Official Title: **A Pilot Study to Explore the Use of Percutaneous Spinal Stimulation in Participants with Multiple Sclerosis**

NCT Number: **NCT06019611**

Document Date: **05 December 2023**

A Pilot Study to Explore the Use of Percutaneous Spinal Stimulation in Participants with Multiple Sclerosis

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Funding Sponsor:

Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology

Study Product:

Abbott percutaneous trial lead for epidural neurostimulation (Model 3086)
Abbott Neuromodulation
6901 Preston Road
Plano, TX 75024

Ripple Nomad Neurostimulator
Ripple Neuro
2056 South 1100 East
Salt Lake City, UT 84106

Abbott clinician programmer for epidural and dorsal root ganglion neurostimulation (Model 3874)
Abbott Medical
6901 Preston Road
Plano, TX 75024

Protocol Number: (IRBe) 23-003967

IDE Number: G210292

Initial version: 10/01/2021 (Version 1.0)
Revision: 02/08/2023 (Version 2.0)
Revision: 06/13/2023 (Version 2.1)
Revision: 06/23/2023 (Version 2.2)
Revision: 12/05/2023 (Version 2.3)

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BWS	Body weight support
CFR	Code of Federal Regulations
CMSAN	(Mayo Clinic) Center for Multiple Sclerosis and Autoimmune Neurology
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EDSS	Expanded Disability Severity Scale
EMG	Electromyography
ES	Epidural electrical spinal stimulation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protection Office
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MAS	Modified Ashworth Scale
MS	Multiple sclerosis
MSQLI	MS Quality of Life Inventory
NSTEP-MS	NeuroStimulation Therapy to Alleviate Symptoms of Progressive MS
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SCI	Spinal Cord Injury
SOP	Standard Operating Procedure
TUG	Timed up and Go
UADE	Unanticipated Adverse Device Effect

Study Summary

Title	**A Pilot Study to Explore the Use of Percutaneous Spinal Stimulation in Participants with Multiple Sclerosis**
Running Title	**ES in MS**
IRB Protocol Number	**23-003967**
Phase	**Pilot Study**
Methodology	**Prospective study**
Overall Study Duration	**3-year duration**
Subject Participation Duration	**Less than 2 months per subject**
Objectives	**a) Evaluate the effectiveness of percutaneous ES and task-specific training in participants with Progressive MS to impact motor function and spasticity.** **b) Investigate the potential of ES and task-specific training to impact non-motor spinal related dysfunction in the same participants.**
Number of Subjects	**10 subjects**
Diagnosis and Main Inclusion Criteria	**Multiple Sclerosis with EDSS of 6.5**
Study Device	**Abbott percutaneous trial lead for epidural neurostimulation (Model 3086)** **Ripple Nomad Neurostimulator** **Abbott clinician programmer, (Model 3874)**
Duration of Exposure	**All subjects will complete 1 month of temporary epidural spinal stimulation (ES) with task-specific training.**
Reference therapy	**The reference therapy is clinical rehabilitation with MS.**
Statistical Methodology	**Descriptive statistics will be used to describe stimulation-related outcomes. Repeated measures analyses of variance will be used to detect changes in outcomes pre- to post-ES and training.**

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

Up to 75% of patients with MS develop progressive MS, and there is no current treatment to halt clinical progression or axonal loss in patients with progressive MS. Progressive MS is

defined by a sustained clinical worsening, typically of walking difficulties, over more than 1 year in the absence of clinically detectable MS relapses or attacks (Thompson et al., 2018). Pathologically, it is characterized by axonal loss in the absence of inflammatory disease. Patients typically have progressive difficulty walking with associated leg spasticity and urinary, bowel and sexual dysfunction.

Like MS, there is no cure for traumatic injury of the spinal cord which results in lifelong impairment of autonomic, sensory, and motor functions in regions of the body that are distal to the damaged areas of the spinal cord. In response to the complete lack of available therapies to restore volitionally-controlled lower extremity motor function, we recently conducted a pilot-phase clinical trial of epidural spinal electrical stimulation (ES) in combination with task-specific training; ES consists of an implanted stimulator and electrode array placed over the dura mater on the dorsal aspect of the spinal cord. ES with task-specific training resulted in unprecedented outcomes, such as restoration of standing and walking in humans previously diagnosed with complete paralysis of their lower extremities due to a traumatic spinal cord injury (SCI) that occurred several years prior (M. Gill et al., 2020; M. L. Gill et al., 2018; Grahn et al., 2017). Likewise, other research teams have shown remarkable improvements in spinal stimulation-enabled motor functions that are retained after study participation in individuals with incomplete paralysis (Wagner et al., 2018). Herein, we propose leveraging the knowledge and expertise gained during our previous, and active, clinical trials of ES in participants with paralysis to determine the translational potential of epidural spinal electrical stimulation (ES) for improvement of motor function and spasticity in patients with myelopathy due to progressive multiple sclerosis (MS). The following are key aspects of the proposed work:

- ***The proposed research is a pilot study which will explore epidural spinal stimulation (ES) in combination with task-specific training to improve lower limb function in 10 participants with Progressive MS.***
- ***We will temporarily implant percutaneous ES leads through the skin overlying the lumbosacral enlargement and remove the leads following the 4-week study.***
- ***Participants will serve as their own control via a comparison of pre- and post-stimulation outcomes and outcome metrics captured during ES and when ES is off.***
- ***Safety will be continuously evaluated during the 4-week stimulation and task specific training period, and during a post lead removal neurologist visit.***
- ***The percutaneous leads are currently used clinically and are approved for patients with low back pain; use in participants with MS will be possible under an FDA IDE.***

1.1 Background

Clinical Presentation of Progressive Multiple Sclerosis

Multiple sclerosis (MS) is characterized by inflammatory central nervous system demyelination which can be subclinical or clinical. Clinical attacks typically manifest as optic neuropathy, sensory or motor myelopathy, which worsen over days to weeks and resolve over weeks to months. Most patients recover a significant degree of function following a clinical attack. Although clinical recovery occurs, persistent demyelination or partial remyelination of the lesion is present. The partially denuded axons redistribute sodium-potassium ATPase channels along the axon to compensate for the myelin loss. This results in increased energy expenditure, and loss of signal coherence in the remaining axons.

Mitochondrial expansion is necessary within the affected axons to compensate for the increased energy demand. Rapid mitochondrial expansion is associated with defects in mitochondrial replication, which ultimately leads to energy failure in the affected axons, and axonal loss. The stressed neurons subsequently retract synaptic connections and disengage from neural networks, triggering additional metabolic stress and engagement of transcriptional programs that push the neurons, axons, and circuits away from homeostasis. Clinically, this manifests as slow worsening of walking ability in the absence of clinical relapses. The presence of progressive disease does not exclude the presence of inflammatory disease. Medications which have been approved for the treatment of progressive MS, exclusively treat the inflammatory component of the disease. No pharmacologic agent has yet been shown to prevent or reverse neuronal death and axonal loss in MS. This process occurs typically over decades, and appears to be an age dependent phenomenon, with the onset of motor progression becoming apparent in the late fifth decade.

Patients typically have gradual worsening of walking with associated leg spasticity and urinary, bowel and sexual dysfunction. Recent work from our group has shown that progressive motor dysfunction in MS is most common in patients who have spinal cord lesions or lesions in the brainstem involving the motor tracts (Kassa et al., 2021; Keegan et al., 2018; Sechi et al., 2019). This can occur even in the presence of a single cord lesion, and in the absence of brain disease. This provides a good rationale for targeting spinal cord disease as a therapeutic target in patients with progressive MS. Crucially, although progressive MS is characterized by axonal loss, complete loss of axons in any particular tract is unusual, meaning that if conduction block and slowing can be overcome, there is potential to facilitate volitional motor function.

Stimulation in MS and SCI

Other research groups have shown benefit of transcutaneous (through the skin) lumbar stimulation in improving spasticity (Keegan et al., 2018), gait dysfunction (Keegan et al., 2018), postural instability (Roberts et al., 2021), and bladder dysfunction (Kreydin et al., 2020) in participants with MS. However continuous use of transcutaneous stimulation is impractical due to the delivery through the skin using an external device, and the results are likely to be short lived in the absence of continued stimulation. By contrast, permanently implanted epidural stimulation leads are widely used in clinical practice for the management of chronic pain. These allow for continuous stimulation which can easily be manipulated to optimize response through means of a remote-control device. Significant progress has been made in the research use of these permanent leads for spinal stimulation in participants with SCI, to enable motor functions previously thought to be permanently lost after SCI. Specifically, Harkema and colleagues reported that, after months of rehabilitation with permanently implanted spinal stimulators for ES, volitional control of joint-specific muscles and independent standing were achieved by four humans with motor complete paraplegia (Angeli et al., 2014; S. Harkema et al., 2011). Recently, our team reported that the same intervention enabled control of stepping leg movements, which over the course of rehabilitation, translated to independent standing and stepping (M. L. Gill et al., 2018; Grahn et al., 2017).

Our initial case report described that our study goals were achieved within the first few sessions of permanent ES. To summarize, in the first study participant we enrolled, ES

enabled: 1) intentional control of motor activity and leg movement; 2) standing; 3) intentional control of step-like movements while side lying with legs suspended in a gravity neutral position, and 4) intentional control of bilateral leg flexion and extension while upright with body weight supported by a harness. More recently, we reported that the same participant achieved independent standing, stepping on a treadmill while using arm support bars to maintain balance, and posture and over ground walking with minimal assistance (M. L. Gill et al., 2018). To date, the second participant demonstrated similar ES-enabled motor achievements. In addition to reports of ES enabling lower extremity motor functions, improvements in upper extremity(Lu et al., 2016), cardiovascular (Aslan et al., 2018; S. J. Harkema, Legg Ditterline, et al., 2018; S. J. Harkema, Wang, et al., 2018; Herrity et al., 2018; West et al., 2018), and urologic functions (Herrity et al., 2018) have been reported in participants with SCI.

Prior to proposing a trial to assess the use of permanently implanted epidural spinal stimulation in participants with progressive MS, it is pertinent to assess whether these individuals are responsive to stimulation using a temporary percutaneous lead used commonly in clinical practice for low back pain and in research for participants with spinal cord injury.

1.2 Investigational Device

Abbott percutaneous trial lead for epidural neurostimulation (Model 3086)

Ripple Nomad Neurostimulator

Abbott clinician programmer (Model 3874)

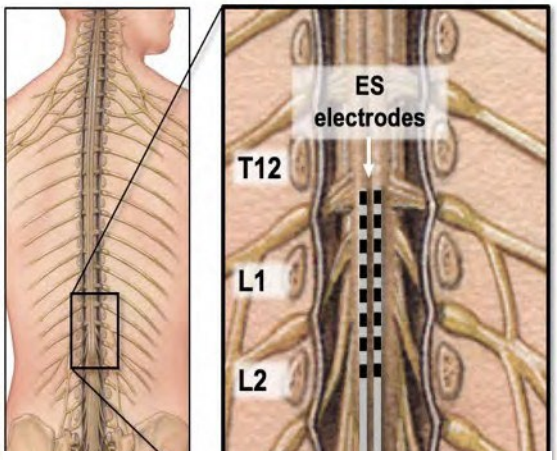


Figure 1. *Epidural stimulation (ES) will be delivered via percutaneous electrodes implanted over the dura mater of the lumbosacral enlargement.*

The temporary percutaneous implantation of epidural stimulation (ES) electrode leads along the dorsal epidural surface of the lumbosacral enlargement (Figure 1) will be performed to activate spinal networks in ten humans diagnosed with Progressive MS. The externalized ends of the ES electrode leads will be connected to the Nomad neurostimulation system. By delivering ES over the spinal cord during task-specific training for one month, we aim to quantify motor and non-motor improvements.

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 how ES may enable functions in humans with multiple sclerosis.

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

1.4.1 Study Rationale

There is no cure for MS, which results in gradual loss of many functions and a significant reduction in quality of life. In parallel, there is no cure for traumatic injury of the spinal cord which results in lifelong impairment of autonomic, sensory, and motor functions in regions of the body that are distal to the damaged areas of the spinal cord. In response to the complete lack of available therapies to restore volitionally-controlled lower extremity motor function, we recently conducted a pilot-phase clinical trial of epidural spinal electrical stimulation (ES) in combination with task-specific training for individuals with complete SCI. Likewise, other research teams have shown remarkable improvements in spinal stimulation-enabled motor functions that are retained after study participation in individuals with incomplete paralysis (Wagner et al., 2018). Herein, we propose leveraging the knowledge and expertise gained during our previous, and active, clinical trials of ES in participants with paralysis to determine the translational potential of ES for improvement of motor function and spasticity in patients with myelopathy due to progressive MS. Completion of the proposed experiments in this protocol will provide data that can be used to improve the scientific understanding of how ES may enable functional improvement after MS onset. This knowledge will be used to help determine if ES is a viable and useful tool in determining which subjects may be best suited for permanently implanted ES in the future.

1.4.2 Anticipated Risks

Risks associated with task-specific training:
In combination with 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 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.
- 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 possible risk factor for subjects as well.

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 electromyography

Risks involved with EMG include skin irritation or allergic reaction from the adhesive used to apply sensors.

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. 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 subjects 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, 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 2 months. Subjects will receive ES and task-specific training sessions for 1 month. Electrodes will be removed following 1 month of sessions.

2 Study Objectives

We propose to compare motor and non-motor outcomes over the course of 1 month of ES in combination with task-specific training in participants with Progressive MS.

2.1 Primary Objective

The primary objective is to evaluate the effectiveness of percutaneous ES and task-specific training over 1 month in participants with Progressive MS to impact motor function and spasticity.

2.2 Secondary Objective

The secondary objective is to investigate the potential of ES and task-specific training to impact non-motor spinal related dysfunction in the same participants with Progressive MS.

3 Study Design

3.1 General Design

This is a pilot study that will include a total of 10 subjects with Progressive MS (EDSS 6.5). All subjects will complete 1 month of ES and task-specific training. Expected duration of subject participation is less than 2 months. Baseline assessments will be obtained prior to implantation and post-stimulation assessments will be obtained prior to explantation, with stimulation on and off.

SCREENING	BASELINE	STIMULATION	POST-STIMULATION	STUDY END
Assessment of Inclusion/Exclusion criteria by study team	Baseline Assessments	Minimum 12 Sessions	End Assessments	
	Clinical, Electromyography, Movement Assessments& Surveys	Stimulation + Task-Specific Training	Clinical, Electromyography, Movement Assessments & Surveys	
	No Stim	**Percutaneous Stimulation**	**Stim on/Stim off**	
1-month pre-enrollment	*Week 0-1*	*Weeks 1-4*	*Week 4-5*	

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 voluntary movement assessments, gait analysis, and functional mobility tests to be the primary sets of endpoints used to quantify ES-related datasets associated with addressing the specific aims of this proposal.

Secondary Study Endpoints

Secondary endpoints include spasticity and MS Quality of Life Inventory.

		Pre/ No Stim	Stimulation + Task-specific Training				Post/ Stim ON and OFF
Outcomes	**Specific Measure**	**wk 0**	**wk 1**	**wk 2**	**wk 3**	**wk 4**	**wk 4/5**
Primary							
Gait Analysis	**EMG, Kinematics, Kinetics**	**X**					**X**
Voluntary Movement	**EMG, Kinematics**	**X**	**X**			**X**	**X**
Spasticity	**MAS, Pendulum Test**	**X**					**X**
Secondary							
Functinal Mobility	**TUG**	**X**					**X**
MS Quality of Life Inventory	**MSQLI**	**X**					**X**

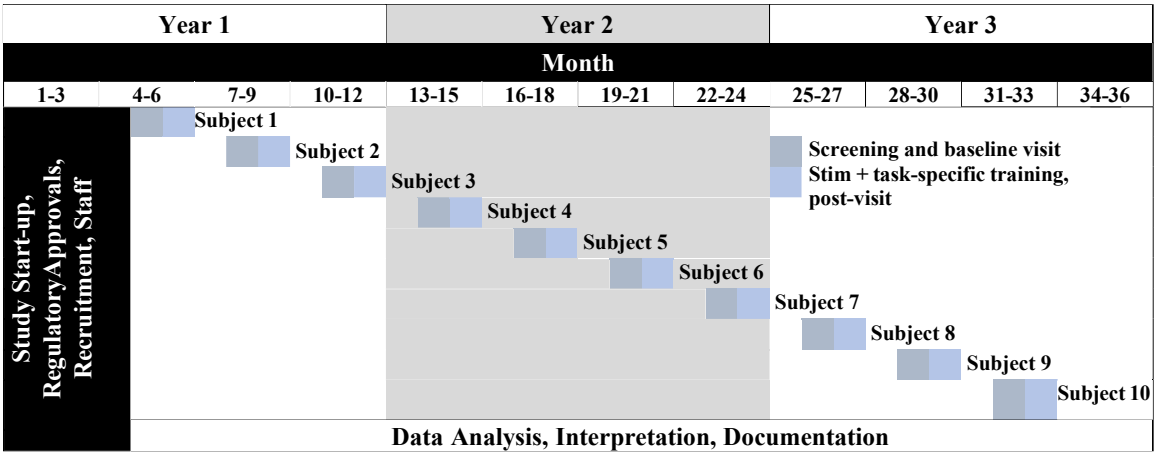
3.3 Primary Safety Endpoints

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 the neurostimulator device as well as to those that could arise from performing the task-specific training sessions. Participants 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 device, X-ray imaging will be performed. To limit adverse events that could result from operating the device, stimulation parameters will be selected within safe ranges as provided by the manufacturer.

4 Subject Selection, Enrollment and Withdrawal



Ten subjects with a diagnosis of Progressive MS (EDSS 6.5) will be enrolled. Subjects will be selected based on the following criteria:

4.1 Inclusion Criteria

- Myelopathy secondary to Progressive MS
- No clinical or radiologic MS relapses for > 5 years
- EDSS score of 6.5 (constant bilateral assistance required to walk about 20 meters without resting) as assessed by a Neurologist with a specialty in MS
- Able to ambulate 10 feet independently with or without gait aid use
- At least 21 years of age
- No changes to spasticity medications or dalfampridine over the last 3 months

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
- Spasticity (grade of 4) measured bilaterally in two muscle groups using Modified Ashworth Scale (MAS). Muscle groups tested will include bilateral knee flexors, extensors; ankle plantarflexors, dorsiflexors
- Unhealed decubitus ulcer
- Unhealed skeletal fracture
- Receiving diathermy treatment
- Active participation in an interventional clinical trial

- Any illness or condition which, based on the research team's assessment, will compromise the patient's ability to comply with the protocol, patient safety, or the validity of the data collected during this study.
- History of coagulopathy or other significant cardiac or medical risk factors for surgery
- Ventilator-dependent respiration
- Diagnosed with cardiopulmonary dysfunction (e.g., chronic obstructive pulmonary disease, cardiac failure, or heart arrhythmia)
- Untreated clinical diagnosis of depression
- History of frequent hypotension characterized by light headedness, or loss of consciousness
- History of frequent hypertension characterized by headache, or bradycardia
- Any active, implanted medical device
- Treatment of chemodenervation and/or neurolysis during the trial, or within 6 months of initiating the trial

4.3 Subject Recruitment, Enrollment and Screening

We will initially recruit participants from existing resources including individuals who have expressed interest in clinical research through the Mayo Clinic Multiple Sclerosis Clinic, Mayo Clinic volunteer research participant database, Mayo Clinic clinical trials website, Mayo Clinic electronic medical record, and ClinicalTrials.gov. The Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology (CMSAN) has prospectively enrolled over 1000 patients with MS in an observational biorepository study. These patients are consented for further contact to discuss enrolment in clinical trials, such as the proposed study. In addition, a subspeciality MS clinic is run daily, 52 weeks per year. Patients are seen by neurology, physiatry, urology, ophthalmology, and neuropsychology. Mayo Clinic's prior research in progressive MS, particularly in remyelinating therapies has resulted in a continuous stream of solicitations from candidates interested in therapy for progressive MS. The rate of up to four subjects enrolled annually will be easily achievable. We have successfully recruited individuals with similar inclusion/exclusion criteria as the proposed work, and we have had very successful recruitment, retention, and compliance.

Prior to participating in the screening phase, a member of the research team will provide an explanation of the study and answer questions asked by the potential study participant.

Participants 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 participant and the PI. A copy of the signed consent documents will be provided to the subject. Following informed consent, screening tests will be performed. A final decision on study participation will be made by the PI and study team.

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 explanted. If explanation surgery is urgent due to concern for the subject's health, the cost of the explanation procedure will be covered by the research study. Aside from standard recovery, no adverse effects are anticipated from the removal of percutaneous electrical stimulator.

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, Abbott Neuromodulation; Nomad, Ripple Neuro)

The ES electrode lead is an implantable neurostimulation device that is FDA-approved for treatment of neuropathic pain disorders. Up to two ES electrode 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 to deliver electrical pulse waveforms to the epidural surface.

5.2 Method for Assigning Subjects to Treatment Groups

Subjects will be all receive ES combined with task-specific training.

5.3 Preparation and Administration/Implantation of Investigational Device

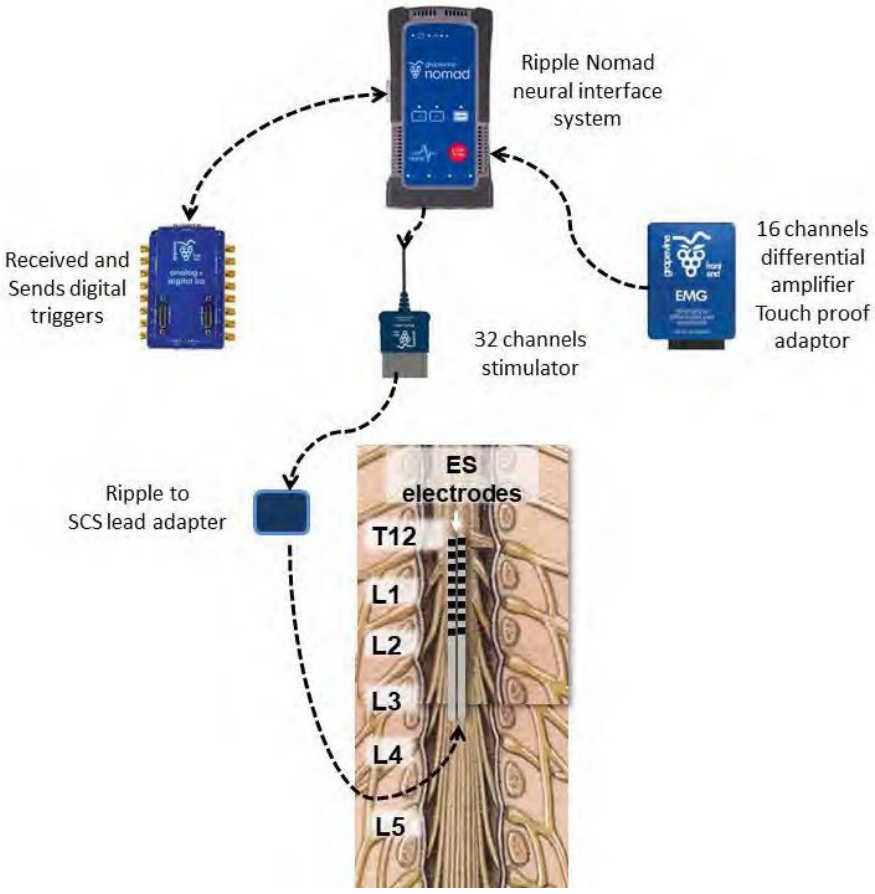
Description of ES system implantation/administration

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.

To implant the temporary spinal electrodes, under fluoroscopy an electrode insertion needle will be placed into the epidural space using a paramedian approach and loss of resistance technique to advance through 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 advancedinto the epidural space.



Then, the leads are advanced in an anterograde fashion to the level of the lumbosacral enlargement utilizing 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. One day post implantation, the first follow up will take place to evaluate for adverse events. Trained

team members will monitor the percutaneous site on an ongoing basis during training session to ensure the site remains intact and sterile. Study team members have received training from a registered nurse within the pain specialty program at Mayo Clinic.

Procedure to explant ES electrode leads
After completing task-specific training 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 task-specific training. Participants will be followed up within 5 days of explantation for adverse events. They will be provided information for monitoring the site remotely as well.

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. If the subject fits the inclusion criteria and does not demonstrate any exclusion criteria characteristics, 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 concurrent activities. For example, if the study subject performed locomotor training at a local gym prior to the study, they would be asked to continue 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 not be blinded, and allparticipants will receive the same treatment.

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

The percutaneously-delivered ES electrode leads will be acquired either through purchase or donation from Abbott. A representative from Abbott will ship the devices to Mayo Clinic and will be properly inventoried prior to the scheduled date of surgical implantation.

The Nomad neurostimulation system has been 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

ES electrode leads will be stored within a secured surgical materials area at Mayo 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

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 thecause 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. The following tests/activities will be performed to determine eligibility based on the inclusion/exclusion criteria listed in this document.

- Review of available medical records
- Neurology and Physical Medicine and Rehabilitation clinical exams
- EDSS score evaluation
- Pregnancy test
- Spasticity examination
- Evaluation of rehabilitation task ability and range of motion of impaired joints
- Spine MRI
- Body weight

6.2 Epidural Electrical Stimulation (ES)

Study engineers, physical therapists, and research technicians perform the device programming and determine maximum stimulation parameters in real time. Device operators have been trained by industry partners (i.e., Abbott) on device manipulation during previous studies utilizing the same technology in SCI patients.

The surface area of each OCTRODE electrode is 0.1319 cm^2 based on manufacturer's specifications.

Based on literature, we conclude that stimulation that results in a charge density per pulse of no more than 30 μC/cm^2, poses no safety concerns.

The charge density per pulse is defined by multiplying the stimulation current amplitude originating from an electrode by the pulse width of the stimulation pulse and dividing by the total electrode surface area.

The lower limit for current amplitude per electrode that will be applied in this study is 0.1 mA; The lower limit for the pulse width that will be applied in this study is 250 μs. Therefore, if we applied the lower limit stimulation amplitude of 0.1 mA, the upper limit of pulse width that could be selected to stay below the current density per pulse threshold per pulse is 39570 μs; since the manufacturing limit of the device is 1000 μs, 1000 μs will be selected as the pulse width upper limit for this study. Similarly, if a stimulation pulse width of the stated minimum of 250 μs was selected, up to 15.8 mA could be applied to stay below the charge density per pulse threshold; therefore, 15.8 mA will be selected as the upper limit for current density in this study. No combination of parameters will be selected to drive the charge density per pulse over 30 μC/cm^2 (S.F Cogan et al., 2016; Mccreery et al., 1990).

ES task-specific daily training 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 at least 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 thebody 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 willbe 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. At or near the conclusion of the training regimen, a Neurologist with a specialty in MS will conduct a clinical examination with stimulation turned on.

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 either ES lead.

6.3 Period of Follow-Up after ES

After 1 month of ES and task-specific training, each subject will be asked to complete follow-up assessments.

6.4 Outcome Measures

The following outcome measures will be collected 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.

		Pre/ No Stim	Stimulation + Task-specific Training				Post/ Stim ON and OFF
Outcomes	**Specific Measure**	**wk 0**	**wk 1**	**wk 2**	**wk 3**	**wk 4**	**wk 4/5**
Primary							
Gait Analysis	**EMG, Kinematics, Kinetics**	**X**					**X**
Voluntary Movement	**EMG, Kinematics**	**X**	**X**			**X**	**X**
Spasticity	**MAS, Pendulum Test**	**X**					**X**
Secondary							
Functinal Mobility	**TUG**	**X**					**X**
MS Quality of Life Inventory	**MSQLI**	**X**					**X**

Aim 1 will quantify the effect of ES and task-specific training on lower extremity motor function in individuals with severe lower extremity motor disability due to progressive MS using the ***primary outcomes*** of kinematics (movement), kinetics (forces), and electromyography (muscle activity, EMG) collected during gait, standing, and side lying motor tasks. Data will be reduced and summarized using standard biomechanical approaches, to quantify gait rhythm, lower extremity joint and body center of mass ranges of motion (during gait, standing, and side lying), and timing of muscle activations and ground reaction force peaks. ***Secondary outcomes*** include functional mobility assessments utilizing motion capture data, as well as the Timed Up and Go (TUG) test. Safety and tolerability will be assessed while monitoring vital signs and stimulation responsiveness during daily sessions and testing dates.

Aim 2 will determine the impact of ES and task-specific training on non-motor spinal related dysfunction in individuals with severe lower extremity motor disability due to progressive MS using the ***primary outcomes*** of the qualitative pendulum test (Smith et al., 2000) and the Modified Ashworth Scale to describe spasticity levels. ***Secondary outcomes*** will include the MS Quality of Life inventory that includes questions about bowel, bladder and sexual function, quality of life and pain, among others.

Aim 3 will be an ***exploratory aim*** to collect electrophysiological and biomarker data that may help us gain a mechanistic understanding of findings in Aims 1 and 2. To assess the

functional states of **spinal connectivity**, we will deliver transcutaneous electrical stimulation via pulses of 1 ms duration at intensities of up to 100 mA using biphasic, charge balanced stimulation (DS8R, Digitimer Ltd., UK). Stimulation will be delivered to the skin over the intra-spinous space between the spinous processes of the T10, T11, T12, L1, L2vertebrae, with subjects in a supine position. Evoked

potentials will be recorded via surface EMG electrodes placed bilaterally over the rectus femoris, vastus lateralis, medial hamstring, tibialis anterior, medial gastrocnemius, and soleus muscles. We will record evoked potentials while relaxed using stimulus intensities from 1-100 mA at increments of 10 mA for each stimulus locationT10-L2. Stimulus intensities that are at the threshold for evoking motor potentials will be delivered during the following actions: while attempting prolonged maximal contractions of all muscles; during attempts to contract the left leg; and during attempts to contract the right leg.

Gait analysis: Full body kinematic parameters will be acquired with a computerized video motion analysis system. A surface electromyography (EMG) system will be used for data collection. Muscle activity will be collected from all or a subset of the following lower extremity and trunk muscles: soleus, gastrocnemius, tibialis anterior, hamstrings, quadriceps, hip adductors, gluteus maximus, gluteus medius, abdominals and spinal extensors. Ground reaction force data will be acquired from force plates or pressure mat technology located in the floor or as in-shoe sensors. EMG and ground reaction force data will be time-synchronized with the motion cameras.

Voluntary movement in side-lying and supine postures: Voluntary movement data will be acquired during a variety of volitional tasks including standing, and supine and side-lying stepping movements. Kinematics and EMG measurements will be obtained from a motion analysis system and surface EMG system. All or 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 and spinal extensors.

Spasticity: One or both of the following will be used to measure lower extremity spasticity: the Modified Ashworth Scale (MAS) (Bohannon et al., 1987) where the subject will be placed in a supine position and flexor and extensor muscles are assessed according to the MAS protocol; and the pendulum test which is a biomechanical method of evaluating muscle tone using surface-based kinematic assessments that uses gravity to provoke muscle stretch reflexes during passive swinging ofthe lower limb.

Functional mobility test: The following test will be performed: Timed Up and Go (TUG) (Podsiadlo et al., 1991). The TUG test is used to assess a person's mobility and requires both static and dynamic balance.

MS QOL Inventory (MSQLI): Multiple Sclerosis Quality of Life Inventory (Fischer et al., 1999), a comprehensive outcomes assessment battery will be administered to assess many facets of the participants' quality of life. Several scores, are captured, including Overall Health Status, Modified Fatigue Scale, Sexual Satisfaction Scale, Bladder Control Scale, Bowel Control Scale, Perceived Deficits Questionnaire and Mental Health Inventory.

7 Statistical Plan

7.1 Sample Size Determination

Due to the pilot phase of this study, no formal power calculations were performed for this proposal. The number of subjects was selected based on budgetary, space, and personnel time constraints. Ten participants (five males; five female) will be enrolled to complete this study, depending on need for contingency subjects. Participants will receive 4 weeks of ES and serve as their own control.

7.2 Statistical Methods

Statistical Methods: Continuous data will be summarized as median (inner quartile range). Categorical data will be presented as frequency (percentage). Graphical presentations of subject-level data will be used for all endpoints. Individual data points will be plotted over time, from pre to post stimulation and training.

Modeling: Statistical models will be used both to estimate the ES effect on endpoints, as well as to provide estimates of variability to enable sample size estimation for future studies. Models for post-ES treatment will be fit using linear regression using the baseline measure as a covariate. Both the ES treatment effect and the residual variance estimate will be reported. Standard deviations of the differences in pre- and post-ES measurements will also be reported. Furthermore, correlations between pre- and post-ES assessments, as well as post task specific training stim-off and stim-on assessments will be calculated to aid future study design. Transformations of endpoints to achieve symmetry in the distribution (normality will be difficult to assess with this sample size) will be used as necessary.

Handling of Missing Data: Due to the small sample size, sophisticated missing data techniques like imputation are likely to be unreliable. For all analyses, only subjects with complete data for the necessary analysis will be included. We will attempt to limit missing data by only enrolling participants who have the physical capacity to complete the training sessions. Only prospective enrollees who have been fully optimized from a rehabilitation point of view will be offered enrollment in the study. To minimize the financial burden on study participants and their families, they will be offered money to offset the cost of travel and accommodation during the study. If a study participant ends the study early, a similar replacement participant will be sought. Missing data in survey instruments will be minimized by allocating time during the study for survey completion, and inspection for completion by study coordinators before moving to the next component of the study.

7.3 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 most of the study visits and procedures.

8 Safety and Adverse Events

All adverse events 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 submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will not be reported.

8.1 Definitions

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan orIDE 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 subjects.

Adverse Effect (Event)
Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

Associated with the investigational device: There is a reasonable possibility that theadverse effect may have been caused by the investigational device.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view ofeither the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, mighthave caused death.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, 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.

Unanticipated adverse effect: Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol orelsewhere in the current IDE application.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities thatmeet the definition of an adverse event must also be recorded and documented as an adverseevent.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be

documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event 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 ofan 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 thestudy, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably berelated to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets all of the following three criteria:
Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for thesubject or others (including individuals who are not research subjects). These include:
(1) death; (2) life threatening adverse experience; (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, **AND**
Unanticipated: (i.e. unexpected) problems or events are those that are not alreadydescribed as potential risks in the protocol, consent document, not listed in the Investigator'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 orevent is "unanticipated" when it occurs at an

increased frequency or at an increased severity than expected, **AND**
Related: A problem or event is "related" if it is possibly related to the researchprocedures.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate AE worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects 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 adverse effect and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

Causality and severity assessment
The sponsor-investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or other study treatments; and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the sponsor-investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the adverse effect will be classified as associated with the use of the investigational device or other study treatments for reporting purposes. If the sponsor-investigator'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 subject's case history.

8.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event 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 log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within 10 working days and Mayo IRB within 5 working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

8.3.1 Sponsor-Investigator Reporting, Notifying Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

The sponsor-investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the sponsor-investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

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

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process

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

The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health

Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Deviations from the investigational plan.
The sponsor-investigator shall 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 subject 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 sponsor-investigator 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) also is required.

8.4 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.

8.5 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects 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 subject revokes authorization to collect or use PHI, the investigator, by

regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 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, subjects' 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, subject 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 shall match the Source Data recorded on the Source Documents.

9.3 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.

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.

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.

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.

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

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.

9.4 Records Retention

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

The sponsor-investigator 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.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

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 an independent medical monitor, a physiatrist co-director of the Mayo Clinic Rehabilitation Medicine Research Center.

10.2 Auditing and Inspecting

The sponsor-investigator 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 sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

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.

12 Study Finances

12.1 Funding Source

This study will be funded by the Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the

study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

Participants will be offered a $1,000 remuneration to be submitted at the end of the study. If they do not complete the study, they will be paid $55.55 per visit attended. They will also be offered parking passes for the Mayo Clinic lots on an ongoing basis.

13 Publication Plan

The PI holds the primary responsibility for publication of the results of this study, deciding authorship, and finalizing the order of authorship. If multiple manuscripts result from the research, authorship will be aligned with individuals' expertise and career objectives. 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.

14 References

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