AND REGULATION

## 6.1 Investigational Device Exemption

According to the U.S. Code of Federal Regulations (CFR) 812.2(b) an investigative device is considered to have investigational device exemption (IDE) if it is not considered a significant risk device and follows the described regulations in CFR 812. Our device is considered to have nonsignificant risk in accordance with CFR 812.3(m) because it is not an implant, does not sustain life, not of substantial importance in diagnosing, curing, mitigating, or treating disease, and does not otherwise pose a serious risk to the health, safety, or welfare of the participants. Maintaining an IDE status means that no additional approval is required by the Food & Drug Administration (FDA) to proceed with the study as long as the study is deemed safe by the IRB and Data Safety Monitoring Board (DSMB).

Measures to be taken in accordance with CFR 812.2(b) to maintain IDE:

- Acquire and maintain IRB approval at all institutions for the use of the device;
- Label the stimulator device as an investigational device and list the name and place of the manufacturer, in accordance with CFR 812.5;
- Ensure that each participant is made aware that this is an investigational device in the consent process;
- Maintain compliance between the sponsor and investigator, report any unanticipated adverse device effects to the sponsor so they can immediately conduct an evaluation and terminate use of the device if necessary, in accordance with CFR 812.46;
- The sponsor must maintain records required under CFR 812.150(b) (4) and (5) and makes the required reports under CFR 812.150(b) (1)-3) and (5)-(10);
- The investigator must maintain the records required by CFR 812.30(a)(3)(i) and make the necessary reports in compliance with CFR 812.150(a) (1), (2), (5), and (7); and
- Refrain from any device promotion or other practices described in CFR 812.7.

## 6.2 Safety Monitoring

Close cooperation between the Principle investigator, research coordinators, the Data Safety and Monitoring Board (DSMB), NINDS Program Officer, and other study team members will be necessary in order to monitor participant safety and respond to occurrences of negative events in a timely manner. The study site investigators and interventionists will be responsible for continuous close monitoring of all reporting an unanticipated adverse device effects that occur among study participants, and for alerting the rest of the protocol team if unexpected concerns arise. A DSMB will be appointed for the study. Before the commencement of the study, the team will decide on a timeline and

schedule to hold regular conference calls during the period of study implementation, and additional ad hoc calls will be convened if required. They will also coordinate meetings to overlap with the timeline expected for interim analyses. The DSMB will track any unanticipated adverse device effects and/or study-related injuries if they occur. If a participant experiences an unanticipated adverse device effect and/or study-related injury, the research team will follow that participant for as long as is recommended by the DSMB.

### 6.3 Unanticipated Adverse Device Effect Reporting

An unanticipated adverse device effect as defined per CFR 812.3(s) is any serious adverse effect on health or safety that results in

- A life-threatening problem
- Death
- An outcome that was not previously identified in nature, severity, or degree of incidence in the investigational plan or application
- Another unanticipated serious problem associated with the device that related to the rights, safety, or welfare of the participant

Study participants will be provided a 24-hour telephone number and instructed to contact the study clinician to report any unanticipated adverse device effects they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation with the site physician, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to unanticipated adverse device effects will be obtained and required data elements will be recorded on study case report forms. All participants reporting an unanticipated adverse device effect will be followed clinically, until the unanticipated adverse device effect resolves (returns to baseline) or stabilizes. All reported unanticipated adverse device effects will be reported to the DSMB for review and shared with all institutional IRB's to make any necessary protocol changes that will then be implemented at all institutions based on the DSMB and IRB's discretion. All reporting will also be shared in any progress reporting to NINDS or immediately to the NINDS Program Officer if necessary.

# 7 STATISTICAL CONSIDERATIONS

### 7.1 Review of Study Design

This is a Phase 2b, multi-site, blinded randomized control trial examining the effects of tSCS on gait function and mobility improvement. The statistical plan is delineated for the primary and secondary outcomes in the following sections.

## 7.2 Endpoints

### 7.2.1 Primary Endpoints

6-minute walk test (6MWT): The 6MWT is a sub-maximal exercise test used to assess walking endurance and aerobic capacity (Lam, Noonan, & Eng, 2008). This is a clinical functional test with low inter-rater variability, extensive validity in the SCI population, and minimal required resources. Participants will walk around a 30-meter walkway for a total of 6 minutes. They can take breaks as needed, and at the end of the 6 minutes, their total distance is recorded and converted to speed. We will use the mean change in speed between baseline and the end of the treatment interval as our primary endpoint.

### 7.2.2 Secondary Endpoints

Timed-up-and-go (TUG): TUG will be used to examine participant mobility by timing the participant as they get up from a chair, walk to and around a cone at a set distance, and sit back down (Lam et al., 2008). The timing of this test is used to access participant mobility when doing some activities other than walking. We will use the mean change of time between baseline and the end of the treatment interval as a secondary endpoint.

10-meter walk test (10MWT): The 10MWT is another functional test that assesses participants' self-selected speed over a shorter distance. It is administered by having the participant walking down a 10-meter walkway, timing them, and then converting that to speed in meters/second. We will use the mean change of speed between baseline and the end of the treatment interval as a secondary endpoint.

Spinal Cord Injury – Quality of Life (SCI-QOL) (Tulsky, Kisala, Victorson, Choi, et al., 2015): The item response theory (IRT)-calibrated SCI-QOL comprises of 22 sub-domains across the four broad domains of physical-medical health, emotional health, social participation, and physical functioning which includes both SCI-specific and generic quality of life questions (Tulsky, Kisala, Victorson, Choi, et al., 2015). Mean score difference between baseline and the end of the treatment interval will be calculated as a secondary endpoint to examine the effect of treatment during intervention period. The SCI-QOL questionnaire will be completed at the end of each phase of the study.

6 Minute walk Test long-term – The 6MWT is a sub-maximal exercise test used to assess walking endurance and aerobic capacity. To evaluate the long-term effects of tSCS combined with gait training on gait function compared to gait training alone, we will compare the mean change of speed from the end of treatment to the end of follow-up between groups.

## 7.3 Accrual, Follow-up, and Sample Size

Our study design calls for the recruitment of 182 participants in total with half randomly assigned to tSCS combined with gait training (experimental) group and the other half to gait training only therapy combined with sham stimulation (control) group. Each site is expected to enroll 26 participants. The overall sample size calculation was based on the primary outcome, 6-minute walk test (6MWT). For the purpose of sample size

estimation, we estimate the 6MWT standard deviation for both arms will be 0.28 m/s (Forrest et al., 2014). Several previous studies reported inconsistent minimal clinical important difference (MCID) when detecting the minimal change required for the individual to also feel an improvement in the construct being measured. Forrest et al. calculated the MCID for individuals with incomplete spinal cord injury were 0.11 m/s while Lam et al. also reported the minimum detectable difference of participants with spinal cord injury is 0.12 m/s (Forrest et al., 2014; Lam et al., 2008). Thus, we conservatively selected a clinically important difference in this study of 0.14 m/s to assess meaningful clinical improvement in function between the experimental group and the control group. With all efforts to keep high levels of adherence, we conservatively adjusted for a 10% non-adherence rate in our sample size calculation. A sample size of 182 participants, 91 in each arm, has 90% power to sufficiently detect a clinically important difference of 0.14 m/s between groups in improving walking function assuming a standard deviation of 0.28 m/s using a two-tailed t-test Type 1 error rate of a = 0.09.

## 7.4 **Random Assignment / Study Arm Assignment**

Permuted-block randomization will be used to centrally organize and block participants at the individual center level. For each site, we will use random blocks of size 2 and 4 to avoid potential imbalance in the number of participants assigned to each treatment group. The rationale for combination of random block size is to reduce any selection bias and increase the likelihood of recruiting exactly 26 participants at each site. Randomization will only be performed after a participant meets all the eligible criteria for inclusion in this study and consents to participating in the study. Treatment assignments will be implemented randomly through a password-protected program operated by each site's data analyst, who is not involved with subsequent data collection or analysis process. A random number between 0 and 1 will be generated for each participant and ranked within each block. Participants with even ranked numbers will be assigned to treatment group and the rest will be in control group. Data analysts involved in treatment assignment are not allowed to share any information with physical therapists or participants. Thus, all participants and physical therapists will be blinded. Datasets involving treatment assignment will be collected and stored at the University of Washington with randomization codes masked until all case report are analyzed to make sure the participants, physical therapists, DSMB, and the biostatistician remain blinded during the entire trial.

## 7.5 **Blinding**

Every effort will be made to maintain blinding of the participants and testing clinicians during the entire trial. A password-protected program will be generated and operated by a data analyst at each site to randomly assign treatment for each participant. These data analysts will compile data throughout the study and share it with the University of Washington. They will not be involved in any clinical sessions or statistical analysis. Participants will determine their appropriate level of spinal cord stimulation, either sham or tSCS, with a physician, at the beginning of the study. To avoid additional variability, the level of stimulation will remain constant throughout the entire study and all groups will use the same manufactured device. The stimulation device will be pre-programmed to

deliver either the sham stimulation or tSCS, so physical therapists will not be able to see what each participant receives. Since both the sham spinal cord stimulation and tSCS will not elicit pain even when used at energies required to non-invasively reach the spinal networks, it is very unlikely that participants will be able to differentiate the feeling between the intervention and control. Evaluation of the outcome measures will be done by the physical therapists who are blinded. After data is collected, all datasets will be saved with a randomization code masked to ensure that the research team remains unaware of participant assignment, only the physician and data analyst at each site will know. Additionally, only the DSMB and an independent biostatistician will have access to the full datasets and analysis results to conduct necessary interim analysis using all data. Therefore, the physical therapists who administer the treatment and perform the outcome measures throughout the study and the participants are all blinded to treatment received. The participant and physical therapists will be given a case report form that will ask whether each participant had/did not have tSCS. Using Fisher's exact test, we will formally compare treatment guesses between arms after randomization when the study results are reported to ensure blindness.

## 7.6 **Data Analysis**

### 7.6.1 **Primary Analyses**

Our primary analysis will evaluate clinical difference between transcutaneous spinal cord stimulation (tSCS) combined with physical therapy and physical therapy only on the primary outcome: 6MWT. A two-sample t-test will be used to evaluate the averaged change in speed between baseline and week 8 of the intervention. The null hypothesis is that the change in speed has no difference between experimental group and control group. Since the number of participants in both arms are sufficiently large (>20), the test statistics is assumed to have a standard normal distribution. We also assume that the standard deviation is equal across groups consistent with our estimation in sample size calculation.

Our primary analysis will evaluate clinical difference between transcutaneous spinal cord stimulation (tSCS) combined with physical therapy and physical therapy only on the primary outcome: 6MWT. A two-sample t-test will be used to evaluate the averaged change in speed between baseline and week 8 of the intervention. The null hypothesis is that the change in speed has no difference between experimental group and control group. Since the number of participants in both arms are sufficiently large (>20), the test statistics is assumed to have a standard normal distribution. We also assume that the standard deviation is equal across groups consistent with our estimation in sample size calculation.

From the two-sample t-test, we will report on difference in mean change of speed between tSCS combined with physical therapy group and the physical therapy only group. 95% confidence intervals and p-values will also be provided for further statistical assessment. We will compare the difference in mean change of speed with pre-defined MCID to assess the clinical meaningful improvement between the experimental and control groups. We will not adjust the effect of clinical site in our primary outcome analysis considering that the therapy guidelines and study training ideally decrease potential meaningfully difference distributions of prognostic factors between sites.

Interim analysis will be performed on the primary endpoint 6MWT when 25%, 50% and 75% of participants have been randomized and completed the 8-week treatment. The interim analysis will be conducted by an independent biostatistician, blinded of the treatment allocation. The biostatistician will report to the DSMB, who have unblinded access to all data. The Obrien-Fleming method will be used in every interim timepoint to ensure a conservative evaluation of interim results. These interim analyses will not impact participant recruitment or the treatment procedure unless the DSMB advises otherwise. The results along with non-statistical judgment will be part of a terminating guideline that helps inform whether the trial should be continued, modified, or halted early due to potential benefit, harm, or futility. The DSMB will review all results and make suggestions about the continuation of the trial. After receiving feedback from DSMB, the principle investigator will decide whether the trial is to be continues.

Missing data will be analyzed to examine for randomness of omission. Descriptive analyses of missingness will be used to consider the potential magnitude and direction of bias. If the research team determines that missing data are missing at random, sensitivity analysis will be conducted to explore the sensitivity and robustness of the assumptions about the missing data mechanisms. Data from participants with incomplete data from non-adherence will be included in the final analysis unless the participant requested removal of their record. Predictive mean matching will be used for imputation and incomplete data will be pooled per session.

### 7.6.2 **Secondary Analyses**

Our secondary analysis will evaluate clinical difference between transcutaneous electrical spinal stimulation combined with physical therapy and physical therapy only based on secondary outcomes of 10-meter walk test (10MWT), timed up and go test (TUG), and the Spinal Cord Injury Quality of Life (SCI-QOL) questionnaire. We will further examine if any of the improvements in function are sustained at 6-months follow-up periods using the 6MWT.

We will not adjust the effect of clinical site in our secondary outcome analysis considering that the therapy guidelines and pre-organized training ideally decrease potential meaningfully difference caused by prognostic factors between sites. Missing data will be analyzed to examine for randomness of omission. Descriptive analyses of missingness are provided to consider the potential magnitude and direction of bias. If the research team determines that data are missing at random, sensitivity analysis will be conducted to explore the sensitivity and robustness of the assumptions about the missing data mechanisms. Data from participants with incomplete data due to non-adherence will be included in the final analysis unless the participant requests removal of their record and withdrawal consent. Predictive mean matching will be used for imputation and incomplete data will be pooled per session.

#### *7.6.2.1 Timed Up and Go*

Participants' functional mobility will be evaluated by the Timed Up and Go test (TUG). Total time of conducting a series of activities including getting up from a chair, walking around a cone at a set distance, and sitting back down will be collected during the baseline, intervention, and follow-up periods. A two-sample t-test will be used to compare the difference in performance at baseline to week 8 of the intervention in both arms.

Normality as well as homoscedasticity are assumed in advance. From the two sample t-test, we will report difference in mean change of testing time between the experimental and control groups. 95% confidence intervals and p-value will also be provided for further statistical assessment

*7.6.2.2 10-Meter Walk Test*

Participants' functional walking speed will also be assessed by the 10-meter walk test (10MWT) in our exploratory analysis. The 10MWT is another functional test that assesses participants speed over a shorter distance. It is administered by having the participant walking down a 10-meter walkway, recording the time it takes them to walk the middle 6 meters, and then converting that to speed. Self-selected walking will be recorded during the baseline, intervention, and follow-up periods to reflect participants' walking ability over a shorter period compared to the 6MWT. We will use a two-sample t-test to evaluate the average change of speed between baseline measurements and week 8 outcomes. Normality as well as homoscedasticity are assumed in advance. From the two-sample t-test, we will report on difference in mean change of speed between the experimental and control groups. 95% confidence intervals and p-value will also be provided for further statistical assessment. Forrest et al. reported the MCID of 10MWT for individuals with incomplete spinal cord injury to be 0.15 m/s (Forrest et al., 2014). Thus, we will compare the difference in mean change of speed for 10MWT with MCID to evaluate whether there is a clinical meaningful improvement between the experimental and control groups

*7.6.2.3 Spinal Cord Injury Quality of Life Questionnaire*

All subdomains of the Spinal Cord Injury Quality of Life questionnaire (SCI-QOL) will be collected from each participant at baseline, intervention, and follow-up period to evaluate participants ability in everyday life. Categorical variables will be described by frequencies, proportions, and number of missing values. A two-sample t-test will be conducted to compare the performance at week 8 with baseline outcomes in both arms. Outcomes between baseline and the week-8 visit will be calculated based on mean score difference in the experimental and control groups. Normality as well as homoscedasticity are assumed in advance. We will report on difference in mean change of outcomes with 95% confidence intervals and p-value to further investigate any significant treatment effect.

*7.6.2.4 Long-term 6 Minute Walk Test (6MWT)*

Follow-up analysis will be conducted to further explore improvements in function or quality of life are sustained at 6-months follow-up periods. We will use repeated measures ANOVA to compare long term treatment effects from week 8 through the follow-up phase in both treatment groups by 6MWT. The alpha and power are set to be 0.05 (two tailed) and 0.90, respectively. Normality as well as homoscedasticity are assumed in advance. The data will be displayed with means and 95% confidence intervals between the experimental and control groups.

### 7.6.3 **Exploratory Analysis**

Exploratory analysis will be conducted to further investigate the long-term effects for all outcomes other than 6MWT through 6-months follow-up. Additionally, we will also

explore the variation of treatment effect for 6MWT, TUG, and 10MWT at each time point (baseline, week 4 of intervention, week 8 of intervention, and each month during the follow-up period). We will also explore the variation of treatment effect on SCI-QOL throughout the study (baseline, week 8 of intervention, and end of follow-up period). Noticing that the study is not designed to powerfully examine the effect size for any of these outcomes, we will only use these outcomes to explore potential associations for further study rather than providing any evidence.

# 8 HUMAN SUBJECTS CONSIDERATIONS

## 8.1 Ethical Review

The study will be conducted under current Food and Drug Administration (FDA) guidelines as specified by the U.S. Code of Federal Regulations 812 for Investigative Device Exemption to maintain safeguards on quality, safety and efficacy, and regulatory obligations to protect all the participants using the device. The ethical principles in accordance with the declaration of Helsinki and local laws and regulations will also be followed rigorously in this study. Each site's Institutional Review Board (IRB) will review all study documents (protocol, participant recruitment procedure, written informed consent, progress reports, safety monitoring reports, case report forms, any supplementary files or revisions, etc.). All research will be conducted in the sites where IRB are approved to review a proposed and on-going clinical trial to ensure that procedures are compliant with international and local ethical standards as well as to the relevant regulatory requirements.

After initial review and approval, the site IRBs will review the protocol at least annually. The principle investigator will make safety and progress reports to the IRBs and the DSMB at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated adverse effects involving risks to human subjects or others. In addition, all open DSMB reports will be provided to the site IRBs.

## 8.2 Informed Consent

When a clinician identifies a candidate for the study, participant eligibility will be confirmed through a screening process with the research team. Once approved for the study, the individual will be offered participation in the research study. If they decide to participate, they must come to their local research site to go through the study consent form with the research team. The consent form must be signed before any participant proceeds to the next phase of the study. Each study site is responsible for developing a study informed consent form for local use, based on the sample in Section 0. This consent form describes the purpose of the study and procedures to be followed as well as costs, risks and benefits of participation, in accordance with all applicable regulations. After a thorough discussion to inform the participant and family of the rationale and objectives of the study and the risks, benefits, and alternatives to participation, written informed consent will be

obtained from the participant themselves. Participants will be provided with a copy of their informed consent form for their own records.

## 8.3 Risks

### 8.3.1 Risks Associated with Spinal Stimulation

- There is a minor risk of mild and temporary discomfort during spinal stimulation. This is mostly likely to happen during the first stimulation procedure as the appropriate location and stimulation parameters are selected. This stops when the stimulation stops, after which uncomfortable locations will be avoided.
- There is also a risk of a thermal reaction in the tissue underneath the placement of the electrodes. To date, no adverse events have been reported, and there is a cutoff switch on the stimulator to prevent stimulation levels above an appropriate limit.
- Stimulation is delivered through hydrogel electrodes that are commonly used for other applications. There is a minor risk of skin irritation at the location where the electrodes are applied.
- The skin may also have an allegoric reaction from autonomic nervous system potentiation because of the stimulation. This will be monitored closely.
- Spasticity, or the increase of muscle tone during movement, may change due to stimulation. Previous research has shown that any adverse changes in spasticity return to normal within a few weeks. These changes are considered mild to moderate and have never excessively affected day-today activities in participants.

### 8.3.2 Risks Associated with Physical Therapy Procedures

The following risks are associated with physical therapy interventions that focus on walking and gait training, both over ground and on treadmill with body weight support:

- Increased respiration or shortness of breath
- Increased heart rate
- Muscle and joint soreness
- Changes in blood pressure
- Feeling of fatigue and dizziness
- Skin irritation from hand placement of physical therapist
- Muscle strain or join sprain
- Bone injury, such as a fracture or brake
- Exercise induced allergic reaction
- Fall an injury during training or assessments

We do not expect changes in respiration or heart rate to exceed those of regular physical activity, but they will be carefully monitored. There is also the possibility that someone with a spinal cord injury is more sensitive to skin irritation from either the electrodes or the hand placement of the physical therapist during physical therapy. This risk is considered minimal and is reversible. If any of the above risks develop to a level that is not considered acceptable for regular exercise, then physical therapy and stimulation will cease immediately. A participant may be immediately transport to the nearest emergency room if they develop chest pain or high blood pressure that does not stop after

a few minutes. A physician will be consulted in a non-emergent fashion if the participant suffers from a muscle strain, joint sprain, or bone fracture during physical therapy. These risks are considered minimal. For safety and fall prevention during walking and standing, participants will receive one of the following three protections: a) wearing a gait belt with contact guard assist by two clinically trained persons (e.g. physical therapists, physical therapist students, occupational therapists, physicians), b) wearing a safety harness with close supervision by one clinically trained person or c) using bodyweight support system with close supervision by one physical therapist (e.g. body weight support systems, such as LiteGate, Kineassist, Ekso Bionics, and Andago).

### 8.3.3 Psychological, Sociological, Economical, or Legal Risks to the Participants

There are no known psychological, sociological, economical, or legal risks to the participants. Each site will have at least one social worker to help participants if any issues arise during the study.

## 8.4 Benefits

### 8.4.1 Potential Benefits to Society

If this study unveils the efficacy of spinal stimulation combined with physical therapy over the administering of physical therapy alone, then a phase 3 clinical trial will follow. If these results continue to confirm the efficacy of spinal stimulation as a method of neurorehabilitation, then this could move toward the approval of non-invasive spinal stimulation as a clinical intervention by the FDA. These steps could lead to non-invasive spinal stimulation becoming available in clinics and help many other people with spinal cord injury, or other neurological conditions, to improve their recovery and quality of life.

If this study reveals that there are no added benefits of spinal stimulation on top of physical therapy, then we have still learned the importance of rigorous physical therapy and learned about the limited capacity of non-invasive spinal stimulation. This could lead to future research focusing more on invasive spinal stimulation and deep brain stimulation to target these outcome measures.

### 8.4.2 Potential Benefits to the Individual Participant

All participants in this study will be provided 8 weeks of gait training therapy from a licensed physical therapist as a part of the study as no additional cost. The gait training will take place three days a week, approximately 2 hours a day. It will include both treadmill and over-ground components. The positive effects on functionality, that are induced through gait training will be another benefit. These benefits apply to all participants, whether in the experimental group or not and regardless of the efficacy of tSCS.

If this study unveils the efficacy of tSCS combined with physical therapy over the administering of physical therapy alone, then participants in the experimental arm may experience enhanced neurologic recovery outside of what they have experienced with traditional physical therapy. They may also experience improved sensory and voluntary motor control of the lower extremities that brings significant improvements in their quality of life and dramatically reduce the cost of healthcare for them. This neurologic recovery may lead to greater independence in their daily life as well.

## 8.5 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study with reimbursements for travel to study visits and time away from work. Participants will receive $20 for each visit, as specified in the study informed consent forms (see the informed consent in Section 0). With a total of 44 visits, each participant will receive a total compensation of $880. Additionally, provided accessible transportation free of cost will be available for participants, if needed.

## 8.6 Confidentiality

Information obtained in this study will be stored in a locked file cabinet at each study site. No access is permitted to the study files except core study staff. Participant information will appear as a coded number ID (participant ID) to maintain confidentiality on reports, collected data, and administrative forms. Participants' information located in forms, lists, logbooks, appointment books and any other listings will also be tagged with participant ID and stored separately with limited access. All identifiable information and data will be input into REDCap (REDCap,Vanderbilt University, Nashville, TN, USA). Data will be de-identified and stored in databases to use in statistical analysis. All study information will be used for research only.

Information collected during the study will not be released without the permission from that participant. De-identified data may be shared with the DSMB; the US Food and Drug Administration, hospital auditors, other government and regulatory authorities, and/or site IRBs to monitor the performance, safety, effectiveness, and conduct of the research. A Federal Certificate of Confidentiality will be sought for this study. This certificate will apply to all study sites to protect study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other proceedings.

## 8.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

## 8.8 Study Discontinuation

The study also may be discontinued at any time by the IRB at any of our participating institutions, DSMB) or if the company that makes the stimulator, NeuroRecovery Technologies, deems the device unsafe.

# 9 FACILITIES, RESOURCES, AND EQUIPMENT

## 9.1 Facilities

This is a multi-site study, including a total of seven sites. A multi-site study design is necessary to reach the required number of participants. Each site will recruit approximately 26 participants, with a total of 182 participants across all site locations. It will take each site approximately five years to recruit 26 participants. Each site was selected because they met certain criterion including the proper expertise in SCI, the needed laboratory space, connection with a research institution, and geographical location around the country.

### 9.1.1 University of Washington Medical Center

The University of Washington (UW) will serve as the primary site. The UW will have administration and data analysis responsibilities for this research study. As a large, research institution, the UW has a strong infrastructure for supporting research, data management, and dissemination. The University of Washington is a leading research institution in engineering and medicine, with resources and facilities that will enhance and support the proposed research to evaluate the efficacy of transcutaneous spinal cord stimulation in chronic SCI. The University of Washington Medical Center (UWMC) will be one of the seven sites where the research study is conducted. The UWMC is a part of the Northwest Regional Spinal Cord Injury System (NWRSCIS), which is a regional center of spinal cord injury care, research, and education. The Human Subjects Division at the University of Washington is the service compliance unit within the Office of Research and manages the four Institutional Review Board (IRBs) that review and oversee UW human subjects research. It is located in Seattle, WA, USA.

### 9.1.2 Shirley-Ryan AbilityLab

Shirley-Ryan AbilityLab is a collaborating organization in this proposal. Study participants will be recruited from the Spinal Cord Innovation Center at the Shirley-Ryan AbilityLab. The Shirley-Ryan AbilityLab is a nationally ranked physical medicine and rehabilitation research hospital affiliated with Northwestern University. Their Spinal Cord Innovation Center is the leading center for care for people with SCI. For the last 29 years they have been listed as the U.S. News Best Hospital in Rehabilitation. Northwestern University serves as the IRB location for Shirley-Ryan AbilityLab. It is located in Chicago, IL, USA

### 9.1.3 Spaulding Rehabilitation Hospital

The Spinal Cord Injury Rehabilitation at Spaulding Boston (SRH) is led by SCI experts at Spaulding Boston. The hub of their SCI program is the Spaulding New England Regional Spinal Cord Injury Center (SNERSCIC) which is led by SCI experts at Spaulding Boston. Partners Healthcare, which SRH is a part of, has a Partners Human Research Committee that is the Institutional Review Board (IRB) of Partners HealthCare. It is located in Boston, MA, USA.

### 9.1.4 **Kessler Institute for Rehabilitation**

The spinal cord injury rehabilitation center at Kessler Institute for Rehabilitation (Kessler) has a team of spinal cord injury rehabilitation specialists with great expertise and experience. Each year Kessler treats more than 600 individuals with spinal cord injuries. The Kessler Foundation IRB committee provides an independent review of all research studies at the Kessler Institute for Rehabilitation. It is located in West Orange, NJ, USA.

### 9.1.5 **Mayo Clinic**

Mayo Clinic has a SCI rehabilitation center in which multiple departments work together to promote recovery of people with SCI. Specialists including neurologists, physical medicine and rehabilitation physicians, pulmonary physicians and physical therapists collaborate to improve the life of people with SCI. The IRB at Mayo Clinic reviews all studies involving human subjects for compliance with both Mayo Clinic institutional policies and with state, local, and federal laws. It is located in Rochester, MN, USA.

### 9.1.6 **TIRR Memorial Hermann**

TIRR Memorial Hermann is one of the best rehabilitation hospitals in Texas and among the best in the nation, offering both inpatient and outpatient rehabilitation for various neurological injuries including spinal cord injuries. The Spinal Cord Injury Treatment Center includes a team made up of spinal cord injury specialists, therapist, nurses, case managers, and social workers that are dedicated to expert care of people with SCI. TIRR is a leader in both rehabilitation and research. Committee for the Protection of Human Subjects (CPHS) through the University of Texas Health Science Center at Houston serves as the IRB location for TIRR Memorial Hermann. It is located in Houston, TX, USA.

### 9.1.7 **Craig Hospital**

Craig Hospital is a world-renowned rehabilitation hospital that exclusively specializes in the neurorehabilitation and research of individuals with spinal cord injury and brain injury. It has been named top 10 Rehab Center consecutively since 1990. The Craig Hospital Research Department manages the IRB that review all research studies at Craig Hospital. It is located in Denver, CO, USA.

## 9.2 **Resources**

- Matlab License: Matlab license with required toolboxes to (MathWorks Inc., Natick, MA, USA)
- REDCap license via institute of Translational Health Sciences (ITHS) at the University of Washington (REDCap – Vanderbilt University, Nashville, TN, USA)
- 6MWT procedure (see Section 15)
- 10MWT procedure (see Section 16)
- TUG procedure (see Section 17)
- SCI-QOL

## 9.3 Equipment

### 9.3.1 Spinal Cord Stimulation Equipment

- External Spinal Cord Neuromodulator: See Section 4.1 for further description of the transcutaneous spinal stimulator used in this study. The stimulator to be used in this study is the alpha prototype of the 'External Spinal Cord Neuromodulator – Coulomb-3M & Multichannel 9CES' (NeuroRecovery Technologies, Inc., San Juan Capistrano, CA, USA). 28 devices will be purchased directly from the manufacturer and distributed to each site included in the study.
- 2.5 cm round electrodes: approximately 17,500 electrodes are needed (4 electrodes × 24 visits ×182 participants) (Lead-Lok, Sandpoint, USA).
- 3cm x 4 cm rectangular electrodes: approximately 2100 electrodes are needed (2 electrodes × 8 weeks × 182 participants).

### 9.3.2 6-minute walk test equipment

- Stopwatch: No specific brand of stopwatch is preferred. Every site should make sure the stopwatch is available and functioning before a session begins.
- Chair: at least one chair should be placed at the end of the walking course so that the participant could take rest as wanted.
- Cones or premeasured marks along the track or corridor.
- Measuring instrument (meters)
- At least a 12-meter-long hallway or open area with a smooth, consistent surface where the participant will not be interrupted
- Clipboard with pen and reporting sheet.

### 9.3.3 10 Meter walk test equipment

- Stopwatch: the same stopwatch used in the 6-minute walk test can be used for the 10-meter walk test.
- Tape markings or cones should be placed 10 meters apart on a clear pathway with a smooth, consistent surface.
- Chair: at least one chair should be placed at the end of the walking course so that the participant could take rest as wanted. Multiple chairs on the sideway is recommended
- Tape to mark the 2 meter and 8-meter location.
- Clipboard with pen and reporting sheet.

### 9.3.4 Timed up and go test equipment

- Stopwatch: the same stopwatch used in the 6-minute walk and 10-meter test can be used for the timed up and go test.
- Standard armchair: a standard armchair will be used to allow the participant to remaining in a sitting position before the test starts. The height of the chair should not be adjusted between each test, and it should be approximately 46 cm in height.
- Tape or a cone to mark the 3-meter distance from the armchair.

- Clipboard with pen and reporting sheet.

### 9.3.5 **Physical Therapy Equipment**

- Harness: a harness of any brand should be prepared at each visiting site to provide full protection for the participants from falling or other types of injury.
- A ceiling track attached to the harness should be used to provide full protection against falling.
- Gait belt: a gait belt should also be prepared as an alternative to a harness for use in areas where a harness is not possible.
- Parallel bars should be available so that the participant can have support to grab on.
- Body weight support machine such as the as LiteGate (LiteGate, Tempe AZ, USA), Kineassist (Exoskeleton, San Jose, CA, USA), EksoEN (Ekso Bionics, Richmond, CA, USA), Andago (Hocoma, Volketswil, ZH , Switzerland), and SpinoFLEX ® (Advanced Fitness Components, Hudson, NH, USA).
- Treadmill: No specific model of treadmill is required. Each site will use the current treadmill that that specific site currently uses for rehabilitation. The only requirements are that the treadmill includes an emergency stop function, retractable handrails, and variable speeds within .1 m/s.

# 10 ADMINISTRATIVE PROCEDURES

## 10.1 **Protocol Approval**

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB). Upon receiving final approval, sites will submit all required protocol registration documents to the PI who will review the submitted protocol registration packet to ensure that all the required documents have been received.

Clinical trial registration at clinicaltrials.gov will begin after the approval of this study by all appropriate regulatory entities, including institutional IRBs. The University of Washington will be the main IRB site, all other sites will request permission for an external IRB review. Any changes to the protocol, however, will require the notification of all participating IRB agencies. There will be site-specific consent forms. An example of the consent form for the University of Washington can be found in Section 0. The only changes made between sites will be the contact information, research study location, and research team. Upon receiving initial IRB approval from the University of Washington and external IRB approval from other sites, all versions of the consent form must be approved.

Upon receiving final IRB approval for an amendment, sites should implement the amendment immediately. Any modifications and approval of those modifications will be shared with the DSMB and updated on clinicaltrials.gov.

## 10.2 Study Activation

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local IRB. Pending successful protocol registration and submission of all required documents, research study staff will "activate" the site to begin study operations on clinicaltrials.gov. Study implementation may not be initiated until a study activation notice is provided to the site.

## 10.3 Study Coordination

Each site will be assigned a research coordinator. The research coordinator will be responsible for maintaining appropriate correspondence with the NINDS, FDA, DSMB, and research coordinators at other participating research sites. They will also be responsible for maintaining and tracking all conversations with NeuroRecovery Technologies, Inc to ensure proper communication between all participating institutions and the device company.

Study implementation will be directed by this protocol. The DSMB will be notified of all appropriate updates on management and reporting; dispensing study products and documenting product accountability; and other study operations.

Study case report forms and other study instruments will be developed by the protocol team. Data will be pre-processed by the data analyst(s) at each site for cleaning and organization. The data analyst(s) at the University of Washington will be responsible for compiling all data and working with the independent biostatistician to generate the interim and final analyses for the overall study. The study coordinator at each site will be responsible for the secure sharing of de-identified data between their site and the University of Washington. As needed, quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Study coordinators at each site will be responsible for the inter-site coordination. Rates of accrual, adherence, follow-up, and unanticipated adverse device effect incidence will be monitored closely by the team as well as the DSMB. The principle investigator and independent biostatistician will address issues related to study eligibility and adverse effect management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

## 10.4 Primary Site Personnel

Primary site personnel will only be at the University of Washington or contracted as part of the study, they will not be at each individual site. This includes:

### 10.4.1 Principle Investigator

- 1 across all sites

- Will be responsible for the execution or the research at all sites, notifying the DSMB of issues and updates, as well as coordinating training session

#### 10.4.2 **Independent Biostatistician**

- 1 across all sites
- Will run interim and finally analyses of all study data

#### 10.4.3 **PhD or Postdoc**

- 1 across all sites
- Will assist with correspondence to the independent biostatistician and writing of the publication under the direction of the PI

#### 10.4.4 **Data Safety Monitoring Board**

- 1 across all sites; ~5 professionals in the field of spinal cord stimulation and/or SCI
- Will set up a meeting schedule at the beginning of the study to regularly meet about the progress of the study and safety updates
- Will be notified via the PI of any unanticipated adverse events to determine if the study needs to be discontinued
- We meet to discuss the interim and final analyzes of the clinical trial

### 10.5 **Site-Specific Study Personnel**

Study personnel will include several researchers at each institution. There will be a research coordinator at each site that will be responsible for maintaining the appropriate guidelines and regulations set by the NINDS and the FDA as outlined in this proposal. Each site will also have:

#### 10.5.1 **Physical Therapists**

- 2-3 at each site
- Trained on the appropriate protocol for this study and how to administer spinal cord stimulation
- Deliver 2-3 physical therapy sessions each week
- Administer all data assessments

#### 10.5.2 **Physician Specializing in SCI**

- 1-2 at each site
- Will determine parameters of spinal cord stimulation for each participant once they have completed the baseline phase of the study
- May serve as an on-site consultant during the study if any unanticipated adverse effects occur

#### 10.5.3 **Data Analyst**

- 1-2 at each site
- Responsible for maintaining the appropriate record of the data at each site

- Must continually update the study coordinator of data collection progress for interim and final analyses

#### 10.5.4 **Social Workers**

- 1-2 at each site
- Will work with the study coordinator to schedule the participants appointments
- Help each participant to maintain the support they need to remain in the study, such as finding a ride to physical therapy appointments each week
- General focus on meeting the needs for the research participants to maintain study adherence

#### 10.5.5 **Research Coordinator**

- 1 at each site
- Will maintain correspondence with the DSMD, FDA, NINDS, and NeuroRecovery Technologies, Inc as needed
- Will maintain records of what treatment group a participant is in and assign people to treatment groups.
- Will be responsible to appropriately sharing data with other institutions and the DSMB during interim and final analyses

### 10.6 **Protocol Training**

One physical therapist and the research coordinator from each study site location will be selected to attend a protocol training session to be held in Seattle, WA at the University of Washington to ensure the methods are uniform across site locations. During this training session, materials detailing the protocol of the study, such as the study-specific procedures manual, will be distributed. This will go into detailed on the procedures described in Section 4.2 and review the information to be recorded in each session in the case report form (CRF) and on the Research Electronic Data Capture (REDCap) software. A sample case report form can be found in Section 18. After the multi-site training, site-specific representatives will lead the same training at their respective site to train the local physical therapists and researchers that will be working with the participants in each session.

### 10.7 **Study Monitoring**

On-site study monitoring will be performed in accordance with FDA policies for IDE studies. Study monitors will visit the site to

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of NeuroRecovery Technologies, Inc., the NINDS, the NIH, the FDA, and any other US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

### 10.8 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the principle investigator. All protocol amendments must be submitted to and approved by the relevant IRB(s) prior to implementing the amendment.

### 10.9 Investigator's Records

The investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. All study records will be maintained in accordance with Federal regulations stated in CFR 812.140(a) for the investigator of IDE studies. All records mentioned here will be maintained for three years after the conclusion of the study. However, if there is a plan to file more market approval of the device through the FDA, then the materials must be maintained for 3 years following the date of market approval or the data at which the study coordinators are notified that it is not approved. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

### 10.10 Use of Information and Publications

Deidentified data from this trial will be used to publish papers in peer-reviewed journals. This data may also be used for abstracts and poster presentations in conferences. No identifiable information will be included in any publications and all participants will consent to the use of their data in the informed consent form prior to study participation. Publication may occur at any time during the study, although, it will most likely occur after study completion. Several publications may result from this trial. Beyond the selected clinical trial data that are disclosed in journal publications, identifiable participant data will not be shared with the broader scientific community or the public.

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# 12 APPENDICES

# 13 I SCHEDULE OF STUDY VISITS AND PROCEDURES

| Visit | Procedures |
|---|---|
| **Pre-screening/ Screening** | • Signing of informed consent form<br>• An exam by the research physical therapist<br>• Questions about past medical history and current medications<br>• Demonstration of the participant's current gait function |
| **Baseline**<br><br>Visit 1-8/<br>Week 1-4 | • An exam by the research physical therapist<br>• Measurements of heart rate, blood pressure, temperature, respiratory rate.<br>• Outcome measure of 10 meters walk test, Timed Up and Go, 6-minute walk test<br>• Quality of life questionnaire during final baseline visit (week 4) |
| **Intervention**<br><br>Visit 9-20/<br>Week 4-8 | • May include an exam by the research physical therapist<br>• Measurement of heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy including 10 minutes of moderate stretching and approximately 90 minutes of gait training with spinal cord stimulation |
| **First Assessment**<br><br>Visit 20/<br>Week 8 | • An exam by the research physical therapist<br>• Measurement of heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy including moderate stretching and gait training with spinal cord stimulation<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test |
| **Intervention**<br><br>Visit 21-32/<br>Week 8-12 | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy and gait training with spinal cord stimulation |
| **Second Assessment**<br><br>Visit 31-32/ | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation |

| | |
|---|---|
| Week 12 | • Physical therapy including moderate stretching and gait training with spinal cord stimulation<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test<br>• Quality of life questionnaire |
| **Follow-up**<br><br>Visit 33-44/ 2 visits each month for 6 months | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test<br>• Quality of life questionnaire during final visit of follow-up period |

# 14 II SAMPLE INFORMED CONSENT FORM

**UNIVERSITY OF WASHINGTON**

**CONSENT FORM**

***Study Title*: Transcutaneous Spinal Cord Stimulation for Chronic Spinal Cord Injury Recovery: A Multicenter Randomized Controlled Trial**

**A Randomized, Phase 2b, Blinded, Multi-site control trial**

**Principal Investigator: Charlotte Caskey**

**The Research Team:**

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Clinical Research Center: (864) 207-1155

If you have questions about your rights as a research study participant, you can call the Institution Review Board at (206) 543-2673

**24-hour Emergency Contact Number(s):** (203) 788-2962

- This form explains what will happen if you join this research study.
- Please read it carefully. Take as much time as you need.
- Please ask the research team questions about anything that is not clear.
- You can ask questions about the study at any time.
- If you choose not to be in the study, it will not affect your care at this institute.
- If you said 'Yes', you are still allowed to change your mind later.
- You can quit the study at any time.

- You would not lose benefits or be penalized if you decide not to take part in the study or to quit the study later.

We are asking you to be in a research study. This form gives you information to help you decide whether to be participate the study. Being in the study is voluntary. Please read this carefully. You may ask any questions about the study. Then you can decide whether you want to participate in the study.

The goals of this form are to give you information about what will happen if you choose to participate and help you decide if you want to be in the study.

This is your form and you are free to take notes, ask questions, or highlight any part of this form.

## KEY INFORMATION ABOUT THIS STUDY

This research study will examine the effects of non-invasive spinal cord stimulation on walking function, mobility, and quality of life. We are inviting you to participate in this study because your physician believes that you are eligible for spinal cord stimulation. This page is to give you key information to help you decide whether to participate in the research study. As you read this document, please ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is provided at the top of this document.

### SECTION 1: WHAT YOU SHOULD KNOW ABOUT THIS STUDY:

This is a clinical trial research study that aims to evaluate the effects of spinal cord stimulation, along with walking therapy, to improve walking function of people with chronic spinal cord injury. The main treatment being evaluated in this study is transcutaneous spinal cord stimulation. We are aiming to have approximately 182 people with spinal cord injury participate in this study. If you agree to participate, you will be included in one of the two groups: Group A that receives spinal cord stimulation or Group B that receives the sham (placebo) stimulation. In either case, you will be required to come to the rehabilitation clinic for walking therapy 3 days a week for 8 weeks. However, you will not know if you are in Group A or Group B. You will receive walking training on a body weight supported treadmill and over the ground. Walking training will include various mobility exercises. These have shown to improve walking function in people with spinal cord injury. The spinal stimulator used in this study is an investigational device and not approved by the Food & Drug Administration (FDA) for use in clinics and hospitals. However, the FDA has approved its use for research purposes in people with chronic spinal cord injury.

### SECTION 2: WHAT IS THE GOAL OF THIS STUDY?

The goal of this research is to examine the effects of the non-invasive, transcutaneous spinal cord stimulation along with gait therapy on gait function in people with chronic spinal cord injury. By doing this trial, we hope to learn whether spinal cord stimulation, along with physical therapy for walking, is effective in improving walking function in people with chronic spinal cord injury.

**SECTION 3: HOW IS THE STUDY DESIGNED?**

If you decide to participate in this study, we will assign you to a spinal cord stimulation or placebo for 2 months. In either case, you will have sticker electrodes placed on the skin over your spine. These will connect to a device that controls the spinal cord stimulation. The placebo is a treatment with low stimulating intensity that will have minimal to no influence on your function. Both treatments will feel the same. We use placebos in studies like this so that we can learn whether the device we are testing has an effect. You will not know whether you are being treat with non-invasive spinal cord stimulation or placebo stimulation. You will be randomly chosen by a computer and assigned to the spinal cord stimulation or placebo groups. You will have an equal chance of receiving one or the other. Your study physical therapist and the UW research team are blinded, so they will not know whether you are on non-invasive spinal cord stimulation or placebo stimulation. The physician on your site's study team will know what you are receiving.

**SECTION 4: WHY MIGHT YOU <u>NOT</u> WANT TO BE IN THIS STUDY?**

If you are in this study, you may receive a non-invasive spinal cord stimulation or sham spinal cord stimulation. You or your physical therapist will not have the opportunity to choose which stimulation you will receive. The spinal cord stimulator used in this study is an investigational device and does not have FDA approval for clinical applications. During the study, the computer will pick which stimulation you will receive instead of a physical therapist or researcher choosing it. You might not want to participate in this study if you already prefer receiving or not receiving one of the two stimulations included in this study. Section 10 in this form provides a list of possible risks for each treatment. After reading section 10, if you feel like this study will do more harm than better, you are free to not participate in the study. You do not have to participate in the study to receive your regular rehabilitation or medicines. If you decide not to be in the study, your doctor will choose a treatment he/she thinks is best for you.

Standard of care treatments for spinal cord injury include the following:

1. Neuromuscular electrical stimulation (NMES) to the muscle on the arms and legs
2. Implanted spinal cord stimulation
3. Physical therapy or strength training
4. Occupational therapy
5. Pharmaceutical management

**SECTION 5: WHY MIGHT YOU WANT TO BE IN THIS STUDY?**

Participating in this study will help us know if non-invasive spinal cord stimulation should be offered as a treatment for people with spinal cord injury. No matter which type of stimulation you are receiving (treatment or placebo), both treatments groups will receive gait training physical therapy that has shown to improve gait function in the past in people with spinal cord injury. Someone at your site will know which treatment you are taking in case there is a reason for your personal physician or doctor needs to know. The research team will monitor your rehabilitation process closely. If your recovery does not improve or you cannot tolerate the evaluation process, you are free to leave from the study at any time. Your physician can assign you to another treatment

plan as required. Your contribution to this study will help us understand how non-invasive spinal cord stimulation will help individuals with spinal cord injury to recover better in the future.

**SECTION 6: DO YOU HAVE TO TAKE PART IN THE STUDY?**

Taking part in the study is in not mandatory. It is your choice. If you decide to take part in the study, it should be because you want to volunteer. If you decide not to take part, you will not lose any services, benefits, or rights you would normally have. You will still receive treatment for your spinal cord injury as usual. You can choose to withdraw at any time during the study.

**SECTION 7: HOW MANY PARTICIPANTS ARE INVOLVED IN THIS STUDY?**

26 people will take part in this research study at University of Washington Medical Center. Approximately 182 people will take part at hospitals or rehabilitation labs around United States.

**SECTION 8: WHAT WOULD YOU NEED TO DO IF YOU AGREE TO JOIN THIS STUDY?**

If you join the study, you will be required to come to the rehabilitation clinic at UW Medical Center for assessments and therapy. Assessments will include walking tests and filling out different paper questionnaires. All the visits that you would need to make are listed in the table below.

The assessments will help the research team to assess if spinal cord stimulation causes any effects that are important to know about. We will use information from the pre-screening assessments to check if your condition is stable enough to participate in the study. We will also use your data to learn if this experimental treatment is helping or not. You must know that your data will be deidentified and utilized for research purposes.

Overview of Study Timeline:

| Visit | Procedures | Location | Time duration |
|---|---|---|---|
| **Pre-screening/ Screening** | • An exam by the research physical therapist<br>• Questions about your past medical history and current medications<br>• You may be asked to demonstrate your current gait function<br>• Signing for informed consent form | University of Washington Medical Center | 2 hours |
| **Baseline**<br><br>Visit 1-8/ Week 1-4 | • An exam by the research physical therapist<br>• Measurements of your heart rate, blood pressure, temperature, respiratory rate.<br>• Outcome measure of 10 meters walk test, Timed Up and Go, 6-minute walk test | University of Washington Medical Center | 2 hours |

| | | | |
|---|---|---|---|
| | • A paper questionnaire (This will be completed during the last visit before the intervention starts) | | |
| **Intervention**<br><br>Visit 9-20/<br>Week 4-8 | • May include an exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy including 10 minutes of moderate stretching and approximately 90 minutes of gait training with spinal cord stimulation | University of Washington Medical Center | 2 hours |
| **First Assessment**<br><br>Visit 20/<br>Week 8 | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy including moderate stretching and gait training with spinal cord stimulation<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test | University of Washington Medical Center | 2 hours |
| **Intervention**<br><br>Visit 21-32/<br>Week 8-12 | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy and gait training with spinal cord stimulation | University of Washington Medical Center | 2 hours |
| **Second Assessment**<br><br>Visit 31-32/<br>Week 12 | • An exam by the research physical therapist<br>• Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Spinal cord stimulation<br>• Physical therapy including moderate stretching and gait training with spinal cord stimulation<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test<br>• A paper questionnaire | University of Washington Medical Center | 2 hours |
| **Follow-up** | • An exam by the research physical therapist | University of Washington | 2 hours |

| | | | |
|---|---|---|---|
| Visit 33-44/ 1 visits each month for 6 months | • Measurement of your heart rate, blood pressure, temperature, respiratory rate.<br>• Outcome measure of 10 meters walk test, Timed Up and Go, and 6-minute walk test<br>• A paper questionnaire (This will only be completed during the final visit) | Medical Center | |

Time schedule for each physical therapy:
A licensed physical therapist will hold each training session. One other member of the research team may or may not be present. Physical therapy training will include the following:

- Mild to moderate stretching exercises to warm up lower extremity muscles (10 minutes)
- Gait training on the treadmill using body weight system as needed (45 minutes)
- Walking over ground with or without mobility devices (45 minutes)

You will get as many rest breaks as you like. During the breaks you will be allowed to sit down, drink water or have a small snack. You can request rest breaks whenever you feel tired. The physical therapist may request that you take rest breaks if they feel it is necessary for your safety.

**SECTION 9: HOW LONG WOULD I BE IN THE STUDY?**
If you choose to take part in all the study visits, you would be in the study for 9 months.
If you decide to participate, please know that you can decide to stop at any time for any reason.

**SECTION 10: WOULD YOU BE ABLE TO WITHDRAW FROM THE STUDY?**
You can withdraw any time from the study. The research team can also decide to no longer give you the intervention. This might happen if we find that it is not safe for you to stay in the study or if the study procedures are doing more harm than benefitting you.
If you experience any adverse effects during the intervention. Some potential risks that of being in the study are listed below in SECTION 11.

**SECTION 11: WHAT ARE THE POTENTIAL HARMS OR RISKS IF I JOIN THIS STUDY?**
Potential harm or risks associated with spinal cord stimulation. Some are common and some are rare which are described below.

- There is a minor risk of mild and temporary discomfort during spinal cord stimulation. You may feel tingling like sensation when the stimulation is on. This is most likely to happen during the first spinal cord stimulation treatment when selecting the appropriate location and stimulation parameters. The discomfort will stop when the stimulation stops, after which those locations will be avoided.
- There is also a risk of a thermal reaction to the tissue underneath the placement of the electrodes. However, to date, no adverse events have been reported, and there is a cutoff switch on the stimulator to prevent stimulation levels above an appropriate limit.
- There is a minor risk of skin irritation at the location where the electrodes are applied.

- The skin may also have an allegoric reaction from autonomic nervous system potentiation because of the stimulation.
- Adverse changes in muscle sensitivity. This may return to normal within a few weeks.

These changes are considered mild to moderate and have never excessively affected day to day activities in participants in the prior studies with this non-invasive spinal cord stimulation.

Potential harm or risks associated with physical therapy procedures

Following risks are associated with physical therapy interventions that focus on walking and gait training, both over ground and on treadmill with body weight support:

- Increased respiration or shortness of breath
- Increased heart rate
- Muscle and joint soreness after training
- Changes in blood pressure
- Feeling of fatigue and dizziness
- Skin irritation from hand placement of physical therapist
- Muscle strain or join sprain from exercise
- Bone injury, such as a fracture or brake, from weight-bearing exercises
- Exercise induced allergic reaction
- Fall an injury during training or assessments

Because this research study involves experimental electrical stimulation, we do not know all the possible harms or risks.

A Data Safety Monitoring Board will review the information from this research study throughout the study. This board is made of a group of experts who are responsible for looking at how people in the research study are doing. If you take part in this study, we will keep you updated of any new information we learn that might affect your health or your willingness to stay in the study.

## SECTION 12 WHAT ARE THE POTENTIAL BENEFITS IF YOU JOIN THIS STUDY

Potential Benefits for you:

- You may experience improved walking function from the physical therapy.
- You may experience enhanced neurologic recovery outside of what they have experienced with traditional physical therapy.
- You may also experience improved sensory and voluntary motor control of the lower extremities. This may bring significant improvements in your quality of life and dramatically reduce the cost of healthcare. This neurologic recovery may lead to greater independence in your daily life as well.
- Even if there are no benefits from non-invasive spinal cord stimulation or you were assigned to the placebo treatment, you will still receive the standard of care, physical therapy, at top institutions around the country for 2 months, free of financial charge.

Potential Benefits for others:

- This study can help us to understand the difference in treatment, if any, of physical therapy alone and physical therapy combined with non-invasive spinal cord stimulation.
- If these results continue to confirm the efficacy of spinal cord stimulation as a method of neurorehabilitation, then this could move toward the approval of non-invasive spinal cord stimulation as a clinical intervention by the Food & Drug Administration (FDA).

These steps could lead non-invasive spinal cord stimulation to become available in clinics and help many other people with spinal cord injury, or other neurological conditions, to improve their recovery and quality of life all over the world.

If this study reveals that there are no added benefits of non-invasive spinal cord stimulation on top of physical therapy, we have learned the importance of rigorous physical therapy and learned about the limited capacity of non-invasive spinal cord stimulation. This could lead to future research focusing more on invasive spinal cord stimulation or other types of treatment.

**SECTION 13: HOW WOULD WE KEEP YOUR INFORMATION CONFIDENTIAL?**

**If you take part in this study, we will make every effort to keep your information confidential.** We will store your research records in locked cabinets and secure computer files. We will not put your name on any research data. Instead, you will appear as a participant identification number in our study. The master list that links a person's name to their study number is stored in a locked cabinet and on a secure computer file.

If results of this research are published, we would not use information that identifies you.

- We would use your information for research only. These are the reasons that we may need to share the information that you give us with others:
  1. If it is required by law
  2. If we think, you or someone else could be harmed
  3. Sponsors, government agencies, or research staff sometimes look at forms like this and other study records. They do this to make sure the research is done safely and legally. Anyone who reviews study records would keep your information confidential.
- Agencies or sponsors that may look at study records include:
  - The US Food and Drug Administration (FDA)
  - Hospital Auditors
  - Government Agencies
  - Other relative officers responsible for watching over the safety, effectiveness, and conduct of the research.

**SECTION 14: WILL IT COST OR WILL YOU GET PAID IN THIS STUDY?**

If you decide to participate in this study, there will be no cost and we will **NOT** charge you or your insurance company. In fact, you will be compensated for your time and effort. We will pay you $20 per visit to appreciate your help and be involved in this study for each site visit. You will be

paid with a check or a gift card at the end of each week. Additionally, parking vouchers will be provided for each participant as appropriate and social workers will help coordinate rides to the study site you require transportation.

**SECTION 15: WHAT IS COVERED IF YOU GOT INJURED BECAUSE OF JOINING THIS STUDY?**

If you were injured as the direct result of this research study, your study site would provide treatment for you. We would refer you for treatment if other practices are needed. You or your insurance company do **NOT** need to pay for any treatment.

**SECTION 16: WHAT WOULD YOUR SIGNATURE ON THIS FORM MEAN?**

Your signature on this form would mean:

- By signing this form, you provide an **INFORMED CONSENT** to participate in this study.
- This means that the research study was explained to you by one of our research team members.
- All your questions are answered at this time. In case you have more questions, you can always reach our research team members via email or phone. The contact details have been provided at the beginning of this document.
- You have some rights as a research participant. We will inform you if there are any new changes to this study. Especially changes that may affect your health or willingness to continue in participating in this study.
- By signing this consent form, you do not give up any of your legal rights. The researchers or sponsors are not relieved of any liability they have.

_____

Printed Name of Participant

_____

Signature of Research Participant Date (MM/DD/YY)

**SECTION 17: RESEARCHER'S SIGNATURE**

I have fully explained the research study described by this form. I have answered the participant's current questions and will answer any future questions to the best of my ability. I will communicate any changes in the procedures with the participant. I will also communicate possible harms/benefits of the study that may affect their health or willingness to stay in the study as the study progresses.

_____

Printed Name of Researcher Obtaining Permission or Consent

_____

Signature of Research Participant Obtaining Permission or Consent Date (MM/DD/YY)

# 15 III 6MWT PROCEDURE

| | |
|---|---|
| **Overview** | • The 6MWT is a sub-maximal exercise test used to assess walking endurance and aerobic capacity. Participants will walk around the perimeter of a set circuit for a total of six minutes. |
| **Scoring** | • The score of the test is the distance a participant walks in 6 minutes (measured in meters and can round to the nearest decimal point).<br>• The scoring can be converted to speed by dividing the final distance by 360 seconds. |
| **Equipment** | • Stopwatch<br>• Chair<br>• Measuring instrument (meters)<br>• At least a 12-meter long hallway or open area (e.g., quiet gym) with a smooth, consistent surface<br>• Markings to indicate turnaround (e.g.: cones)<br>• Mechanical lap counter or pencil and paper |
| **Time** | • Less than 10 minutes |
| **Logistics-Setup** | • A hallway or open area at least 12 meters long with a smooth, consistent surface<br>• There should be a clear pathway on the sides and at either end<br>• A turnaround points approximately 49 in (124 cm) wide with clear markings should be set up at both ends<br>• A chair should be placed at one end |
| **Logistics-Administration** | • Prior to administering the measure, the participant should be sitting in a chair, rested, near the starting point of the test.<br>• Instructions to the participant in sitting:<br>o *"The aim of this test is to walk as far as possible in six minutes. You will walk around the cones. Six minutes is a long time to walk, so you will be exerting yourself. You may get out of breath or become tired. You are allowed to slow down, to stop, and to rest as necessary. You may stand and rest but resume walking as soon as you are able. Are you ready to do that?"* |

# 16 IV 10MWT PROCEDURE

| | |
|---|---|
| **Overview** | • The 10MWT is used to assess walking speed in meters/second (m/s) over a short distance. |
| **Scoring** | • The total time taken to ambulate the middle 6 meters (m) of the 10 m walkway is recorded to the nearest hundredth of a second. 6 m is then divided by the total time (in seconds) taken to ambulate and recorded in m/s |
| **Equipment** | • Stopwatch<br>• A clear pathway of at least 10 m (32.8 ft) in length in a designated area over solid flooring |
| **Time** | • 5 minutes or less |
| **Logistics-Setup** | • A clear pathway of at least 10 m (32.8 ft) in length in a designated area over solid flooring is required<br>• Measure and mark the start and end point of a 10-m walkway<br>• Add a mark at 2 m and 8 m (identifying the central 6 m which will be timed)<br>• Quiet and uninterrupted area |
| **Logistics-Administration** | • Comfortable walking speed: Have the participant start on the 0-m mark (start line)<br>• Instructions to participant: *"Walk at your own comfortable walking pace and stop when you reach the far mark."*<br>• Two trials are administered at the participant's comfortable walking speed, per the below instructions. The 2 trials are averaged, and the gait speed is documented in meters/second.<br>• Participants may use any assistive device or bracing that they are currently using. The type of device and/or bracing must be documented.<br>• When administering the test, do not walk in front of or directly beside the participant, as this may "pace" the participant and influence the speed and distance they walk. Instead, walk at least a half step behind the participant. |

# 17 V TUG PROCEDURE

| | |
|---|---|
| **Overview** | • This will measure how long it takes the participant to rise from a chair, walk 3 m, return to the chair, and sit back down |
| **Scoring** | • The total time taken to stand, walk to a line that is 3 meters away, turn around, walk back to the chair, and sit down is recorded to the nearest hundredth of a second. |
| **Equipment** | • Stopwatch<br>• A clear pathway of at least 10 m (32.8 ft) in length in a designated area over solid flooring |
| **Time** | • 5 minutes or less |
| **Logistics-Setup** | • A clear pathway of at least 10 m (32.8 ft) in length in a designated area over solid flooring is required.<br>• Measure and mark a 3-meter walkway.<br>• Place a standard height (seat height ~ 46 cm, arm height 67 cm) at the beginning of the walkway.<br>• Quiet and uninterrupted area |
| **Logistics-Administration** | • Instruct the participant to sit on the chair, place his/her back against the chairback, and rest his/her arms on the chair's arms.<br>• Participants may use any assistive device or bracing that they are currently using. The type of device and/or bracing must be documented.<br>• If applicable, the upper extremities should not be on the assistive device at the start. The assistive device should be nearby to use once the participant stands-up to begin walking.<br>•Demonstrate the test to the participant, describing what you are doing.<br>• The participant should be instructed to: "*Use a comfortable and safe walking speed*".<br>• When the participant is ready, say "*Go*".<br>• The stopwatch should start when the administrator says "go" and should be stopped when the participant's buttocks return to touching the seat. |

# 18 VI SAMPLE CASE REPORT FORMS

*Initial entry visit (after consent is signed):*
**Participant ID code: 03- 002 – ABC (site number – participant number – participant initials)**
Example: John Apple Smith attending Mayo Clinic and is the 1st participant at this specific site. His Participant ID would be: [05 - 001 – JAS]

**Site numbers:**
**01 – UWMC**
**02 – Shirley-Ryan AbilityLab**
**03 – Spaulding Rehabilitation Hospital**
**04 – Kessler Institute for Rehabilitation**
**05 – Mayo Clinic**
**06 – TIRR Memorial Hermann**
**07 – Craig Hospital**

Assigned Participant ID: _____ [##-###-ABC]

Date of Visit: _____ [MM-DD-YYYY]

| | |
|---|---|
| Participant Name [Last, First] | |
| | |
| Physician present [Last, First] | |
| PT present [Last, First] | |
| Research Coordinator present [Last, First] | |
| | |
| DOB [DD-MMM-YYYY] | |
| Sex | |
| Level of Injury | |
| AISA Score | |
| Date of injury [DD-MMM-YYYY] | |
| | |
| Institution | |

*Data collection visit:*

| | |
|---|---|
| Participant ID [##-###-ABC] | |
| | |
| PT present [Last, First] | |
| Institution | |
| Date of Visit | |

**Vitals at the Beginning of the Session:**

| | |
|---|---|
| Blood pressure [mmHg] | |
| Heart rate [beats per minute] | |

**Assessments:**

| | | |
|---|---|---|
| | Distance [meters] | Speed [meters/second] |
| 6MWT | | |
| | Time [seconds] | Speed [meters/second] |
| 10MWT | | |
| | Time [seconds] | |
| TUG | | |
| | Score | |
| SCI-QOL | | |

**Vitals at the End of the Session:**

| | |
|---|---|
| Blood pressure [mmHg] | |
| Heart rate [beats per minute] | |

*Intervention visits:*

| | |
|---|---|
| Participant ID [##-###-ABC] | |
| | |
| PT present [Last, First] | |
| Institution | |
| Date of Visit | |

**Vitals at the Beginning of the Session:**

| | |
|---|---|
| Blood pressure [mmHg] | |
| Heart rate [beats per minute] | |

**Vitals at the End of the Session:**

| | |
|---|---|
| Blood pressure [mmHg] | |
| Heart rate [beats per minute] | |

# 19 VII BUDGET

| | | Year 1 | | Year 2 | | Year 3 | | Year 4 | | Year 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **01 Salary** | Name | # months | | # months | | # months | | # months | | # months | | Base |
| | Independent Biostatistician | 1 | $6,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | $6,000.00 |
| **UW** | PI | 2 | $31,600.00 | 2 | $31,600.00 | 2 | $31,600.00 | 2 | $31,600.00 | 2 | $31,600.00 | $15,800.00 |
| | Data Analyst | 1 | $6,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | 3 | $18,000.00 | $6,000.00 |
| | PhD or PostDoc | 6 | $36,000.00 | 12 | $72,000.00 | 12 | $72,000.00 | 12 | $72,000.00 | 12 | $72,000.00 | $6,000.00 |
| | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| **UWMC** | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **Shirley-Ryan AbilityLab** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **Spaulding Rehabilitation Hospital** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **Kessler Institute for Rehabilitation** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **Mayo Clinic** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **TIRR Memorial Hermann** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **Craig Hospital** | Research Coordinator | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | 3 | $33,762.99 | $11,254.33 |
| | Physician | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 1 | $25,000.00 | 0.5 | $12,500.00 | $25,000.00 |
| | Social Worker | 1 | $5,000.00 | 2 | $10,000.00 | 3 | $15,000.00 | 3 | $15,000.00 | 2 | $10,000.00 | $5,000.00 |
| | Data Analyst | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | 1 | $6,000.00 | $6,000.00 |
| | Physical Therapists | 1 | $7,333.00 | 3 | $21,999.00 | 6 | $43,998.00 | 6 | $43,998.00 | 3 | $21,999.00 | $7,333.00 |
| **03 Travel** | | | | | | | | | | | | |
| | Training | 1 | $10,000.00 | 0 | $0.00 | 1 | $10,000.00 | 0 | $0.00 | 0 | $0.00 | $10,000.00 |
| | Team meetings | 1 | $500.00 | 1 | $500.00 | 1 | $500.00 | 1 | $500.00 | 1 | $500.00 | $500.00 |
| **04 Supplies** | | | | | | | | | | | | |
| | Therapy supplies | 2 | $10,000.00 | 1 | $5,000.00 | 1 | $5,000.00 | 1 | $5,000.00 | 0 | $0.00 | $5,000.00 |
| **05 Equipment** | | | | | | | | | | | | |
| | 2.5 cm round electrodes | 4,375 | $5,468.75 | 4,375 | $5,468.75 | 4,375 | $5,468.75 | 4,375 | $5,468.75 | 0 | 0 | $1.25 |
| | 3 cm x 4 cm rectangular electrodes | 525 | $1,575.00 | 525 | $1,575.00 | 525 | $1,575.00 | 525 | $1,575.00 | 0 | 0 | $3.00 |
| | Spinal Cord Stimulator | 28 | $140,000.00 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | $5,000.00 |
| **06 Other** | | | | | | | | | | | | |
| | Participant Compensation | 10 | $8,800.00 | 30 | $26,400.00 | 50 | $44,000.00 | 55 | $48,400.00 | 37 | $32,560.00 | $880.00 |
| | Participant Support | 11 | $2,750.00 | 31 | $7,750.00 | 51 | $12,750.00 | 56 | $14,000.00 | 38 | $9,500.00 | $250.00 |
| | Software (Matlab) | 1 | $1,000.00 | 1 | $1,000.00 | 1 | $1,000.00 | 1 | $1,000.00 | 1 | $1,000.00 | $1,000.00 |
| | Publication | 0 | 0 | 0 | 0 | 0 | | 0 | | 1 | $2,000.00 | $2,000.00 |
| **TOTAL DIRECT** | $4,607,078.65 | | $799,365.68 | | $864,627.68 | | $1,086,220.68 | | $1,081,870.68 | | $774,993.93 | |
| **TOTAL INDIRECT** (30%) | $1,382,123.60 | | $239,809.70 | | $259,388.30 | | $325,866.20 | | $324,561.20 | | $232,498.18 | |

| | |
|---|---|
| **TOTAL COST** | **$5,989,202.25** |