Study Title: A Pilot Study to Compare Short-Term Transcutaneous or Epidural Spinal Stimulation for Enabling Motor Function in Humans with Spinal Cord Injury

NCT#: NCT05095454

Document Date: 07 November 2022

A Pilot Study to Compare Short-Term Transcutaneous or Epidural Spinal Stimulation for Enabling Motor Function in Humans with Spinal Cord Injury

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Funding Sponsor:

Mayo Clinic Center for Regenerative Medicine
Multi Organ Functional Neuro-regeneration Practice Improvement Project

Study Product:

DS8R Isolated Biphasic Constant Current Electrical Stimulator
Digitimer North America, LLC
Suite 700, One East Broward Boulevard.
Fort Lauderdale,
FL 33301, USA

Abbott percutaneous trial lead for epidural neurostimulation (Model 3086)
Abbott Neuromodulation
6901 Preston Road

Plano, TX 75024

Ripple Nomad Neurostimulator
Ripple Neuro
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Salt Lake City, UT 84106

Abbott clinician programmer for epidural and dorsal root ganglion neurostimulation (Model 3874)
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Protocol Number: (IRBe) 21-006340

IDE Number: G200133

Initial version:	07/30/2021 (Version 1.0)
Revision:	10/22/2021 (Version 1.1)
Revision:	01/10/2022 (Version 1.2)
Revision:	02/23/2022 (Version 1.3)
Revision:	05/24/2022 (Version 1.4)
Revision:	07/28/2022 (Version 1.5)
Revision:	08/25/2022 (Version 1.6)
Revision:	11/07/2022 (Version 1.7)

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AIS	American spinal injury association Impairment Scale
ASIA	American Spinal Injury Association
BWS	Body Weight Support
BWST	Body Weight Support Treadmill
CFR	Code of Federal Regulations
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DSMB	Data and Safety Monitoring Board
DEXA	Dual Energy X-Ray Absorptiometry
ES	Epidural Electrical Stimulation
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HDL	High-Density Lipoprotein
IDE	Investigational Device Exemption
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
LDL	Low-Density Lipoprotein
MAS	Modified Ashworth Scale
MEP	Motor Evoked Potentials
mFRT	Modified Functional Reach
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant Staphylococcus aureus
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SCI	Spinal Cord Injury
SCI-SET	Spinal Cord Injury Spasticity Evaluation Tool
SCS	Spinal Cord Stimulator
6-MWT	Six Minute Walk Test
SOP	Standard Operating Procedure
SSEP	Somatosensory Evoked Potentials
TS	Transcutaneous Electrical Spinal Stimulation
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Effect
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others
WISCI-II	Walking Index for Spinal Cord Injury
X-Ray	X-Radiation

STUDY SUMMARY

Title	A Pilot Study to Compare Short-Term Transcutaneous or Epidural Spinal Stimulation for Enabling Motor Function in Humans with Spinal Cord Injury
Running Title	Service Line Comparison of Transcutaneous or Epidural Stimulation
IRB Protocol Number	21-006340
Phase	Pilot study
Methodology	Prospective study
Overall Study Duration	1-year duration
Subject Participation Duration	Less than 6 months duration per subject
Objectives	a. Identify relationships between stimulation inputs delivered to lumbosacral spinal circuitry and the corresponding electrophysiological outputs, during 4 weeks of motor training with stimulation, and over 16 weeks post-stimulation to determine residual effects, in individuals with SCI. b. Assess motor, sensory, and functional outcomes during 4 weeks of motor training with stimulation, and the retained effects over 16 weeks post-stimulation, in individuals with SCI.
Number of Subjects	8 subjects
Diagnosis and Main Inclusion Criteria	American Spinal Injury Association Impairment Scale A-D
Study Device	DS8R Isolated Biphasic Constant Current Electrical Stimulator (Digitimer Ltd) Abbott percutaneous trial lead for epidural neurostimulation (Model 3086) Ripple Nomad Neurostimulator
Duration of Exposure	All subjects will complete either 1 month of transcutaneous spinal stimulation (TS) or temporary epidural spinal stimulation (ES) enabled rehabilitation sessions. Subjects will then be followed for an additional 4 months to complete follow-up assessments.
Reference therapy	The reference therapy is clinical rehabilitation after SCI.
Statistical Methodology	Descriptive statistics will be used to describe stimulation-related outcomes for each intervention. Repeated measures analyses of variance will be used to detect changes in outcomes over the course of rehabilitation.

1 INTRODUCTION

This document describes the protocol of a pilot stage clinical trial intended to study 8 humans diagnosed with chronic, incomplete, or complete loss of motor function below the level of traumatic spinal cord injury (SCI). The purpose of this trial is to improve the scientific understanding of how two electrical stimulation techniques, one which delivers electricity to the skin surface over the spine (transcutaneous spinal stimulation (TS)) and another which implants temporary percutaneous electrodes into the epidural space of the spinal cord (epidural spinal stimulation (ES)), facilitate spinal circuitry to enable function for individuals with SCI representing all levels of severity. Furthermore, we hope to determine responders versus non responders to spinal stimulation task-specific motor training following a condensed rehabilitation program as well as identify retained effects following 4 months of no intervention. Over the past decade, clinical investigations using either TS or ES have reported positive outcomes, such as regained control of leg movement (Gerasimenko, Lu, et al. 2015; P. S. H. PhD et al. 2011; Angeli et al. 2014; P. J. G. PhD et al. 2017; Gad et al. 2017) and cardiovascular improvements (Phillips et al. 2018; Harkema, Ditterline, et al. 2018; West et al. 2018). Independent investigations of either TS or ES have yielded some knowledge of the interactions between the electric field and spinal cord networks (Minassian, Persy, Rattay, Pinter, et al. 2007; Minassian, Persy, Rattay, Dimitrijevic, et al. 2007; Danner et al. 2016; Hofstoetter et al. 2018; Sayenko, Atkinson, Floyd, et al. 2015; Sayenko et al. 2014; Sayenko, Atkinson, Dy, et al. 2015; Rattay et al. 2000; Danner et al. 2013; Capogrosso et al. 2013).

To summarize, the paradigms used to characterize basic electrophysiological responses to stimulation in prior studies differed significantly from those used to facilitate functional movements in participants with lower extremity paralysis, specifically stimulation intensity and frequency. Therefore, there is a gap in knowledge of the electrophysiological and biomechanical outcomes produced by function-enabling TS and/or ES waveforms. Further, there is a lack of knowledge of the functional impact of brief rehabilitation with spinal stimulation in humans with SCI impairments. Finally, the extent to which stimulation-related changes are retained following the intervention is unknown. This protocol describes the experiments we will carry out to address this gap in knowledge of the interactions of either TS or ES over the course of brief rehabilitation periods. This clinical trial will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations, and Mayo Clinic policies and procedures. All study procedures will be performed at Mayo Clinic's campus in Rochester, Minnesota.

1.1 Background

Spinal cord injury

Severe SCI results in permanent loss of motor, sensory, and autonomic functions below the level of injury, leading to in catastrophic, lifelong changes in quality of life for SCI survivors. In the United States of America, nearly 300,000 people are living with neurological deficits due to SCI (National Spinal Cord Injury Statistical Center 2017). The effects of SCI are defined relative to physical and functional characteristics. It is well accepted that trauma to the spinal cord leads to functional disconnection of ascending and descending neural pathways between brain circuitry, spinal cord networks, and peripheral end organs, impairing

bodily functions innervated by spinal cord networks located below the lesion (Kandel 2013). A systematic review of studies that directly surveyed people with SCI found that the major priorities of functional recovery were: motor function (arm/hand for tetraplegia and mobility for paraplegia), bowel, bladder and sexual function, as well as a desire to improve psychosocial health (Simpson et al. 2012).

Spinal electrical stimulation to enable functions after SCI

Significant progress has been made in the field of spinal electrical stimulation to enable motor functions previously thought to be permanently lost after SCI. Specifically, Harkema and colleagues reported that, after months of rehabilitation with ES, volitional control of joint-specific muscles and independent standing were achieved by four humans with motor complete paraplegia (Harkema et al. 2011; Angeli et al. 2014).Recently, we reported that ES enabled control of stepping leg movements, which over the course of rehabilitation, translated to independent standing and stepping (Grahn et al. 2017; Gill et al. 2018). In addition to reports of ES enabling lower extremity motor functions, improvements in upper extremity (Lu et al. 2016), cardiovascular (Harkema et al. 2018; West et al. 2018; Harkema, Wang, et al. 2018; Aslan et al. 2018), and urologic functions (Herrity et al. 2018) have been reported.

In parallel investigations, electrical stimulation applied to the skin surface over the spine (i.e., TS) has emerged from prior use as a neurophysiological tool to interrogate spinal circuitry, (Danner, 2016; Sayenko, 2015; Sayenko, 2015; Krenn, 2017; Andrews, 2015; Roy, 2014) to a non-invasive approach to facilitate spinal circuitry and generate coordinated motor activity below the level of SCI (Inanici et al. 2018; Gad et al. 2018; Gerasimenko, Lu, et al. 2015; Gad et al. 2017). Similar to ES, TS has recently been shown to improve cardiovascular (Phillips et al. 2018) and urologic functions (Gad et al. 2018).

Pathophysiology relevant to potential study treatment action

Evidence from human cadavers suggests that even in cases diagnosed as complete loss of function below the level of SCI, as defined by the American Spinal Injury Association Impairment Scale-A (AIS-A), a portion of neural tissue commonly remains intact across the injury site (Kakulas 1984). These intact tissues may transmit non-specific supraspinal signals to sublesional spinal circuitry (Dimitrijevic et al. 1983). The unique electrophysiological characteristics associated with this injury profile have led to an injury description known as “discomplete SCI” (Dimitrijevic et al. 1983; McKay et al. 2004; Sherwood et al. 1992). The mechanisms by which TS and ES enable volitional control are thought to involve facilitation of sublesional spinal networks to that a “functional” state of excitability in order to properly receive signals transmitted across the discomplete SCI and to produce functional outputs (Grahn et al. 2017; Gill et al. 2018; Taccola et al. 2018).

TS and ES interactions with spinal circuitry have been preliminarily investigated using computational models (Capogrosso et al. 2013; Danner et al. 2015; Rattay et al. 2000; Danner et al. 2011) and basic properties of the evoked spinal motor potentials have been described (Sayenko et al. 2015; Sayenko et al. 2014; Sayenko et al. 2015; Danner et al. 2016; Hofstoetter et al. 2018). However, the stimulation paradigms used in prior studies were focused on eliciting motor potentials via single stimulus pulses in order to establish a basic

understanding of the evoked response properties during electrical facilitation of spinal circuitry (i.e., the intent was not focused on enabling functional activities that had been lost in subjects with SCI).

Description of the population to be studied
This study will include adult humans that sustained a traumatic SCI at least one year before trial enrollment. To qualify for this study, SCI severity must be previously diagnosed with an AIS classified injury. One participant will be enrolled from each AIS classification (A, B, C, and D) for each intervention. All injuries must be located at or above the tenth thoracic vertebrae. Detailed inclusion and exclusion criteria are provided within the appropriate section of this protocol.

1.2 Investigational Device

DS8R Isolated Biphasic Constant Current Electrical Stimulator (Digitimer Ltd)

Abbott percutaneous trial lead for epidural neurostimulation (Model 3086)

Abbott clinician programmer for epidural neurostimulation (Model 3874)

Ripple Nomad Neurostimulator

The temporary percutaneous implantation of epidural stimulation electrode leads will be surgically implanted to activate lumbosacral spinal networks in four humans diagnosed with chronic, complete, or incomplete loss of motor function below the level of SCI. By delivering electrical stimulation over the spinal cord during rehabilitation we aim to compare electrophysiological activity produced by spinal sensorimotor networks in response to transcutaneous or percutaneous epidural stimulation and quantify changes in motor performance metrics over the course of 12 motor rehabilitation sessions with either transcutaneous or percutaneous epidural stimulation.

1.3 Preclinical Data

Several decades of human investigation have focused on using ES to activate what was thought to be isolated spinal circuitry below the level of functionally complete SCI in order to study central pattern generator activity (Dimitrijevic et al. 1998; Jilge et al. 2004; Minassian et al. 2004; Roy et al. 2012) In 2011, Harkema and colleagues published a landmark report that after months of training, ES facilitated intentional control of joint-specific muscles and independent standing by a human with motor complete paraplegia (Harkema et al. 2011). The same research group successfully replicated their results in three additional subjects (Rejc et al. 2015; Rejc et al. 2017; Angeli et al. 2014). Based on these results, we initiated a clinical trial (NCT02592668) and in 2017, we reported successful replication of Harkema et al., along with additional outcomes (Grahn et al. 2017). Based on observations made during NCT02592668, we have designed this protocol to gain additional scientific knowledge with respect to mechanisms by which TS and ES enables functions in humans.

In addition to studying ES as described in this protocol, we intend to gather comparative data from the non-invasive spinal neuromodulation approach known as transcutaneous electrical spinal stimulation (TS). Prior evidence has shown that TS generates patterned motor activity and limb movements in healthy humans (Gerasimenko et al. 2016; Gerasimenko et al. 2015; Minassian et al. 2007; Minassian et al. 2007). More recently, TS has been reported to enable motor function in humans with SCI (Inanici et al. 2018; Gerasimenko, Lu, et al. 2015).

Our Mayo team recorded preliminary TS data in two subjects during supine activities prior to ES implantation. TS-evoked responses were recorded during low-frequency TS to investigate spinal sensorimotor activity generated to produce leg muscle activity. We compared responses across TS and ES. Preliminary data indicate smaller latency from stimulation to response in ES when compared to TS, indicating different mechanisms of action may underlie each approach. However, more subjects need to be investigated with a more structured study design to determine key differences between TS and ES. Completion of the proposed experiments in this protocol will provide data that can be used to improve the scientific understanding of how each technique enables function after SCI. This knowledge will be used to design future investigations that focus on safety and therapeutic efficacy of TS and ES.

1.4 Study Rationale and Risk Analysis (Risks to Benefits Ratio)

1.4.1 Study Rationale

There is no cure for SCI, which results in permanent loss of movement and sensation in body regions below the level of injury and a significant reduction in quality of life for SCI survivors. To address the lack of curative options following SCI, research efforts over the past decade have led to the development of neuromodulation approaches, such as TS and ES to activate spinal cord circuitry below the injury and enable lost functions. Scientific investigations of small numbers of humans with SCI have demonstrated positive functional outcomes such as standing, stepping, enhanced bladder function, and improved cardiovascular function, can be achieved using spinal stimulation. However, from a scientific perspective, the spinal sensorimotor circuitry activated using TS or ES has yet to be directly compared. Additionally, subjects need to be investigated within a structured study design to better understand the effect of rehabilitation on TS and ES enabled functions. Completion of the proposed experiments in this protocol will provide data that can be used to improve the scientific understanding of how each technique enables function after SCI. This knowledge will be used to help determine if TS is a viable and useful tool in determining which subjects may be best suited for ES through a clinical service line.

1.4.2 Anticipated Risks

Risks associated with rehabilitation:

In combination with TS and ES, the rehabilitation techniques used during this study will focus on maximizing independence, load bearing, body position, and kinematics during motor tasks while providing the minimum amount of trainer assistance and body weight support necessary to safely perform tasks. Risks associated with daily training include skin irritation and minor bruising from pressure applied during trainer assistance and body weight support, musculoskeletal discomfort, fatigue, and bladder or bowel incontinence due to

exertion and abdominal pressure from support harness. There is a slight risk of fracture in the lower extremities. Orthostatic hypotension is a risk associated with abrupt position changes against gravity, specifically transitioning from sit to stand quickly.

Risks associated with weight-bearing tasks:

Risks include muscle soreness, fatigue, skin irritation, fracture, changes in blood pressure, and potential for a fall.

Risks associated with TS:

Skin irritation due to electrical current passing through human tissue, skin irritation due to adhesives used to apply skin surface electrodes, discomfort or abdominal tightness during TS, increased or decreased spasticity, bowel or bladder incontinence, shortness of breath, muscle soreness, or fatigue may occur. Autonomic dysreflexia is a risk for those with mid-thoracic or higher-level injuries. Skin irritation or burns may occur during high-amplitude stimulation and/or prolonged stimulation sessions; skin breakdown may also occur as a result of this stimulation, with ensuing infection being a potential risk.

Risks associated with temporary percutaneous implantation of ES electrode leads:

ES electrodes will be implanted via commonly used percutaneous implantation techniques for FDA-approved treatment of medically refractory pain conditions. Therefore, the risks associated with percutaneous implantation of the ES system for this study match the risks associated with ES system implantation for treatment of FDA-approved conditions.

- Undesirable changes in stimulation may occur over time. These changes in stimulation are possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, loose electrical connections and/or lead failure.
- Placement of a lead in the epidural space is a surgical procedure that may expose the patient to risks of epidural hemorrhage, hematoma, infection, spinal cord compression, and/or paralysis.
- Radicular chest wall stimulation.
- Cerebrospinal fluid (CSF) leakage.
- Persistent pain at the electrode site or receiver site.
- Seroma at the incision site, as well as serosanguinous drainage.
- Implant migration.
- Allergic or rejection response to implant materials.
- Lead migration and/or local skin erosion.
- Paralysis, weakness, clumsiness, numbness, or pain below the level of implantation.

Risks associated with ES following implantation:

Hardware malfunction, discomfort, or abdominal tightness during ES, increased or decreased spasticity, bowel or bladder incontinence, shortness of breath, muscle soreness, or fatigue may occur during ES. Autonomic dysreflexia is a risk for those with mid-thoracic or higher-level injuries.

Risks associated with MRI
Dislodgement of some metal implants and claustrophobia may occur during MRI. Subjects will be rigorously screened in the same fashion as clinical patient by MRI technicians prior to each scan. Earplugs will also be provided to keep MRI noise within a safe audible range. Due to the potential for tissue heating, image artifacts, induced voltages in the neurostimulator or leads, and lead dislodgement, MRIs will not be obtained after epidural stimulator implantation.

Risks associated with Transcranial magnetic stimulation
Transcranial magnetic stimulation is electrical pulses from the magnet to the brain. Risks are possible hearing changes, headache, and a chance of heating on the skull where the magnet is placed.

Risks associated with electromyography and electroneurography
Risks involved with EMG include skin irritation or allergic reaction from the adhesive used to apply sensors. Additionally, electroneurography carries the risk of pain and discomfort from needle placement, and infection at the needle stick site.

Risks associated with urodynamic studies
Urodynamic studies may carry the risk of autonomic dysreflexia, mild irritation of the urethra, and infection.

Steps taken to minimize the occurrence and severity of associated risks:
Trained study staff and medical technicians will directly oversee all tasks. Body weight support, a safety gait belt, and other safety measures as necessary will be utilized to lessen the risks involved with rehabilitation and weight-bearing tasks. Transcutaneous electrode sites will be checked routinely throughout rehabilitation sessions, and if skin irritation or damage is observed, no further stimulation will occur until the site has healed. To mitigate risks in general, the protocol will be conducted as stated, medical professionals will be consulted, and care will be provided to address any study-related concerns that arise. All members of the research team will be trained to identify the occurrence of risks related to this study. If risk occurrence is observed, study-related activities will be halted until appropriate medical care is given and it is deemed safe for the subject to continue study-related activities. Because the interventions have been used for individuals with spinal cord injury and subjects will have been carefully screened, we do not anticipate any serious adverse events in this study. However, if they do occur, serious adverse events will be reported to the PI, medical monitor, IRB, and FDA within the appropriate reporting timeframes. Adverse events will be reported to the PI, the site medical monitors IRB, and FDA within the appropriate reporting timeframes.

1.4.3 Potential Benefits

The benefits which may result from this research study may include recovery of sensorimotor function below the level of SCI, recovery of bladder, bowel, or sexual function, improved thermoregulation, improved body mass composition, and improved sense of wellbeing. The certainty and degree to which these benefits may or may not occur is unknown.

1.5 Anticipated Duration of the Clinical Investigation

The anticipated duration of study participation for each human subject is approximately 6 months. During the 6 months, subjects will complete either TS rehabilitation sessions for the 1 month, or ES rehabilitation sessions for 1 month. After 1 month of either TS or ES, subjects will be followed for an additional 4 months for follow-up assessments. ES electrodes will be removed following 1 month of rehabilitation sessions.

2 STUDY OBJECTIVES

We propose to compare motor activity and clinical outcomes over the course of 1 month of TS or ES in combination with physical rehabilitation.

2.1 Primary Objective

The primary outcome data collected will be used to compare spinal sensorimotor activity in muscles below the level of injury during TS or ES-enabled motor tasks in persons with chronic motor complete paralysis of the lower extremities due to traumatic SCI.

2.2 Secondary Objective

Quantify changes in motor performance metrics over the course of 12 motor rehabilitation sessions with transcutaneous or percutaneous epidural stimulation

3 STUDY DESIGN

3.1 General Design

This is a pilot study that will include a total of 8 subjects with chronic, motor complete or incomplete paralysis below the level of SCI. All subjects will complete either 1 month of TS or ES driven physical rehabilitation sessions **(Table 1)**. All subjects will then be followed for an additional 4 months for follow-up assessments. Expected duration of subject participation is less than 6 months.

Table 1: Study Design

	PRE-INTERVENTION	INTERVENTION	POST-INTERVENTION	Follow-Up		
50% of Subjects	Baseline Assessments	Minimum 12 Sessions	End Assessments	Clinical, Electrophysiology, Kinematic Assessments & Surveys	Clinical, Electrophysiology, Kinematic Assessments & Surveys	STUDY END
	Clinical, Electrophysiology, Kinematic Assessments & Surveys	Stimulation + Motor Training	Clinical, Electrophysiology, Kinematic Assessments & Surveys			
	Transcutaneous Stimulation					
50% of Subjects	PRE-INTERVENTION	INTERVENTION	POST-INTERVENTION			
	Baseline Assessments	Minimum 12 Sessions	End Assessments			
	Clinical, Electrophysiology, Kinematic Assessments & Surveys	Stimulation + Motor Training	Clinical, Electrophysiology, Kinematic Assessments & Surveys			
	Percutaneous Epidural Stimulation					
	Week 0-1	Weeks 1-4	Week 4	Week 8	Week 20	

3.2 Primary Study Endpoints

Due to the pilot phase design of this clinical trial, it is not feasible to designate primary study endpoints. With this in mind, we do consider the biomechanical assessments and electrophysiology tests to be the primary sets of endpoints used to quantify TS and ES-related datasets associated with addressing the specific aims of this proposal.

3.3 Secondary Study Endpoints

Similarly, it is not feasible to designate secondary study endpoints. We do consider clinical assessments of spasticity and subjective surveys to be secondary study endpoints.

3.4 Primary Safety Endpoints

Primary safety endpoints of the study will be oriented to adverse events that could originate from the implantation of the ES electrodes, or the operation of either neurostimulator device as well as to those that could arise from performing the locomotor rehabilitation sessions. Patients will be asked to report any discomfort that they encounter throughout the study. A detailed selection of the candidates by the Principal Investigators and the study team will be crucial to select individuals who fit the inclusion criteria of the study, minimizing risk for potential adverse events throughout the study. Subjects will undergo a screening phase oriented to identify conditions that could potentially represent a higher than the expected risk for conducting this study.

To visualize electrode positioning of the ES neurostimulator system, fluoroscopy and spine computed tomography will be performed. To limit adverse events that could result from operating the neurostimulator device, stimulation parameters will be selected within safe ranges as provided by the manufacturer's specifications of ES pulse generators. Specifically, we will deliver stimulation within the following ranges:

ES parameters: pulse width 50-1000 microseconds; frequency 0.5-200 Hz; amplitude 0-25.5 mA

The procedure to connect the externalized ends of the percutaneous electrodes (model 3086) to the Ripple NOMAD will consist of minimizing strain on the connections by creating loops in the externalized lead wires and lead extensions (model 3386). The loops will be positioned in proximity to the implant site using adhesive tape. Additionally, each connection will be secured using adhesive tape. Finally, each connection and implantation site, as well as the strain relief loops, will be protected using an adhesive bandage.

During sessions of rehabilitation with stimulation, the looped lead wires and lead extensions will be connected to Abbott's battery-powered pulse generator (model 3599) via "multilead trial cables" (model 3013). Stimulation waveforms and electrode configurations will be transmitted wirelessly from the "clinician programmer" (model 3874) to the battery powered pulse generator. The battery-powered pulse generator, multilead trial cables, and clinician programmer are manufactured by Abbott for use with their ES system.

4 SUBJECT, SELECTION, ENROLLMENT, AND WITHDRAWAL

A total of **eight** humans with a history of a traumatic SCI will be enrolled in this pilot phase clinical trial **(Table 2)**. **Four** subjects will be assigned to "intervention 1" cohort and **four** will be assigned to the "intervention 2" cohort. Subjects will be selected based on the criteria described within sections 4.1 and 4.2:

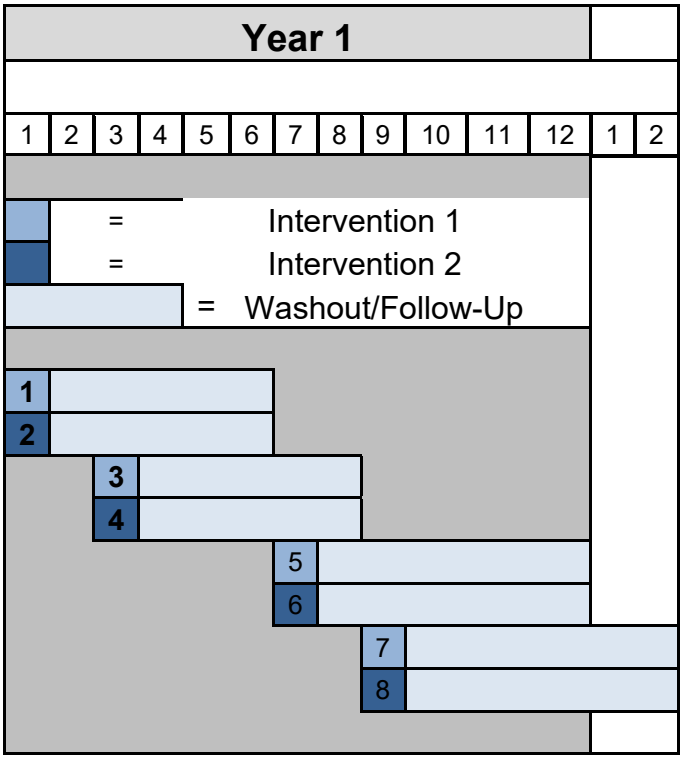


Table 2: Study Timeline

4.1 Inclusion Criteria

- Spinal cord injury due to trauma located at or above the tenth thoracic vertebrae (T10)
- American Spinal Injury Association grading scale of A-D (2 from each) below the level of SCI
- Intact spinal reflexes below the level of SCI
- At least 1-year post-SCI
- At least 22 years of age
- Willing to use medically acceptable methods of contraception, if female and of child-bearing potential

4.2 Exclusion Criteria

- Currently a prison inmate, or awaiting trial, related to criminal activity
- Pregnancy at the time of enrollment
- History of chronic and/or treatment resistant urinary tract infection
- Unhealed decubitus ulcer
- Unhealed skeletal fracture

- Untreated clinical diagnosis of depression
- Undergoing, or planning to undergo, diathermy treatment
- Active participation in another interventional clinical trial
- Presence of conditions or disorders which require MRI monitoring
- Other implanted stimulation devices (e.g. deep brain stimulator, cardiac pacemaker, diaphragmatic pacer, etc.)
- A history of coagulopathy or other significant cardiac or medical risk factors for surgery
- Current use of a ventilator
- Clinically diagnosed cardiopulmonary complications such as chronic obstructive pulmonary disease, cardiac failure, or heart arrhythmia that contraindicate changes in body position such as supine-to-sit-to-stand activities, prolonged standing, or stepping
- History of frequent hypotension characterized by light headedness, or loss of consciousness
- History of frequent hypertension characterized by headache, or bradycardia
- History of frequent, severe, autonomic dysreflexia
- Any illness or condition which, based on the research team's assessment, will compromise with the patient's ability to comply with the protocol, patient safety, or the validity of the data collected during this study.

4.3 Subject Recruitment, Enrollment and Screening

A total of 8 subjects will undergo the experiments described within this protocol. Subjects will be recruited from the following:

- Mayo Clinic's volunteer research subject database
- Mayo Clinic's clinical trials website
- Mayo Clinic's electronic medical record database search tools
- ClinicalTrials.gov

Prior to participating in the screening phase, a member of the research team will provide a detailed explanation of the study and answer questions asked by the potential study subject. If the potential subject is willing to participate in the study, they will be given sufficient time to make an informed decision, review relevant informed consent documents, and ask questions. Once questions and concerns have been addressed to the potential subject's satisfaction, the informed consent form will be signed and dated by the subject and an Investigator. A copy of the signed consent documents will be provided to the subject. The original signed consent documents will be retained within study records.

Following informed consent, screening tests will be performed including a thorough history and physical examination by a physician and physical therapist. Pre-existing clinical results to screening assessments may be accepted at the investigators' discretion if the testing was done within the timeframe specified for each test in the Study Procedures section. The ASIA Impairment Scale (AIS) examination will also be completed during screening to determine severity and classification of SCI. Urine tests will be completed to rule out an active urinary tract infection; if the testing is positive for a urinary tract infection, the subject will be

retested after two weeks' time for resolution. The subject will also be screened during a mock-up therapy session utilizing body weight supported harness system over the treadmill and trainer assistance to facilitate stand and step activities while monitoring blood pressure, tolerance, and range of motion. Due to an absence of standardized clinical practice guidelines that inform rehabilitation task safety decisions, if any concerns related to upright and load bearing activities exists, i.e. limited range of motion of load bearing joints, high spasticity, low blood pressure, osteoporosis (defined as a DEXA t-score of -3.5 or lower at the spine and hip), or high body weight, participants will receive motor training while seated and/or supine on a mat table, to avoid injury related to load-bearing activities. Based on screening results, a final decision on study participation will be made by the PI and study team. If any exclusionary screening results are transitory in nature, the subject may be re-screened at the discretion of the investigators. Screening tests will be repeated as indicated in the Study Procedures section.

4.4 Early Withdrawal of Subjects

Subjects will be informed that they have the right to withdraw from the study at any time. Similarly, the PI has the authority to withdraw the subject from the study at any time.

4.4.1 When and How to Withdraw Subjects

Factors that may lead to withdrawal:

- Study subject health concerns
- Protocol violation (e.g., non-compliance)
- Study-related serious adverse events
- Study subject's decision to pursue activities outside of the study protocol, that in the opinion of the PI, may compromise data collected within the study protocol
- The emergence of other problems, events, or information, that may adversely affect the rights, safety, or welfare of the study subject, or may substantially compromise data collected within the study protocol

If a serious adverse event occurs during an activity described in this protocol, a consensual decision will be made between the study subject and the PI regarding withdrawal from the study.

In the event of study withdrawal, the ES electrodes will be surgically explanted. If explanation surgery is urgent due to concern for the subject's health, the cost of the explanation surgery will be covered by the research study. Aside from standard surgical recovery, no adverse effects are anticipated from the removal of an epidural electrical stimulator.

If a subject is withdrawn from the study for any reason other than treatment-related adverse events, an additional subject may be recruited as a replacement within the same study cohort.

If a subject fails to attend protocol activities and fails to respond for follow-up, a communication attempt will be made to determine if non-compliance is related to an adverse event.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws or is withdrawn from the study for any reason before study completion, an attempt will be made to carry out an exit interview. The reason for withdrawal will be documented by the research team.

5 STUDY DEVICE

5.1 Description

Epidural spinal cord stimulator
(Model 3086, Model 3874, Abbott Neuromodulation; Nomad, Ripple Neuro)

The ES electrode lead is an implantable neurostimulation device that is FDA-approved for treatment of neuropathic pain disorders. ES leads will be implanted temporarily along the dorsal epidural surface of the lumbosacral enlargement (i.e., L2-S1 spinal segments). The externalized ends of the ES electrode leads will be connected to the Nomad neurostimulation system in order to deliver testing-specific electrical pulse waveforms to the epidural surface (Figure 4). ES pulses will be synchronized to electrophysiological and biomechanical recordings of spinal motor output, and in turn, motor functions that are enabled by ES. Electrophysiological data will be collected from skin surface electrodes. Additionally, during ES using the Ripple Nomad, signals will also be captured from passive electrodes (i.e., not configured as an anode or cathode during stimulation) on the ES lead (Abbott, Model 3086). During ES-enabled rehabilitation sessions, when non-testing-specific electrical pulse waveforms are applied, the Abbott clinician programmer device designated for the ES leads will be used.

Transcutaneous spinal cord stimulator
(DS8R, Digitimer LLC)

The DS8R is designed for human research rather than diagnosis or therapy; it does not have a medical device certification. The DS8R is an isolated, constant current stimulator for human research studies involving nerve and muscle stimulation via surface electrodes. It features a high compliance voltage and can be triggered and controlled by multiple external sources. For the purpose of delivering TS to the surface of the skin over the spine, customized electrical waveforms built within Labchart electrophysiological data acquisition software (ADInstruments Inc., Colorado). The DS8R will be triggered to deliver TS waveforms via PowerLab digital outputs (ADIstruments Inc., Colorado). The DS8R is capable of delivering monophasic or biphasic current pulses of up to 2ms duration, with an output range of 2mA to 1000mA* (from 400V). The actual current achieved will be restricted by a pulse energy limit of 300mJ per pulse and the skin/electrode resistance.

5.2 Method for Assigning Subjects to Treatment Groups

Four subjects will be assigned to each treatment arm based on availability at the time the subject volunteers to participate (Total subjects studied: 8). If both arms are enrolling in

parallel at the time a subject volunteers to participate, he/she will be allowed to choose the treatment arm in which to enroll.

5.3 Preparation and Administration/Implantation of Investigational Device

Description of TS administration

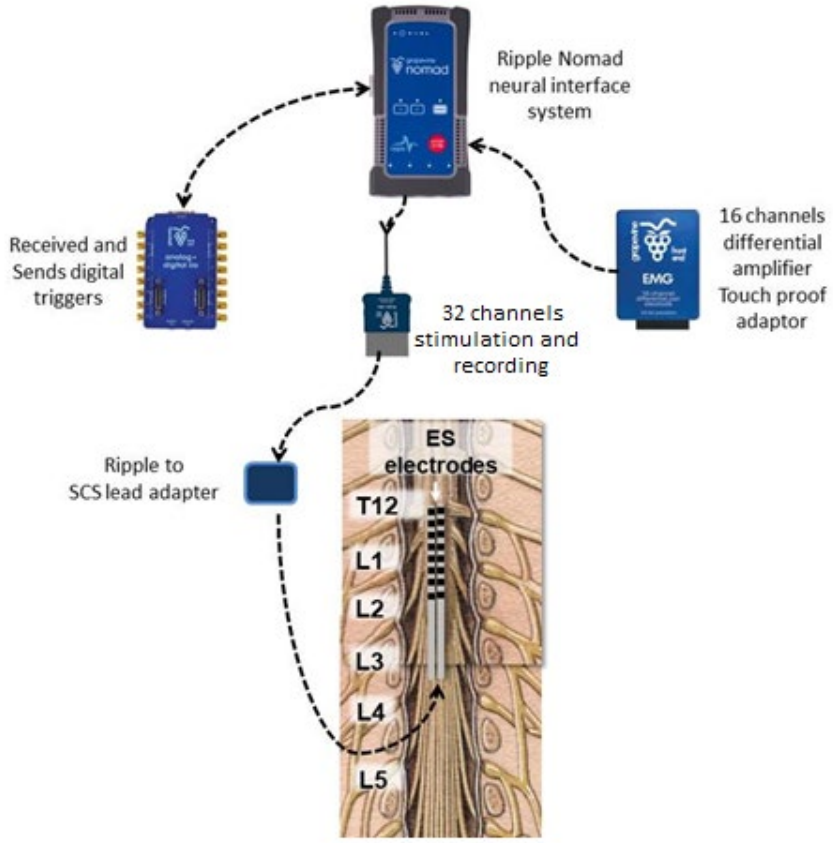
A constant-current stimulator DS8R (Digitimer LLC) will be used to deliver TS to the skin surface over the spine. At locations where self-adhesive bipolar recording electrodes will be placed onto the skin, the area will be cleaned with alcohol to ensure secure attachment and enhance signal recordings. The stimulation will be administered using self-adhesive electrodes placed as cathodes on the skin between the T7 and L3 vertebrae, with the option of ultrasound (US) guided imaging to locate the spinous processes at each segment. In addition, self-adhesive electrodes will be placed symmetrically on the skin serving as anodes. A foam pad may be placed over the cathode and secured using adhesive tape and/or an elastic belt to tightly wrap around the subject's trunk to ensure cathode electrodes do not shift or peel away during rehabilitation activities. The stimulation waveform will consist or bi-phasic pulses (duration between 0.1 – 1.0 ms), at frequencies between 0.2 –100Hz. We will also test the efficacy of a recently developed carrier frequency of 4 – 10 kHz, using stimulation intensities of up to 100 mA. Skin under the electrodes will be inspected frequently during sessions to ensure no irritation occurs from stimulation.

Description of ES system implantation/administration

We recently published a detailed explanation of the procedure to implant a permanent electrode array connected to an implanted pulse generator, along with a detailed description of the electrophysiological approach used to guide electrode positioning over the lumbosacral enlargement in humans with SCI (Calvert, 2018). The same approach will be used during this study to guide electrode placement via electrophysiological monitoring of spinal motor evoked potentials.

The procedures for percutaneously implanting Abbott ES electrodes are performed daily at Mayo Clinic to treat patients suffering from neuropathic pain. Prior to implantation, subjects will undergo a pre-operative evaluation to minimize the risk of unexpected complications. Pre-operative assessments may be performed to check for any signs of infection.

In order to implant the temporary spinal electrodes, an incision will be made at the entry site to the depth of the subcutaneous fascia. Under fluoroscopy, an electrode insertion needle will be place into the epidural space using a paramedial approach until resistance is felt from the ligamentum flavum, followed by fluoroscopic visualization of the needle's position. Once positioning is confirmed, the needle stylet will be removed and the needle will be advanced into the epidural space.



Then, the leads are advanced in an anterograde fashion to deliver them into the intervertebral foramen under fluoroscopic guidance. Following electrophysiologic confirmation of electrode positioning, the needle and stylet will be removed, the implantation site will be dressed, and the leads will be secured to the skin via an adhesive bandage. The implantation site will be monitored for signs of infection, tissue erosion, or dislodged lead wires.

Procedure to explant ES electrode leads

After completing 12 sessions of rehabilitation with ES, the adhesive bandage covering the implantation site will be removed, the incision site will be opened, and the leads will be carefully retracted. Finally, the incision site will be cleaned and dressed.

If complications associated with temporary lead implantation (e.g., infection, severe lead migration, device malfunction, etc.) are observed, the PI will make an informed decision whether to perform explantation prior to completion of 12 rehabilitation sessions.

5.4 Subject Compliance Monitoring

Throughout the study, research staff will monitor study protocol compliance. This will include review and verification of all protocol-related procedures and records. The PI will oversee compliance and determine the appropriate response to non-compliance events.

5.5 Prior and Concomitant Therapy

A subject's prior therapy regimen will not impact the PI's decision regarding enrollment into the study. As long as the subject fits the inclusion criteria and does not demonstrate any exclusion criteria characteristics (i.e., bone fractures, joint contractures, or skin lesions), prior exercise or therapy programs will not exclude their participation in the study. While enrolled in the study, subjects will be asked to follow the instructions from the study staff regarding the home exercise program prescribed from the research team. For example, if the study subject performed locomotor training at a local gym prior to the study, they would be asked to discontinue that activity while participating in the trial.

5.6 Packaging and Labeling

The packaging of the devices will be from the manufacturer's clinical supply. The following will be added to the devices used within this investigation:
"CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use"

5.7 Masking/Blinding of Study

This is an unblinded study. The PIs, co-investigators, and subjects will know what treatment they received.

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

The ART laboratory owns two transcutaneous electrical spinal stimulators (DS8R Isolated Biphasic Constant Current Electrical Stimulator, Digitimer Ltd), which serve as a primary unit and a reserve unit. If either device becomes damaged or unusable, use of the device will be discontinued until the supplier repairs the unit. All communication between study staff and the supplier will be documented in the study files.

A representative from Abbott will ship the devices to Mayo Clinic and they will be properly inventoried prior to the scheduled date of surgical implantation. The representative will also train study personnel on how to use the clinician programmer during non-testing rehabilitation sessions.

The Nomad neurostimulation system will be purchased from Ripple Neuro, shipped to Mayo Clinic, and inventoried within the ART Lab.

Any product discrepancies or damage will be documented in the study files and the supplier will be notified. Then, appropriate action will be taken by the PI to fully address the issue.

5.8.2 Storage

The TS device (Digitimer) is stored in the ART laboratory, a secured area requiring badge access.

ES electrode leads will be stored within a secured surgical materials area of Mayo Clinic's Pain Clinic. Access to this area is granted solely to Mayo Clinic staff involved in surgical implantation procedures.

The Ripple Nomad system will be stored in the ART Lab, which is a secured area that can only be accessed by ART Lab staff.

5.8.3 Distribution of Study Device

The TS devices (Digitimer) will not be assigned to individual subjects, but the devices on hand will be tracked in the Device Accountability form, and the serial number of the device used in a given session will be tracked in the subject's case file.

In accordance with Mayo Clinic policy, the brand, model, date of implantation, and date of explantation of all ES electrode leads will be recorded in the Surgical Inventory Management System. This information will be made available within the electronic medical record of each subject. Additionally, a copy of this information will be stored within each subject's case file.

5.8.4 Return or Destruction of Study Device

At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the PI will be notified, and an investigation will be conducted to determine the cause of the discrepancy.

6 STUDY PROCEDURES

6.1 Screening:

Subjects will complete a variety of assessments and procedures to determine their enrollment eligibility. When possible, eligible subjects will have their screening data used as baseline data collection. Primary outcomes include biomechanical assessments related to motor tasks, electrophysiology tests, and an ASIA examination. Secondary outcomes include spasticity assessments, subjective surveys, and various spine imaging.

6.2 Intervention 1: Transcutaneous Electrical Spinal Stimulation (TS) and Task Specific Training Sessions

Subjects will report to the ART lab at St. Mary's Hospital for daily sessions of TS and task-specific training interventions. TS stimulation will be applied to the skin surface over the spine as described previously.

Training sessions will begin upon completion of baseline testing. Subjects will participate in a 3 days per week training regimen over 1 month with a goal of achieving 12 sessions. Activities include tasks specific to supine intentional leg movement training, balance training, stand and step (reciprocal flexion/extension) training. Heart rate will be recorded prior to, and after, each session, and at any time the intervention is paused due to a concern. Environments include the body weight support treadmill (BWST) system to allow trainer-assisted stand and step activities as needed, custom standing frame, and a hi/lo mat for supine

and seated activities. As the subjects progress their intentional motor ability with standing and stepping, BWS will be removed, and assist will continue to be provided on an as needed basis. Any visit to the laboratory when TS is enabled will be considered a training session. Activities chosen for each session will be based on the subject's progression.

6.3 Period of Follow-up after TS

After 1 month of TS and motor training, each subject will be asked to complete two follow-up assessments at time points 1 month and 4 months after completing the intervention to monitor changes in primary and secondary outcome measures. Subjects will be asked to refrain from partaking in additional therapies or interventions with the goal of improving functional measures related to their SCI during this 4-month follow-up period.

6.4 Intervention 2: Epidural Electrical Stimulation (ES)

ES rehabilitation daily sessions will consist of lower extremity stretching, supine and side lying activities, seated trunk strengthening and balance activities, and locomotor training including task-specific stand and step training on a treadmill and over ground. Standing and stepping training activities may be performed with body weight support and trainer assistance as needed to ensure the safety of subjects.

Training sessions will begin upon completion of baseline testing. Subjects will participate in 3 days a week training regimen over 1 month with a goal of achieving 12 sessions. Activities include tasks specific to supine intentional leg movement training, balance training, stand and step (reciprocal flexion/extension) training. Heart rate will be recorded prior to, and after, each session, and at any time the intervention is paused due to a concern. Environments include the body weight support treadmill (BWST) system to allow trainer-assisted stand and step activities as needed, custom standing frame, and a hi/lo mat for supine and seated activities. As the subjects progress their intentional motor ability with standing and stepping, BWS will be removed, and assist will continue to be provided on an as needed basis. Any visit to the laboratory when ES is enabled will be considered a training session. Activities chosen for each session will be based on the subject's progression.

6.5 Period of Follow-Up after ES

After 1 month of ES and motor training, each subject will be asked to complete two follow-up assessments at time points 1 month and 4 months after completing the intervention to monitor changes in primary and secondary outcome measures. Subjects will be asked to refrain from partaking in additional therapies or interventions with the goal of improving functional measures related to their SCI during this 4-month follow-up period.

6.6 Outcome Measures

The following outcome measures will be collected as scheduled in **Table 3** with tests occurring over an approximately one-week period of time for each time point. Photographic and video images will be recorded throughout the study, but will not be shown to anyone outside the study team without the subject's written consent.

6.6.1 Primary:

Biomechanical assessments

During a variety of tasks including supine, side-lying, reaching, standing, and stepping activities, kinematics, EMG, and foot pressure measurements may be obtained, with or without spinal stimulation, using the following metrics:

Kinematics: We will use commercially available markers placed on the skin surface via a non-irritant adhesive to record limb movement and joint angles. Available systems we may use include video-based, inertial measurement units, electromagnetic.

Electromyography: We will collect muscle activity using skin surface electrodes placed at anatomical locations of muscle groups below the level of injury. Activity will be recorded using a 16-channel signal amplifier and data acquisition system (PowerLab, ADInstruments, Colorado). At locations where self-adhesive bipolar recording electrodes will be placed onto the skin, the area will be cleaned with alcohol to ensure secure attachment and enhance signal recordings. A subset of the following muscles or muscle groups will be tested: soleus, gastrocnemius, tibialis anterior, hamstrings, quadriceps, hip adductors, gluteus maximus, gluteus medius, abdominals, triceps, trapezius, and spinal extensors.

Foot pressure: Foot pressure will be measured with shoe-insole pressure sensors (F-SCAN, Tekscan Inc., Boston, MA).

Seated pressure: Seated pressure will be assessed via a force sensing array placed beneath the buttocks (Vista Medical BodiTrak force sensing array, Winnipeg, MB, Canada).

Over the course of rehabilitation, if the research team observes stimulation-enabled functions that could be enhanced by further optimization of stimulation parameters, biomechanical assessment equipment may be used during select rehabilitation sessions in addition to the main assessment timepoints described in **Table 3**.

Table 3: Outcome Measures

Study Timeline										
	Screening	Pre	Implant	Spinal Stimulation + Motor training				Explant	Post	Follow-Up
Weeks	0	Baseline		1	2	3	4		5	8, 20
Motor Training				X	X	X	X			
Urinalysis	X									
DEXA[1]	X									
Primary Outcomes										
Kinematics[2]				X			X			X
EMG[2]		X		X			X		X	X
SSEPs		X							X	X
TMS MEPs		X							X	X
TMS + ES or TS2		X							X	X
TS MEPs	X								X	X
ES MEPs				X			X			
BBS, TUG, 6MWT		X							X	X
FRT/mFRT				X			X			X
ISNCSCI	X								X	X
Secondary Outcomes										
Spine CT or MRI	X			X			X			
Urodynamic Studies		X							X	
Surveys		X							X	X

1. DEXA scan measured at either left or right femur, and AP spine; not to include total body scan.

2. Further optimization may occur during training weeks 1-4.

DEXA=Dual Emission X-ray Absorptiometry, EMG=Electromyography, SSEPs=Somatosensory Evoked Potentials, TMS=Transcranial Magnetic Stimulation, MEPs=Motor Evoked Potentials, ES=Epidural Stimulation, TS=Transcutaneous Stimulation, BBS=Berg Balance Score, TUG=Timed Up and Go, 6MWT=6 Minute Walk Test, mFRT=Modified Functional Reach Test, ISNCSCI=International Standards of Neurological Classification of Spinal Cord Injury

Electrophysiology tests

Somatosensory evoked potentials (SSEPs): SSEPs will be recorded through surface electrodes to measure conduction in the peripheral nerves, cervical and lumbosacral spinal cord, deep brain structures, and sensory cortex. Skin will be cleaned with alcohol and prepared using mild abrasive tape for placement of surface electrodes. For tibial recordings the tibial nerve will be stimulated behind the medial malleolus with recordings on the scalp utilizing a Fz,-CZ montage (International 10-20 System for EEG electrode placement), the cervical spine (C5 reference to Fz), the L1 spine (referenced to iliac crest), and the popliteal region. For median SSEPs, the median nerve will be stimulated at the wrist with recording electrodes at the scalp (C3-C4), the cervical spine (C5-Fz), Erb's point (referenced to contralateral Erb's) and the elbow. Repeated single-pulse electrical stimulation will be delivered at intensities of 1-1.5 times motor threshold for visual twitch for each of the four nerves evaluated. Averaged responses for up to 256 stimuli will be recorded for each of these two intensities for the right and left median and tibial nerves. Simultaneous bilateral stimulation will be applied if no recognizable responses are recorded from the scalp leads. Stimulation delivery rates will not exceed 2 per second. Recorded data will include amplitudes, peak latencies and interpeak latencies. Existing SSEPs within 6 months of screening may be acceptable for Baseline results at the investigators' discretion.

Transcranial magnetic stimulation (TMS) Motor evoked potentials (MEP): TMS MEPs will be evoked by placing a magnetic coil over the vertex of the head to elicit MEP. Upper limb MEPs will be recorded from the deltoid, triceps brachii, flexor carpi radialis and abductor pollicis brevis using the EMG system described in the biomechanics testing. The "threshold" TMS intensity will be defined as the minimum stimulus intensity required to elicit a response, recorded from muscles above the injury, that appears in response to >50% of the stimuli pulses delivered. If no MEPs are observed in EMG recordings from muscles that are innervated by the spinal cord below the level of injury, but are present in muscles innervated by spinal segments above the injury, then the injury severity will be deemed functionally motor complete. Data will be digitized, and MEPs responses averaged for each muscle. Latencies (interval from stimulus artifact to onset of response) and peak-to-peak amplitudes of MEPs responses will be assessed from all muscles. Existing TMS-MEPs within 6 months of screening may be acceptable for Baseline results at the investigators' discretion.

TMS Pulses Paired to TS or ES Pulses

In order to interrogate the corticospinal connectivity which may be responsible for transmitting volitional motor commands during TS and/or ES through the injury site in participants with SCI, we will apply pulses of TMS at time intervals ranging from 5-100ms prior to activation of lumbosacral spinal circuitry via pulses of either TS or ES. Evidence suggests both TS and ES, applied over the thoracolumbar spine, activate dorsal roots to elicit a motor reflex root-evoked potential. At each assessment time point, we will incrementally increase TS or ES pulse amplitudes to identify the stimulus intensity that consistently generates spinal reflex activity recorded via lower extremity EMG. Then, two TS or ES pulses will be delivered 50 ms apart to characterize the trans-synaptic nature of the reflex which will be determined by observing suppression of a

response to the second stimulus pulse (i.e., post activation depression). Next, we will examine the conditioning effect (e.g., no change, increased amplitude of reflex, or decreased amplitude of reflex) of delivering TMS pulses at time intervals ranging from 5-100ms prior to pulses of TS or ES while recording spinal circuitry outputs via lower extremity EMG.

TS MEPs

To assess the functional states of the spinal circuitry, we will deliver transcutaneous spinal stimulation via pulses of 1 ms duration at intensities of up to 100 mA. Stimulation will be delivered to multiple locations of the lumbosacral region with participants in a supine position. Evoked potentials will be recorded via surface EMG electrodes placed bilaterally over the soleus, gastrocnemius, tibialis anterior, hamstrings, quadriceps, hip adductors, gluteus maximus, gluteus medius, abdominals and spinal extensors. We will record evoked potentials while relaxed using stimulus intensities from 1-100 mA at increments of 10 mA for each stimulus location. Evoked potentials for each stimulus location and intensity will be averaged and visualized in real-time to determine the optimal location for evoking threshold potentials across all recorded muscles. Stimulus intensities that are at the threshold for evoking motor potentials will be delivered: while attempting prolonged maximal contractions of all muscles; during attempts to contract the left leg; and during attempts to contract the right leg. Evoked potentials will be analyzed according to task, stimulus intensity, and stimulus location.

ES MEPs

To assess the effects of delivering ES pulses to various regions of the lumbosacral spinal cord, we will record skin surface EMG from lower extremity muscles while ES is delivered to the temporarily implanted electrodes using a subset of anode/cathode configurations. Electrode configurations will be selected in order to selectively stimulate the rostral or caudal regions of the spinal cord within the T11-L1 vertebral bodies. This region of the spinal cord innervates the left and right proximal or distal muscles of the left/right lower extremities. ES pulses will be delivered as biphasic charge-balanced rectangular pulses ranging in pulse width (0.05-1ms), amplitude (0-25.5mA), and frequency (0.5-200 Hz). Within the implanted lead, each electrode could be configured as a cathode, anode, or off, and individual electrode configurations in order to target specific rostral-caudal and medial-lateral regions of the spinal cord to generate specific motor outputs.

Overground mobility

For subjects with motor incomplete injuries, attempts to stand and generate steps with varying degrees of body-weight support will be assessed using the Timed Up and Go (TUG), Berg Balance Score (BBS) while using the 6 Minute Walk Test (6MWT) to assess endurance changes. Measurements made as part of intake for the SCI Service Line may be used, if available.

Balance Assessment
A motion capture camera system will be used to assess trunk stability according to the protocol from the modified functional reach test (mFRT) for subjects unable to stand. The subject will be outfitted with reflector markers on specific upper limb, trunk, pelvic, and lower limb landmarks. This procedure will consist of the subject sitting with hips, knees, and ankles position at 90 degrees of flexion with feet positioned flat on the floor. The subject is then asked to reach forward and laterally with their upper extremities while maintaining trunk stability. The extent to which the subject can reach before trunk balance becomes unstable (requiring assistance to regain balance from the physical therapist) is measured for multiple reaching trials.

During the trunk stability assessment, skin surface EMG will be collected bilaterally from lower extremity and trunk muscles, as well as the trapezius. Pressure recordings will also be collected from under both feet and under the buttocks.

Subjects capable of standing will undergo assessment via Berg Balance Assessment, the standing version of the Functional Reach Test (FRT), and the modified functional reach test (mFRT).

International Standards of Neurological Classification of SCI (ISNCSCI)
We will conduct ASIA Impairment Scale (AIS) to assess severity of the injury. This test focuses mainly on sensory and motor functions. Measurements made as part of intake for the SCI Service Line may be used, if available.

6.6.2 Secondary:

Spine Imaging
Baseline CT of the spine will be used to evaluate the structural integrity of the spine prior to study onset, and to visualize spine fusion hardware with respect to TS location and preparation of ES implantation location. Baseline spine MRI will be used to evaluate injury severity and assess potential of spared tissue (discomplete SCI) despite complete loss of motor function. Spine CT will be repeated for subjects following ES implantation to visualize array location, and at the end of the study to evaluate changes in array location. Existing spine CTs and MRI within 6 months of screening may be acceptable for Baseline results at the investigators' discretion.
Over the course of rehabilitation sessions with ES, one additional x-ray may be performed to visualize the location of implanted leads. This x-ray will be performed if stimulation-enabled motor activity is remarkably inconsistent from session to session, which might indicate migration of the ES lead(s).

Bladder function
A urodynamic test consisting of a filling phase and a voiding phase cystometrogram along with perineal patch muscle electromyography (EMG) will be performed with the stimulator both on and off. Specifically, a 9F double-lumen catheter will be introduced transurethrally into the bladder. One lumen of this catheter will be used for bladder filling at an average flow rate of 20-25 ml/min (according to ICS guidelines), and another will record intravesical pressure. Intra-abdominal pressure will be recorded by a 12F rectal catheter. Through multichannel pressure transduction, intravesical and intra-abdominal pressures will be simultaneously

transduced on a strip chart recorder. Detrusor pressures will be simultaneously calculated by subtracting vesical from abdominal pressures. Sphincter EMG activity is observed by using patch electrodes. Existing urodynamic studies within 6 months of screening may be acceptable for Baseline results at the investigators' discretion.

Surveys
A battery of clinical surveys will be captured to assess subjects' assessment of quality of life, and health habits such as bowel and bladder function, and sexual function. Any of these surveys done as part of intake for the SCI Service Line may be used, if available.

7 FDA IDE-RELATED DEVICE PREPARATION AND ADMINISTRATION PROCEDURES

Study-related device packaging will not be altered with respect to the device manufacturer's clinical supply packaging. However, the following label will be added to the devices described within the FDA IDE protocol associated with this clinical trial:

*** CAUTION ***
Limited to Investigational Use by Federal Laws and Regulations

7.1 Receipt of FDA IDE-related Devices

A representative from Abbott will ship the devices to Mayo Clinic and they will be properly inventoried prior to the scheduled date of surgical implantation. The representative will also train study personnel on how to use the clinician programmer during non-testing rehabilitation sessions.

The Nomad neurostimulation system will be purchased from Ripple Neuro, shipped to Mayo Clinic, and inventoried within the ART Lab.

Any product discrepancies or damage will be documented in the study files and the supplier will be notified. Then, appropriate action will be taken by the PI to fully address the issue.

7.2 FDA IDE-related Device Storage

ES electrode leads and the clinician programmer will be supplied directly by the Abbott distribution representative and/or stored in the ART Lab, which is a secured area that can only be accessed by ART Lab staff.

The Nomad system will be stored in the ART Lab.

7.3 Distribution of FDA IDE-related Devices

In accordance with Mayo Clinic policy, the brand, model, date of implantation, and date of explantation of all ES electrode leads will be recorded in the Surgical Inventory Management System. This information will be made available within the electronic medical record of each participant. Additionally, a copy of this information will be stored within each participant's case file.

7.4 Return or Destruction of FDA IDE-related Devices

Each month, as well as upon receipt of new or repaired devices, and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged, signed, and dated within the Device Accountability Form. Any discrepancies noted will be documented and an investigation will be conducted to determine the cause of the discrepancy.

8 STATISTICAL DESIGN AND POWER

8.1 Sample Size Determination

Due to the pilot phase of this clinical trial, no formal power calculations were performed for this study. The number of subjects was selected based on budgetary, space, and personnel time constraints. Eight subjects will be enrolled to complete the activities of this clinical trial, depending on need for contingency subjects. All subjects will receive either 1 month of TS and rehabilitation or 1 month of ES and rehabilitation. Following either intervention, all subjects will be followed for follow-up assessments at 2 time points during 4 additional months.

8.2 Statistical Methods

Descriptive Statistics and Graphics

Continuous data will be summarized as median (inner quartile range). Categorical data will be presented as frequency (percentage). Graphical presentations of data will be used for all endpoints. Individual data points will be plotted over time, with distinctions made between data from TS and ES groups. Additionally, associations between measurements prior to and following ES intervention will be assessed using bivariate scatterplots. These associations will be summarized numerically with Spearman's correlation coefficient.

Modeling

The overall ES effect will be assessed by comparing models with and without the treatment indicators. Additionally, measurements taken under various conditions can be modeled simultaneously with appropriate effects for the different conditions. For example, SSEPs will be measured at the tibial and median nerves, each at 2 intensities. Effects for the different locations and intensities will be added to the model, along with effects for the 2 nerves as random effect nested within subject. Models will also be used to quantify associations between assessments at baseline and during the first month, with assessments at the end of the study. This may be used to determine whether there may be markers available to predict which subjects may respond to treatment.

Handling of Missing Data
Mixed modeling will not require complete data collection to conduct the analysis. Other analysis, such as bivariate analyses, which require complete data will be, conducted primarily using complete cases analysis. Sensitivity analyses will be conducted by imputing missing data with predictions from regression models based on baseline data.

8.3 Subject Population(s) for Analysis
All-completed population: Only subjects who completed all study related procedures and follow-up will be included; however, the PI may adjust this to include a subject who completed the majority of the study visits and procedures.

9 SAFETY AND ADVERSE EVENTS

All AEs occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained, and reports will be submitted to the FDA and IRB according to the regulatory requirements. Expected clinical AEs and nonsignificant (not serious) clinical AEs will not be reported.

9.1 Unanticipated Adverse Device Event (UADE)
A UADE is any SAE that impacts the health or safety, or any life-threatening problem or death caused by, or associated with, a device if that event, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

9.2 Adverse Event (AE)
Any untoward medical occurrence of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s). The following categorization of AEs will be used:

9.2.1 Associated with the Investigational Device
There is a reasonable possibility that the AE may have been caused by the investigational device.

9.2.2 Life-threatening AE
Any AE that places the participant at immediate risk of death from the event as it occurred, excluding events where a reaction that, had it occurred in a more severe form, might have caused death.

9.2.3 Serious AE
An AE will be considered “serious” if it results in any of the following outcomes:

- death

- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

9.2.4 Unanticipated AE

Any AE, the nature, specificity, severity, or frequency of which is not consistent with the anticipated risks described within the clinical study protocol.

9.3 General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE will also be recorded and documented as an AE.

9.4 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization will be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator

9.5 Post-study AE

All unresolved AE will be followed by the PI until the AE is resolved, the participant is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the PI will instruct each participant to report any subsequent event(s) that might reasonably be related to participation in this study. The PI will notify the institutional regulatory office of any death or AE that occurs at any time after participants have discontinued or terminated study participation and may reasonably be related to this study.

9.6 Preexisting Condition

Any preexisting conditions that do not result in exclusion during screening will be recorded as an AE if the frequency, intensity, or the character of the condition worsens.

9.7 Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problems or AEs that meet all of the following three criteria:

9.7.1 Serious
Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening AE; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data.

9.7.2 Unanticipated
Events that are not already described as potential risks in the protocol, consent document, not listed in the PI's brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

9.7.3 Related
A problem or event is "related" if it is possibly related to the research procedures.

9.8 AE Recording
At each contact with the participant, the PI will seek information on AEs. Study participants will be routinely questioned about AE at study visits. Information on all AE will be recorded immediately in the source document, and also in the appropriate AE section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results will be recorded in the source document.

All observed or volunteered AEs (serious and non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational device, will be recorded in the participant's case history. For all AEs, sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the AE and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious AEs that are unresolved at the end of the study period will be followed up to determine the final outcome. Any serious AE that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation will be recorded and reported immediately.

9.9 Abnormal Clinical Testing Results
If an unexpected abnormal clinical testing result is observed, and is believed to be unrelated to participation in study-related activities, the abnormal result it will be documented as an AE and the study participant will be instructed to consult with their clinical provider to determine if additional testing is needed.

9.10 Relationship and Severity Assessment

The PI, or their delegate, will promptly review documented AEs and abnormal test findings to determine if:

- The abnormal test finding will be classified as an AE
- There is a reasonable possibility that the AE was caused by the investigational device or other study treatments
- The AE meets the criteria of serious AE

If the PI's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the AE will be classified as associated with the use of the investigational device or other study treatments for reporting purposes. If the PI's final determination of causality is "unknown but not related to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective participant's case history.

9.11 AE Relationship Index

The relationship of an AE to the investigational device will be decided by the PI based on all available information at the time of the completion of the CRF and will be graded as follows:

9.11.1 Unrelated

Sufficient information exists to indicate that the etiology is unrelated to the study device; the temporal sequence of the AE onset relative to administration of the study device is not reasonable or the event is clearly related to other factors such as the participant's clinical state, therapeutic intervention, or concomitant therapy.

9.11.2 Remotely Possible

Temporal relationship to device administration which makes a causal relationship improbable, and in which other drugs, chemicals, procedures, surgeries, or underlying disease provide plausible explanations.

9.11.3 Possible

A reasonable relationship to administration of the device could be established but the AE could also be explained by concurrent disease or other drugs, chemicals, procedures, or surgeries.

9.11.4 Probable

A clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the device, unlikely to be attributed to concurrent disease or other drugs, chemicals, procedures, or surgeries.

9.11.5 Definite
A reaction that follows a reasonable temporal sequence from administration of the device, or which is confirmed by imaging or clinical laboratory values, that follows a known or expected response pattern to the study device and/or procedure.

9.12 AE Severity Index
The maximum intensity of an AE during a day will be graded according to the definitions below and recorded in detail as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries will be made having distinct onset dates. The PI will systematically determine the severity of each AE:

9.12.1 Mild
Transient, requiring no special treatment, and tolerable. Does not interfere with daily activities.

9.12.2 Moderate
Sufficient reaction interfering with daily activities and/or reduced level of activity. AE is ameliorated by simple therapeutic measures.

9.12.3 Severe
Significant impairment resulting in an inability to carry out usual activities and/or the participant's life is at risk due to the event. Management may include systemic drug therapy or other treatment.

9.13 AE reporting
When an AE has been identified, the PI will take appropriate action to protect the participant and then complete the Study Adverse Event Worksheet and log. The PI will evaluate the AE and determine the necessary follow-up and reporting required. Then, the PI will promptly review documented UADE and report the results to the FDA within 10 working days and the Mayo Clinic's IRB within 5 working days Thereafter, the PI will submit additional reports as requested.

Additionally, information related to the AE will be recorded on CRFs and within the research database. The PI will review all AE reports to determine if specific reports need to be made to the IRB and FDA. The PI will sign and date the AE report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

9.14 Notifying the FDA
The PI will report all unanticipated AEs to the FDA according to the required reporting timelines, formats, and regulations.

The PI will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported AE that is determined to be an unanticipated AE. A copy of this completed form will be provided to the DSMB and all co-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible, but no later than 10 working days after receiving notice of the AE.

If the results of the PI's follow-up evaluation indicate that an AE that was initially determined to not constitute an unanticipated adverse device effect meets the requirements for reporting, the PI will submit a completed FDA Form 3500A as soon as possible, but no later than 10 working days after the determination was made.

For each submitted FDA Form 3500A, the PI will identify all previously submitted reports that that addressed a similar AE experience and will provide an analysis of the significance of newly reported AE in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the PI will submit additional information concerning the reported AE as requested by the FDA.

Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A.

Contact information for submitting reports:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

9.15 Deviations from the investigational plan

The PI will notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the PI is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA, and IRB notification in accordance with 21 CFR 812.35(a) will occur.

9.16 Stopping Rules

Study enrollment and treatment procedures will be suspended in the event:

- A participant experiences an SAE probably or definitely related to the study device or due participation in the study.
- The PI determines that the study should be discontinued for any reason.

In the event that the study enrollment is suspended for any reason, enrollment and treatment would only be resumed after a thorough review of the incidents and any corrective and preventative actions have been put in place along with consultation between the study team and the IRB.

9.17 Medical Monitoring

Safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious AEs.

9.17.1 Safety Monitoring

Safety monitoring and oversight will be performed the PI. The PI will have the authority temporarily or permanently to discontinue a particular protocol and/or the involvement of a given subject, if deemed necessary or appropriate for the safety of the subject. We will establish an internal Data and Safety Review Group (DSRG) comprised of the co-Investigators. The internal DSRG will meet quarterly. In addition to our internal DSRG, we are prepared to appoint a medical health care professional or appropriate expert with relevant expertise to serve as Independent Safety Monitor. His/her duties will be to review study protocols, procedures, AEs, outcomes, and milestones. If any concern or unexpected issue is identified by the Independent Safety Monitor appointed with any subject that could be of potential risk or concern to other subjects, action will be taken to address, mitigate, and/or eliminate such risk from the study. AEs will be reported immediately, i.e., within 24 hours, to the study coordinator and PI. The PI and independent safety monitor will determine if any action is required to resolve the AE. The PI will also report the AE to the IRB, and to the study coordinator and PI.

9.17.2 Risk Management and Emergency Response

Risks will be managed by study staff who will accompany the subjects, and who will be reachable by cell phone or pager when the subject is not on-site. Study staff will communicate with the PI if any concerns arise.

9.17.3 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The PI will ensure the availability for inspections of applicable study-related facilities (e.g., laboratories, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

9.17.4 Monitoring AEs and Unanticipated Problems

Assessment of AEs (including Unanticipated Problems) will be performed continuously during the study period. Possible AEs will be detected through spontaneous reports by the subject, direct questioning of the subject, and direct examination during study visits. When an AE has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and/or log. Recording for each AE will include a description of the event, whether or not it is considered serious (SAE), duration (onset and resolution dates), severity (mild, moderate, severe), potential contributory factors, treatment rendered, and outcome. The PI will have the

authority temporarily or permanently to discontinue a particular protocol and/or the involvement of a given subject, if deemed necessary or appropriate for the safety of the subject. If any AE or unanticipated problem is identified with one subject that could be of potential risk or concern to other subjects, action will be taken by the PI to address, mitigate, and/or eliminate such risk from the study, with the direction of the Independent Safety Monitor. Any such AE will be reported immediately, i.e., within 24 hours, to the PI. The PI will consult with the Independent Safety Monitor as appropriate, and will determine if any action is required to resolve the AE. The PI will also report any such AE to the IRB. The clinical course of each AE will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. The PI will evaluate all apparent AEs and determine the necessary follow-up and reporting required.

10 DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Participant information will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the PI, by regulation, retains the ability to use all information collected prior to the revocation of authorization. For participants that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status at the end of their scheduled study period.

10.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF will match Source Data recorded on the Source Documents.

10.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded, and all missing data explained as follows:

- If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”.
- If the item is not applicable to the individual case, write “N/A”.
- All entries should be printed legibly in black ink.
- If a data entry error is identified, it will be corrected by drawing a single straight line through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated.
- Clarification of illegible or uncertain entries will be printed above the item, then initialed and dated.

10.4 Data Management

Study Source Data will be kept in hard copy (where applicable) within participant case files, which will be kept in limited-access space reserved for study staff only. Electronic data will be managed within a password-protected study-specific internal database.

10.5 Data Processing

Data will be processed within a study-specific Mayo Clinic internal database. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Original data will be preserved in such a way that any data transformed during processing can be compared to the original data.

10.6 Data Security and Confidentiality

The Mayo Clinic internal database system has built in systems for control of access, data integrity and audit trails. Access and confidentiality are controlled in a manner similar to other institutional systems.

10.7 Data Quality Assurance

A Quality Assurance audit may be conducted by the PI, or designee, at any time during or after this study. The audit may include, but not be limited to:

- A review of all ICFs
- A review of CRFs and source documents
- A review of regulatory documents
- An assessment of trial conduct and compliance
- And a review of investigational device storage and accountability records

10.8 Data Clarification Process

In response to a query on the part of the FDA, or in the event that the Mayo Clinic internal database program identifies a discrepancy, missing value, or other discrepancy in the CRF database, the error will be addressed, and a Data Clarification Form will be completed.

10.9 Records Retention

The PI will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The PI will retain the specified records and reports during the study and for the longer of the following;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717,

   OR

2. A period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

11 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Protocol Compliance Monitoring

Throughout the study, research staff will monitor study protocol compliance by reviewing all protocol-related procedures and records. The PI will oversee compliance and determine the appropriate response to instances that are deemed non-compliant.

11.2 Study Monitoring Plan

The PI will allocate adequate time for study monitoring activities. The PI will also ensure that the monitor, compliance, and/or quality assurance reviewer is provided access to all study-related documents and study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.). Study monitors will be provided adequate space and resources to successfully conduct monitoring activities.

This study will be monitored on a routine basis during the conduct of the trial. The Mayo Clinic Office of Research Regulatory Support will assist the PI with monitoring of the trial. Clinical trial monitoring requires review of the study data generated from protocol activities to ensure the validity and integrity of the data while also protecting the rights and safety of study participants. They will also assist the PI with maintaining compliance to appropriate Food and Drug Administration regulations.

Medical safety monitoring will be conducted on an ongoing basis by medical doctor sub-investigators and clinician study staff with the appropriate credentials to treat this patient population in a clinical setting.

11.3 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The PI will ensure the

capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

The PI will also permit inspection by government regulatory authorities and applicable compliance offices.

12 PRIOR AND CONCOMINANT THERAPY

Participation in therapy regimens prior to study enrollment will not influence the PI's decision regarding enrollment into the study. While enrolled in the study, participants will be asked to follow the instructions from the study staff regarding participation in exercise programming that is outside the scope of this clinical trial.

13 STUDY FINANCES

13.1 Funding Source

This study will be funded by the Mayo Clinic Center for Regenerative Medicine.

13.2 Conflict of Interest

If a conflict of interest is identified by study personnel, (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) it will be reviewed by a Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the PI prior to participation in this study.

13.3 Stipends or Payments

Participants will not be remunerated $500 for time spent performing the activities of this protocol.

14 PUBLICATION OF RESULTS

The PI holds the primary responsibility for publication of the results of this study, deciding authorship, and finalizing the order of authorship. Approval will be obtained from the PI before any information related to this study can be used or passed on to a third party. Once this study is approved, it will be registered to ClinicalTrials.gov.

15 ETHICAL CONSIDERATIONS

This study is to be conducted according to United States government regulations and Mayo Clinic's institutional research policies and procedures.

This protocol, and any future amendments, will be submitted to Mayo Clinic's Institutional Review Board (IRB) for formal approval. The decision of the IRB will be made in writing to the PI before commencement of this study.

All subjects for this study will be provided a consent form that was previously reviewed and approved by the IRB. The consent form will provide an overall description of this study

along with sufficient information of activities the subject is expected to participate in as described within this protocol. The formal consent of a subject will be documented using the IRB-approved consent form. Consent will be obtained before participation in any study-related activities. The consent form must be signed and dated by the subject, or the subject's legally authorized representative. The consent form will also be signed and dated by a research team member that is approved to obtain informed consent.

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

16 REFERENCES

Angeli, C.A. et al., 2014. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*, 137(5), pp.1394–1409.

Aslan, S.C. et al., 2018. Epidural Spinal Cord Stimulation of Lumbosacral Networks Modulates Arterial Blood Pressure in Individuals With Spinal Cord Injury-Induced Cardiovascular Deficits. *Frontiers in Physiology*, 9, pp.1394–11.

Capogrosso, M. et al., 2013. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *The Journal of Neuroscience,* 33(49), pp.19326–19340.
Danner, S.M. et al., 2016. Body Position Influences Which Neural Structures Are Recruited by Lumbar Transcutaneous Spinal Cord Stimulation N. Weidner, ed. *PLoS ONE*, 11(1), pp.e0147479–13.

Danner, S.M. et al., 2011. Can the Human Lumbar Posterior Columns Be Stimulated by Transcutaneous Spinal Cord Stimulation? A Modeling Study. *Artificial Organs*, 35(3), pp.257–262.

Danner, S.M. et al., 2015. Human spinal locomotor control is based on flexibly organized burst generators. *Brain*, 138(3), pp.577–588.
Danner, S.M. et al., 2013. Pattern Generating Networks in the Human Lumbar Spinal Cord: Electrophysiology and Computer Modeling. *Biomedizinische Technik. Biomedical engineering*, 58(SUPPL. 1 TRACK-A).

Dimitrijevic, M.R. et al., 1983. EMG evidence of suprasegmental influence on motor unit activity in paralyzed muscles. *Electroencephalography and Clinical Neurophysiology*, 56(3), p.S68.

Dimitrijevic, M.R., Gerasimenko, Y. & Pinter, M.M., 1998. Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, 860, pp.360–376.
Gad, P. et al., 2017. Weight Bearing Over-ground Stepping in an Exoskeleton with Non-invasive Spinal Cord Neuromodulation after Motor Complete Paraplegia. *Frontiers in Neuroscience*, 11, pp.1394–8.

Gad, P., Lee, S., et al., 2018. Noninvasive activation of cervical spinal networks after severe paralysis. *Journal of Neurotrauma*.

Gad, P.N., Kreydin, E., et al., 2018. Non-invasive Neuromodulation of Spinal Cord Restores Lower Urinary Tract Function After Paralysis. *Frontiers in Neuroscience*, 12, p.432.

Gerasimenko, Y. et al., 2016. Integration of sensory, spinal, and volitional descending inputs in regulation of human locomotion. *Journal of Neurophysiology*, 116(1), pp.98–105.

Gerasimenko, Y., Gorodnichev, R., et al., 2015. Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. *Journal of Neurophysiology*, 113(3), pp.834–842.

Gerasimenko, Y.P., Lu, D.C., et al., 2015. Noninvasive Reactivation of Motor Descending Control after Paralysis. *Journal of Neurotrauma*, 32(24), pp.1968–1980.

Gill, M.L. et al., 2018. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nature Medicine*, 377, pp.1–11.

Grahn, P.J., Lavrov, I.A., Sayenko, D., et al., 2017. Enabling Task-Specific Volitional Motor Functions via Spinal Cord Neuromodulation in a Human With Paraplegia. *Mayo Clinic Proceedings*, 92(4), pp.544–554.

Harkema, S.J., Ditterline, B.L., et al., 2018. Epidural Spinal Cord Stimulation Training and Sustained Recovery of Cardiovascular Function in Individuals With Chronic Cervical Spinal Cord Injury. *JAMA Neurology*.

Harkema, S.J., et al., 2011. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *The Lancet*, 377(9781), pp.1938–1947.

Harkema, S.J., Wang, S., et al., 2018. Normalization of Blood Pressure With Spinal Cord Epidural Stimulation After Severe Spinal Cord Injury. *Frontiers in human neuroscience*, 12, p.83.

Herrity, A.N. et al., 2018. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. *Nature Publishing Group*, 8(1), p.8688.
Hofstoetter, U.S. et al., 2018. Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: Elicitation of posterior root-muscle reflexes. *PLoS ONE*, 13(1), p.e0192013.

Inanici, F. et al., 2018. Transcutaneous Electrical Spinal Stimulation Promotes Long-Term Recovery of Upper Extremity Function in Chronic Tetraplegia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 26(6), pp.1272–1278.
Jilge, B. et al., 2004. Initiating extension of the lower limbs in subjects with complete spinal cord injury by epidural lumbar cord stimulation. *Experimental Brain Research*, 154(3), pp.308–326.

Kakulas, B.A., 1984. Pathology of spinal injuries. Central nervous system trauma: journal of the American Paralysis Association, 1(2), pp.117–129.
Kandel, E., 2013. *Principles of Neural Science, Fifth Edition*, McGraw Hill Professional.
Lu, D.C. et al., 2016. Engaging Cervical Spinal Cord Networks to Reenable Volitional Control of Hand Function in Tetraplegic Patients. *Neurorehabilitation and Neural Repair*, 30(10), pp.951–962.

McKay, W.B. et al., 2004. Clinical Neurophysiological Assessment of Residual Motor Control in Post-Spinal Cord Injury Paralysis. *Neurorehabilitation and Neural Repair*, 18(3), pp.144–153.

Minassian, K. et al., 2004. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Paraplegia*, 42(7), pp.401–416.
Minassian, K., Persy, I., Rattay, F., Dimitrijevic, M.R., et al., 2007. Posterior root-muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord. *Muscle & Nerve*, 35(3), pp.327–336.

Minassian, K., Persy, I., Rattay, F., Pinter, M.M., et al., 2007. Human lumbar cord circuitries can be activated by extrinsic tonic input to generate locomotor-like activity. *Human Movement Science*, 26(2), pp.275–295.

National Spinal Cord Injury Statistical Center, 2017. Spinal Cord injury facts and figures at a glance: 2017 data sheet.

Phillips, A.A. et al., 2018. An Autonomic Neuroprosthesis: Noninvasive Electrical Spinal Cord Stimulation Restores Autonomic Cardiovascular Function in Individuals with Spinal Cord Injury. *Journal of Neurotrauma*, 35(3), pp.446–451.

Pierrot-Deseilligny, E. & Mazevet, D. 2000. The monosynaptic reflex: a tool to investigate motor control in humans. Interests and limits. *Neurophysiol Clin*, 30(2), pp. 67-80.

Rattay, F., Minassian, K. & Dimitrijevic, M.R., 2000. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. Quantitative analysis by computer modeling. *Paraplegia*, 38(8), pp.473–489.

Rejc, E. et al., 2017. Effects of Stand and Step Training with Epidural Stimulation on Motor Function for Standing in Chronic Complete Paraplegics. *Journal of Neurotrauma*, 34(9), pp.1787–1802.

Rejc, E., Angeli, C. & Harkema, S., 2015. Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. *PLoS ONE*, 10(7), pp.e0133998–20.

Roy, F.O.D., Gibson, G. & Stein, R.B., 2012. Effect of percutaneous stimulation at different spinal levels on the activation of sensory and motor roots. *Experimental Brain Research*, 223(2), pp.281–289.

Sayenko, D.G. et al., 2014. Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals. *Journal of Neurophysiology*, 111(5), pp.1088–1099.

Sayenko, D.G., Atkinson, D.A., Dy, C.J., et al., 2015. Spinal segment-specific transcutaneous stimulation differentially shapes activation pattern among motor pools in humans. *Journal of Applied Physiology*, 118(11), pp.1364–1374.

Sayenko, D.G., Atkinson, D.A., Floyd, T.C., et al., 2015. Effects of paired transcutaneous electrical stimulation delivered at single and dual sites over lumbosacral spinal cord. *Neuroscience Letters*, 609(C), pp.229–234.

Sherwood, A.M., Dimitrijevic, M.R. & McKay, W.B., 1992. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *Journal of the Neurological Sciences*, 110(1-2), pp.90–98.

Simpson, L.A. et al., 2012. The health and life priorities of individuals with spinal cord injury: a systematic review. *Journal of Neurotrauma*, 29(8), pp.1548–1555.
Taccola, G. et al., 2018. And yet it moves: Recovery of volitional control after spinal cord injury. *Progress in Neurobiology*, 160, pp.64–81.

West, C.R. et al., 2018. Association of Epidural Stimulation With Cardiovascular Function in an Individual With Spinal Cord Injury. *JAMA Neurology*.