BMJ Open

Effect of epidural spinal cord stimulation after chronic spinal cord injury on volitional movement and cardiovascular function: study protocol for the phase II open label controlled E-STAND trial

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To cite: Darrow DP, Balser DY, Freeman D, *et al*. Effect of epidural spinal cord stimulation after chronic spinal cord injury on volitional movement and cardiovascular function: study protocol for the phase II open label controlled E-STAND trial. *BMJ Open* 2022;**12**:e059126. doi:10.1136/bmjopen-2021-059126

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059126).

Received 09 November 2021
Accepted 17 June 2022

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ABSTRACT

Introduction Spinal cord injury (SCI) leads to significant changes in morbidity, mortality and quality of life (QOL). Currently, there are no effective therapies to restore function after chronic SCI. Preliminary studies have indicated that epidural spinal cord stimulation (eSCS) is a promising therapy to improve motor control and autonomic function for patients with chronic SCI. The aim of this study is to assess the effects of tonic eSCS after chronic SCI on quantitative outcomes of volitional movement and cardiovascular function. Our secondary objective is to optimise spinal cord stimulation parameters for volitional movement.

Methods and analysis The Epidural Stimulation After Neurologic Damage (ESTAND) trial is a phase II single-site self-controlled trial of epidural stimulation with the goal of restoring volitional movement and autonomic function after motor complete SCI. Participants undergo epidural stimulator implantation and are followed up over 15 months while completing at-home, mobile application-based movement testing. The primary outcome measure integrates quantity of volitional movement and similarity to normal controls using the volitional response index (VRI) and the modified Brain Motor Control Assessment. The mobile application is a custom-designed platform to support participant response and a kinematic task to optimise the settings for each participant. The application optimises stimulation settings by evaluating the parameter space using movement data collected from the tablet application and accelerometers. A subgroup of participants with cardiovascular dysautonomia are included for optimisation of blood pressure stabilisation. Indirect effects of stimulation on cardiovascular function, pain, sexual function, bowel/bladder, QOL and psychiatric measures are analysed to assess generalisability of this targeted intervention.

Ethics and dissemination This study has been approved after full review by the Minneapolis Medical Research Foundation Institutional Review Board and by the Minneapolis VA Health Care System. This project has received Food and Drug Administration investigational device exemption approval. Trial results will be disseminated through peer-reviewed publications, conference presentations and seminars.

Trial registration number NCT03026816.

Strengths and limitations of this study

- ⇒ This is the first study to use a validated quantifiable outcome to objectively measure volitional movement and autonomic function during epidural stimulation in participants with motor complete spinal cord injury.
- ⇒ The high-volume data collected in this study will be used to assess for optimal stimulation programming parameters.
- ⇒ The criteria for participation are broadened compared with other studies, and participant time and effort investment are limited, allowing the evaluation of populations at varying levels of preparticipation functional status.
- ⇒ Because the inclusion criteria are broadened, more aggressive outcome measures such as standing training are not assessed due to potentially increased risk.
- ⇒ As this study involves no preparatory rehabilitation, the effect size of the function demonstrated with stimulation may be smaller than other studies.

INTRODUCTION

Spinal cord injury (SCI) is a chronic condition with complications that affect all physiological systems, and patients routinely endure challenging secondary dysfunction in cardiovascular, respiratory, urinary and gastrointestinal systems in addition to complex pain syndromes and morbid pressure ulcers.[1] Clinical treatment of SCI has focused on reducing the morbidity and mortality of

these secondary effects.[2–5] Attempts to restore functional connectivity within the spinal cord have achieved limited success in large clinical trials.[6 7]

The discovery of central pattern generators (CPGs) in the spinal cord[8 9] has led to efforts to activate these circuits through many methods of electrical stimulation to restore or force patterned locomotion, which has been successful in animal models.[10 11] A study investigating the use of epidural spinal cord stimulation (eSCS) to initiate CPG-mediated locomotion discovered its potential to restore supraspinal control of movement in patients with motor complete paraplegia.[12] Patients categorised as American Spinal Injury Association Impairment Scale (AIS)[13] A or AIS B motor complete SCI regained the ability to volitionally move or stand years after their original injury when stimulation was combined with structured, intensive and long-term rehabilitation.[14] Since this discovery, reported outcomes from several small single-arm trials have consistently shown recovery of volitional movement with possible improvement in autonomic function.[15–17]

Several factors have limited the breadth and scope of clinical trials for eSCS to restore volitional function in motor complete SCI. Existing trial protocols are time and labour intensive, requiring substantial preimplantation and postimplantation physical therapy and monitoring in a heavily staffed assessment centre with unique outcome measures.[12 14 15 17–19] These trials require daily in-person appointments for 30–80 min/day for 1 or more years.[17] While these factors are necessary in trials focused on assessing the joint efficacy of rehabilitation and eSCS, they also limit the generalisability and specificity of the treatment in these intensive trials. Trials that necessitate daily or weekly intervention may require participants to relocate near the institution, which may not be an option for several patients with SCI.

Summarising and quantifying the changes in volitional movement also remains a challenging aspect of evaluating trial effectiveness. While structured tasks have been created to non-invasively capture electromyography (EMG) to correlate with volitional commands, sufficiently summarising changes across pertinent muscle groups remains an active area of research.[20] Quantifying autonomic outcomes has historically relied on validated surveys, but substantial progress has been made on accessible physiological measurements such as cardiovascular[21 22] and bladder[23 24] outcomes.

Lastly, eSCS platforms generally provide a robust number of parameters (amplitude, frequency and pulse width) as well as a customisable set of spatial patterns of stimulation. Given a clear history of biological specificity for stimulation with respect to both location and parameter space, the inherent question of marginal benefit with optimisation remains critical.[25] Parameter optimisation is a significant barrier to widespread device use.

The aim of this study is to assess the effects of tonic epidural stimulation after chronic SCI on quantitative outcomes of volitional movement and cardiovascular function. This article describes our current phase II study of eSCS in participants with chronic SCI, which was designed to place emphasis on increased convenience of location and logistics for participants, quantitative outcomes, evaluation of the effect on volitional intent and autonomic function, and stimulation optimisation using a remote data collection platform. The central hypothesis of this study is that eSCS will restore some function in patients with chronic SCI that can be optimised using remotely collected data.

METHODS AND ANALYSIS

Study organisation

This study is a greater than minimal risk study approved by the Minneapolis Medical Research Foundation Institutional Review Board (IRB) and the Minneapolis VA Health Care System IRB. The Standard Protocol Items: Recommendations for Interventional Trials[26] checklist can be found in online supplemental additional file 1. Each facility has its own federal-wide assurance number and IRB and reviews and approves the protocol independently. The list of sites are Hennepin Healthcare Research Institute (IRB HSR #16–4115) and Minneapolis VA Healthcare System (IRB #4697-B). Site-specific protocol amendments are available on request from the corresponding author. A waiver of informed consent was obtained for prescreening purposes. All study procedures and data collection take place in academic hospitals in the USA.

Food and Drug Administration (FDA) approval of study protocol was obtained concurrently with IRB approval using an investigational device exemption for the St. Jude Medical Proclaim Elite Neurostimulator and Tripole Paddle.

Study design decisions

The primary outcome, the Brain Motor Control Assessment (BMCA),[27] was chosen for several reasons. It is an National Institute of Neurological Disorders and Stroke Common Data Elements outcome measure and is reliable across assessors and participants.[28] The Voluntary Response Index, which is a calculation of the similarity of all measured volitional EMG manoeuvres to a non-disabled control via waveform comparison, offers high objective granularity compared with an AIS classification system or an AIS subscore. We used a modified version of the Brain Motor Control Assessment (mBMCA). Required elements such as electrode preparation, electrode testing, signal continuity, use of scripts, the relaxation segment, auditory cues, and reinforcement tasks and timing criteria were followed as described in the BMCA manual.[27] The mBMCA is modified from the original described BMCA[20 27] in the following ways: the participant's quadriceps, adductors, hamstrings, tibialis anterior and triceps surae muscle of each leg, as well as the midline over the abdominal muscle at the level of the umbilicus and the lumbar paraspinal muscle, are recorded with multichannel surface EMG. Repeated

testing during a single session required brevity. Stimulation artefact from the device required additional leads to be placed on the torso and back to subtract noise from lower extremity measurements. Tendon taps, clonus, vibration and plantar stimulation assessments were not performed. Healthy control subjects are assessed with the same recording devices to improve the sensitivity of the quantitative measures.

As there is no standard treatment to restore volitional function in chronic SCI, study participants will serve as their own controls until different developed treatment modalities can be compared.

One of the primary goals of the study was to pragmatically limit travel requirements and participatory burden. With a less demanding follow-up regimen, more variation of socioeconomic status and SCI profiles are expected in participants who may feasibly participate in this trial. As a result, each participant may require different stimulation settings and patterns of stimulation to maximise improvement of function. eSCS systems allow software-controlled changes to the pattern of stimulation from the electrode (16 contacts) and to the parameters of tonic stimulation (frequency, pulse width and amplitude). Greater than 10^{15} combinations of these parameters and patterns are possible. To reduce the complexity of the problem to millions of df, electrodes are configured with patterns to stimulate broadly with symmetric responses while patterns within the parameter space are evaluated. Participants evaluate one setting each day in a prescribed sequence. A tablet computer paired to accelerometers worn on their feet is provided to perform a kinematic task and remotely collect forced binary choice preferences as part of a daily routine. Probit modelling and Bayesian optimisation of frequency and pulse width are used to generate sets of settings to be tested each month, programmed during research visits.

Patient surveys have revealed higher priorities given to recovery of sexual function, blood pressure, bowel and bladder when compared with the restored ability to walk.[29 30] Therefore, we included extensive autonomic function testing, psychiatric assessments and patient-reported quality of life (QOL) exploratory outcomes as part of the study.

Stationary cycling testing was introduced after study initiation, as new apparent volitional movement greater than anticipated suggested that task-based gross motor movement could be assessed in participants without extensive preparatory rehabilitation. Stationary cycling minimises falls risk, can be administered in a home environment and generates objective data that can be aggregated and compared.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Patient population and recruitment

The study population consists of participants with thoracic motor complete paraplegia who are healthy enough to safely endure outpatient surgery and who have a non-transected SCI within the thoracic spine. This patient population is similar to previous studies but without requirement for relocation.[12 19] Participants must be able to attend 15 monthly sessions and undergo a simple and straightforward screening process. Inclusion requires a non-penetrating, non-transected SCI between C6 and T10, categorised as AIS A or AIS B, detectable reflexes on physical exam in the lower extremities and status at least 1 year post injury. These criteria ensure that this research intervention does not interfere with recovery from the original SCI and that no clinically detectable lower motor neuron injury exists in the lumbar segments of the spinal cord. Participants are also required to have full motor strength in all key upper extremity motor groups to ensure safe participation in physical assessments.

Participants are evaluated for signs and symptoms of cardiovascular dysautonomia or autonomic dysreflexia for inclusion in a subarm of the study that allows for more extensive cardiovascular testing. Tilt table assessment and 24-hour blood pressure monitoring are used to assess for resting or orthostatic hypotension and autonomic dysreflexia, with stimulation off during this period to prevent confounding. These participants undergo further autonomic assessment as outlined in the Methods and analysis section.

The key exclusion criteria include any disease or condition that would significantly increase the risk of morbidity/mortality from surgical implantation, significant dysautonomia that would prohibit rehabilitation or surgery, presence of volitional movement at screening and an unhealed spinal fracture (Box 1).

Recruitment occurs primarily from the E-STAND website (www.estand.org), with secondary recruitment through flyers, word-of-mouth and department-level meetings.

Device

Participants are implanted with a St. Jude Medical Proclaim Elite 7 Implantable Pulse Generator (model 3662ANS) and tripole electrode paddle. This paddle has 16 electrodes organised in three columns (5–6–5). Stimulator settings for each participant will vary according to our experimental protocol, outlined further.

Design and randomisation

This is a phase II single-arm preclinical–postclinical trial that measures outcomes at every assessment with intervention toggled on or off. All participants are assigned to a single treatment group. Participants will be enrolled in this study for a total of 15 months, including a screening and enrolment period of 3 months. Dysautonomia screening occurs at this time. Follow-up will occur at monthly visits in addition to a 2-week postoperative visit after implantation (figure 1).

Box 1 Inclusion and exclusion criteria

Inclusion
⇒ 22 years of age or older.
⇒ Able to undergo the informed consent/assent process.
⇒ Stable, motor complete paraplegia.
⇒ Discrete SCI between C6 and T10.
⇒ Association Impairment Scale A or B SCI classification.
⇒ Medically stable in the judgement of the principal investigator.
⇒ Intact segmental reflexes below the lesion of injury.
⇒ Greater than 1 year since initial injury and at least 6 months from any required spinal instrumentation.
⇒ Willing to attend all scheduled appointments.

Exclusion
⇒ Diseases and conditions that would increase the morbidity and mortality of SCI surgery (eg, cardiopulmonary issues).
⇒ Inability to withhold antiplatelet/anticoagulation agents perioperatively.
⇒ Significant dysautonomia that would prohibit rehabilitation or assisted standing or any history of myocardial infarction or cerebrovascular accident associated with autonomic dysreflexia. A single tilt table test with syncope, presyncope or SBP of <50 or >200.
⇒ Other conditions that would make the participant unable to participate in testing/rehabilitation in the judgement of the principal investigator.
⇒ Current and anticipated need for opioid pain medications or pain medication that would prevent full participation in the rehabilitation programme in the judgement of the principal investigator.
⇒ Botulinum toxin injections in the previous 6 months.
⇒ Volitional movements present during electromyography testing in bilateral lower extremities.
⇒ Unhealed spinal fracture.
⇒ Presence of significant contracture.
⇒ Presence of pressure ulcers.
⇒ Recurrent urinary tract infection refractory to antibiotics.
⇒ Current pregnancy.

SCI, spinal cord injury.

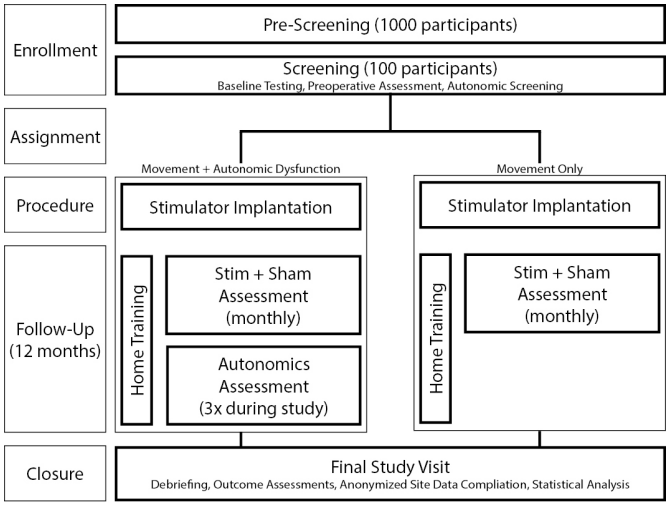

Figure 1 Study schema. Participants are assigned a study group (autonomic+movement vs movement only) and followed for a total of 15 months including the screening and implantation periods.

Each participant will serve as their own baseline during blocked assessments. At follow-up visits, the primary outcome measure assessment (magnitude of VRI mBMCA) is performed twice, once with the stimulator on and once without. Stimulation and 'sham' programmes, defined as stimulator settings that either involve an experimental stimulation configuration or no stimulation through any lead, will be randomly assigned in a group of repeated trials during each session by the assessor. Participants will be randomised to the order in which the assessments are performed. Randomisation was performed using computerised random number generation in a single blinded manner due to safety and technological limitations in preventing assessors from knowing the current stimulation programme. There is no rationale for unblinding participants during the trial.

Study procedures

Screening

Informed consent (online supplemental additional files 2 and 3) is obtained for screening procedures by trained investigators authorised by the site IRB. Participants are assessed for eligibility and enrolled if they meet criteria after review by the principal investigator. Participants are screened for severe autonomic dysfunction using a tilt table test and assigned to the autonomic sub-group if a positive test is observed, or excluded if deemed unsafe for surgery. MRI is reviewed to determine if the SCI is within the C6–T10 levels as well as to evaluate the anatomy for the surgical approach.

Baseline

Demographics and baseline assessments are obtained during enrolment. Participants are assessed again for cardiovascular dysautonomia not apparent with screening tilt table testing with repeat tilt table testing and ambulatory 24-hour blood pressure monitoring. They receive a tablet computer and wireless accelerometers with training software and data storage capabilities and are trained on methods to perform home exercise triple flexion/extension tasks.

Stimulator implantation

The epidural implantable pulse generator is implanted in a fashion similar to surgeries performed on patients with chronic pain.[31 32] A subcutaneous pocket is created to avoid placement in sites susceptible to contact or pressure ulceration. The paddle electrodes are placed at approximately the T12 vertebral level with fluoroscopic confirmation. Intraoperative mapping with EMG recording is performed to verify the coverage and placement of the epidural stimulator paddles with suprathreshold stimulation of the lumbar and upper sacral nerve roots. The paddle electrode wire is tunnelled in the subcutaneous space to the pocket and connected to the neurostimulator. Adjustment by moving the stimulator rostrally or caudally is allowed to ensure that the stimulator coverage area elicits anterograde signals in the maximum number

of L2–S2 myotomes on each side with low frequency (2 Hz) stimulation using the broadest possible anode–cathode configurations (usually with anodes in the three most proximal nodes and cathodes in the three most distal nodes). The criteria for explantation of the device include device malfunction or complications/medical issues requiring device removal as part of clinical best practice.

Postoperative visit

A focused physical exam and inspection of wounds is performed from 7 days to 6 weeks postoperatively. The width of this period allows for variations in postsurgical recovery and the judgement of the neurosurgeon to determine the optimal follow-up time for wound assessment and infection screening. During the first 30 days, antiplatelet agents such as aspirin or non-steroidal anti-inflammatory drugs such as ibuprofen may be held based on a clinical evaluation of each participant. Initial stimulation settings are programmed from the stimulator lead settings associated with the stimulator lead patterns resulting in the broadest coverage during intraoperative EMG. The minimum and maximum stimulator current levels are set based on the maximum comfort and volitional range per participant and physician observation. Participants are educated on the use and report of initial settings for home training. Secondary and exploratory questionnaire-based outcomes are also assessed at this time point.

Follow-up

For each monthly follow-up visit, vital signs, the modified Ashworth scale, a focused physical exam, and a query of adverse or other significant medical events are performed for safety. A 'falls' diary that the participant logs will be reviewed, and data from automated home exercise training and blood pressure monitoring logs for the monthly stimulation parameter set will be downloaded. New stimulation parameters from parameter space analysis will be assigned for these home activities and the next follow-up visit. All primary, secondary and exploratory outcome measures are assessed apart from the non-questionnaire elements of the autonomics assessments. Participant adherence to the follow-up schedule will be monitored, and participants will be contacted directly to assist with scheduling and completing assessments and logs.

Autonomic dysfunction assessment

Additional assessments performed once at baseline, once during the postoperative visit and three times during the follow-up period will occur for participants designated to the autonomic dysfunction subgroup. Participants undergo optimisation of programming specifically for autonomic outcomes. Autonomic-specific assessments as described in the Autonomic assessments subsection of the Secondary outcomes section will be obtained including validated questionnaires for cardiovascular, bladder and bowel functions. Twenty-four-hour blood pressure readings are monitored during a time prior to the sixth follow-up visit. In addition, the home exercise regimen will also include orthostatic exercises while wearing a portable continuous blood pressure monitor.

Primary outcome

The mBMCA data from each participant visit is used for calculating a score that compares the similarity of a participant's movements to a healthy control as well as the maximum power generated. The surface EMG activity from the start and end of each cued manoeuvre is summed into a response vector for each muscle, resulting in a series of response vectors. A similarity index is generated by comparing the set of vectors for the manoeuvre to the vector set of a non-impaired control.[33] This score, termed the mBMCA VRI, will be the primary outcome of this study. Previous studies have used absolute measures gauging volitional movement using EMG activity and accelerometer measures.[12 14 18] We employed a sensitive measure of changing muscle activity (BMCA) at a monthly interval to measure reproducibility and to evaluate any long-term changes (trends over time). A relative metric along a scale approaching full and normal function gives a more complete concept of the possible extent of gains from epidural stimulation and future improvements to its administration.

The BMCA lower-limb protocol elements of relaxation, voluntary movements and passive stretch during stimulation and sham trials are used to gather quantitative EMG data, which are calculated into the VRI.[33]

Secondary outcomes

The secondary outcomes assessed in this study include the optimisation of stimulation parameters, autonomic dysfunction and seated bicycle performance.

Stimulation parameter optimisation

Pulse generator stimulation frequency and pulse width are sampled, and a preference probit response surface is estimated to look for patterns of improvement in volitional movement as observed by participants. The optimisation of parameters is illustrated in figure 2. The initial electrode settings are determined by the electrode configuration providing responses in the most lumbosacral spinal segments during intraoperative monitoring, as mentioned in the Stimulator implantation section. This proximal anode/distal cathode configuration is used for volitional control assessments, and a rostral/caudal mirror configuration is used for autonomic assessments. Cathodic stimulation superiorly is used to improve autonomic symptoms by focusing most of the energy above the lumbosacral segments where sympathetic cells have been reported. Eight volitional settings are chosen using Bayesian sampling over the frequency and pulse width space. The cost function by which settings are selected includes minimising overall uncertainty, refining around promising peaks, minimising power and evaluating

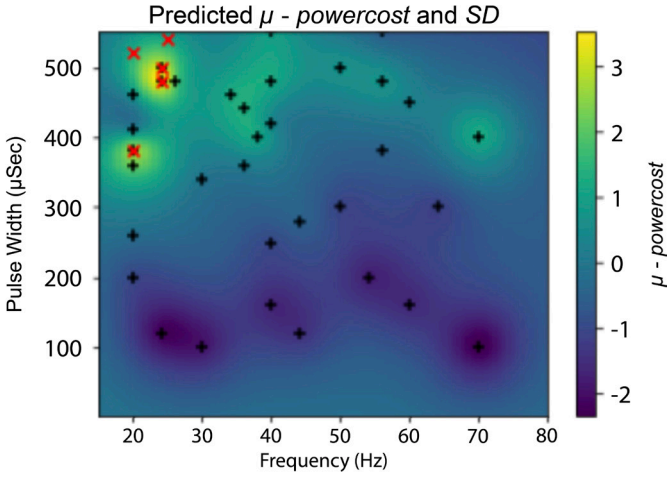

Figure 2 Example preference response surface over frequency and pulse width. Black crosses denote settings evaluated and red crosses denote setting suggested by Bayesian optimisation.

broadly as previously detailed.[34] The initial parameter space is sampled uniformly between 2 and 1200 Hz and 150 and 500 µS. Participants are blinded to the settings and a sequence of settings to evaluate daily is created to maximise binary comparisons as previously described.[34] Daily electronic surveys capture forced-choice preference after a timed triple flexion and extension task while wearing bilateral nine-axis accelerometers, which capture velocity and movement patterns. Participants are asked to evaluate their performance on the task and throughout the day using the prescribed setting and in comparison with the previous day's assigned setting. Immediately prior to each follow-up visit, binary preferences are modelled using probit as a response surface. The preference response surface is composed of all previously evaluated comparisons and settings and then used iteratively to select the next eight settings to improve volitional movement. Participants are blinded to the settings. The settings with the highest preference are repeated to assess reproducibility. Amplitude is provided as a range to allow for adjustments necessary for different positions (supine vs sitting).

Autonomic assessments

The following tests are performed on enrolled participants with autonomic dysreflexia/dysfunction: tilt table testing, orthostatic sit-up test, Stroop neurocognitive assessment[35 36] and cerebral blood flow during tilt table testing. The Autonomic Dysfunction Questionnaire related to Autonomic Dysreflexia Symptoms from Bladder Function and Daily Life questionnaire[37] is also administered.

Seated bicycle performance

During participant follow-up visits to the study site, the participant will complete lower extremity testing in a controlled and supervised environment. These tests involve following simple commands with and without stimulation. Once the participant has developed some motor response with the stimulation at an appropriate setting for the individual, the participant will be asked to do exercises on a stationary bicycle. This bicycle exercise will be attempted at various stimulator settings and with no stimulation. Session performance will be measured using a built-in bicycle ergometer.[38]

Exploratory outcomes

Exploratory outcomes include QOL, bowel function, bladder function and sexual function.

Quality of life

QOL is assessed using the Abbreviated World Health Organization Quality of Life (WHO-QOL BREF),[39] a 26-item questionnaire derived from the WHO-QOL 100,[40] and the Quality of Life Basic Data Set, a three-question summary questionnaire from the International Spinal Cord Injury Data Sets.[41] In addition, the Epworth Sleepiness Scale[42 43] is used to determine the interference of drowsiness from SCI-associated sleep disordered breathing in day-to-day activities.[44]

Bowel function

The Neurogenic Bowel Dysfunction score is used to measure changes in bowel function and incontinence.[45]

Bladder function

The Neurogenic Bladder Symptom score,[46] the Incontinence–Quality of Life Questionnaire[47] and the Qualiveen Questionnaire[48] assess changes in bladder function and incontinence.

Sexual function

Different metrics are administered to men and women in the study. Men receive the International Index on Erectile Function Questionnaire.[49] Women receive the Female Sexual Distress Scale Questionnaire[50–52] and the Female Sexual Function Index Questionnaire.[51 53–55]

Safety endpoints

Adverse event monitoring

A physical examination and blood pressure screening will occur during every in-person visit. Study-specific adverse events include hypotension, other haemodynamic instability, infection, bleeding, significant pain or cerebrospinal fluid leak attributable to study participation.

Pain

The International Spinal Cord Injury Pain Basic Data Set will be used to record and track the general pain profiles of all participants during the study.[56]

Spasticity

The Penn Spasm Scale[57 58] and the modified Ashworth Scale[59] will be used to track spasticity.

Statistical analysis

Descriptive statistics are reported as means with SD. Tests are considered statistically significant when alpha is less

than 0.05 for two-tailed tests. All assumptions for statistical tests are evaluated before use of the test and corrected if necessary and possible.

We assume that each participant can attend at least 10 out of 13 appointments and therefore can undergo 10 mBMCA tests. The repeated measures analysis of variance (ANOVA) is used to compare sham and treatment as well as over time, where alpha is assumed to be 0.025 (two-tailed) and power is assumed as 0.95. A sample size calculation was performed using the following parameters for repeated measures ANOVA: by assuming a baseline mean magnitude of 0.3 and a clinically significant change of 0.2 while assuming a within-group SD of 0.25 (resulting in an effect size of 0.4), we estimate that we will need at least 56 participants to demonstrate significance for the primary outcome. With an estimated enrolment rate of 50% of the combined screening rate/loss to follow-up, the target screening number is rounded to 100. The ANOVA residuals are assessed for normality, and the groups are assessed for homoscedasticity. If there are significant violations of these assumptions, Friedman's test will be used instead.

Missing data are analysed to examine for randomness of omission. If the missing data are determined to be reasonably random, the predictive mean matching is used for imputation. The distribution of the complete data set is examined with and without the imputed data. Data from participants with incomplete data from dropout are included in the final analysis unless the participant requested removal of their data. A detailed statistical analysis plan of the primary and secondary outcomes is documented in the site protocols.

On recommendation from the FDA, it was decided to perform interim analysis of safety after each cohort of 10 participants primarily to examine harm. The FDA will independently analyse adverse event reporting while further enrolment is paused, making recommendations for study modification, halting or termination if necessary. The rate of infection and any serious adverse events will be examined in the context of previous published literature. During these time periods, the principal investigator will review the primary and secondary outcomes.

Data and safety monitoring

Physical study materials with identifying information will be kept on site in secured rooms and cabinets, and electronic study materials will be kept in a secure local drive. Study data will be deidentified before being transported for analysis. The principal investigator will personally review written responses to questionnaires and assessments performed by trained study staff for errors and omissions. Raw data automatically gathered from study applications will be personally reviewed on collection for faulty readings. The BMCA protocol includes data quality control. A study monitor will be selected to verify accuracy regarding enrolment, data collection and adverse event monitoring, and will report to the principal investigator and the local IRB at each site. This study may be temporarily or prematurely terminated by the principal investigator if it results in unacceptable risks to participants, futility of intervention or insufficient protocol compliance. The study is also audited yearly and as needed per Good Clinical Practice guidelines.

ETHICS AND DISSEMINATION

This is protocol revision V.1.69 was approved by the local IRB on 9 May 2019. Each protocol revision requires IRB approval from all sites. As this is a greater than minimum risk clinical trial involving an experimental use of a device, FDA approval of its investigational device exemption is also required. This protocol is current with the aforementioned standards. Interim analysis will be conducted with the intent to disseminate preliminary findings that can inform new studies by other groups to address the challenges of the limited study recruitment pool and the significant expense of each device implantation.

TRIAL STATUS

Protocol V.1.69, 9 May 2019. Trial recruitment was initiated on 20 February 2017 with an approximate recruitment completion date in January 2022.

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Acknowledgements We thank Caleb Hoover for performing the continuing coordination of the study and assisting with protocol revisions, Sena Uzunlar for assisting with study organisation and designing case report forms, and Aliya Ahmadi for assisting with study organisation.

Contributors DPD is the lead investigator of the study and is the primary decision maker in all study design, data collection, reporting and publication decisions. The protocol and manuscript were primarily developed by DPD with assistance from DYB. The statistical plan was developed by DPD. The institutional review board materials were developed by DYB. EP and DF aided in the writing, editing and submission of the manuscript. AK and AP developed the autonomics assessment and autonomics questionnaire portions of the protocol. TN mentored and assisted DPD in developing the parameter space mapping portion of the protocol. AP and US supervised the overall development of the protocol, edited and approved the final manuscript. All authors read and approved this article.

Funding This trial is sponsored by the principal investigator and independently funded. Funds for this project were provided by several grants from the Minnesota Spinal Cord and Traumatic Brain Injury Research Grant Program administered by the Minnesota Office of Higher Education over 2016–2020. The research project was financed by $926 000 in state funds and $0 from other sources (excluding device donation).

Competing interests This study has received a contribution of epidural stimulation devices from St. Jude Medical/Abbott managed by the University of Minnesota. DPD has provisional patents for optimisation methods spinal cord stimulation and

is also the CMO and owner of Stimsherpa Neuromodulation. US's lab has received donations from Abbott through the J. Aron Allen Foundation. AK has received research grants from the Praxis Spinal Cord Institute through the University of British Columbia. He is also on the Coloplast and Convatech advisory boards and is the president of the American Spinal Cord Injury Association.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Addressed on page number (manuscript, protocol)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	16-17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Addl File 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10, 13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6, 12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None required
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Addl Item 3
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	5, 16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Addl Item 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

	Screening	Enrollment	Intervention	Post-Op	Follow Up	Close
TIMEPOINT*	$-t_2$	$-t_1$	0	t_{po}	$t_{1\text{-}12}$	t_x
ENROLLMENT:						
Eligibility screen**	X					
Informed consent	X					
Screening Tilt Table						
Screening EMG						
Spine Imaging Review		X				
INTERVENTIONS:						
Stimulator Implantation			X			
Settings Mapping				X	X	
Home Training					X	
ASSESSMENTS:						
Medical Information ***	X	X			X	X
Baseline Information †		X				
Safety Measures ††	X	X		X	X	X
Brain Motor Control Assessment		X			X	X
International SCI Pain Subset	X			X	X	X
Modified Ashworth Scale		X			X	X
Penn Spasm Frequency Scale		X		X	X	X
PHQ-9	X			X	X	X
Neurogenic Bowel Dysfunction Score		X		X	X	X
Neurogenic Bladder Symptom Score		X		X	X	X
WHO-QOL BREF		X		X	X	X
International SCI QoL Basic Data Set		X		X	X	X
Epworth Sleepiness Scale		X		X	X	X
AD-HR QoL		X		X	X	X
Incontinence QoL		X		X	X	X
Qualiveen 30		X		X	X	X
Female Sexual Function Index		X		X	X	X
Female Sexual Distress Scale		X		X	X	X
IIEF-15		X		X	X	X
Orgasm Rating Scale		X		X	X	X
24 Hour Blood Pressure			One time[b]			
Cardiovascular Assessments[a]		X		X	Three Times	
Visual Neurocognitive Assessment[a]		X		X	Three Times	

* Timepoints: $-t_2$ = within 1 year of enrollment. $-t_1$ = between initial visit and intervention. t_{po} = 10-14 days after intervention. $t_{1\text{-}12}$ are spaced 1 month apart for each visit. t_x occurs on the last monthly visit unless patient participation is terminated early.

** Eligibility Screen includes these elements from the NINDS-CDE for Spinal Cord Injury: Demographics, History of Injury, Other Investigational Treatments, Alcohol and Tobacco Use, Substance Use, AUDIT-C, NINDS Myotatic Reflex Scale, and ISNCSCI
*** Medical Information includes these elements from NINDS-CDE for Spinal Cord Injury: Medical History, Prior and Concomitant Medications, Recent Hospitalizations or Procedures, and Surgical or Procedural Interventions
† Baseline Information includes these elements from NINDS-CDE for Spinal Cord Injury: Family History, Rehabilitation Therapies, Clinical Assessment, Braden Scale for Predicting Pressure Sore Risk, Lipid Profile, Capabilities of Upper Extremities Questionnaire, Spinal Cord Independence Measure, Wheelchair Skills Test Questionnaire, Assistive / Mobility Devices and Orthoses
†† Safety Measures include these elements from NINDS-CDE for Spinal Cord Injury: Physical Exam, Vital Signs and Tests, Modified Ashworth Scale, Falls Diary, SAE Monitoring
a: These assessments occur only in participants with a positive screening tilt table assessment
b: This assessment can be performed at any time prior to the 6 month visit

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CONSENT FOR CLINICAL INVESTIGATION CONDUCTED WITH PATIENTS

180-03913 (4/17) Addressograph / Label

CONSENT FOR CLINICAL INVESTIGATION

Adult Consent to Participate in a Research Study
Epidural Stimulation for Spinal Cord Injury

The purpose of this paper is to give you basic information about a research study. As you read these pages, feel free to ask questions. Being a part of this study is your choice, so please think about the information in this paper carefully. If you choose to be a part of the study, you can sign a consent, or agreement, at the end of these pages.

1. INVESTIGATOR(s) CONDUCTING THIS STUDY
Who will be in charge of this study?

The Principal Investigator of this study is:

- Dr. David Darrow, MD, MPH, Department of Neurosurgery, University of Minnesota, MMC 96, Room D-429, 420 Delaware St SE, Minneapolis, MN 55455

2. SOURCE OF SUPPORT
Who is funding this research study?

A grant from the state of Minnesota called the Spinal Cord Injury and Traumatic Brain Injury Grant Program, managed by the Minnesota Office of Higher Education, is funding this research. St. Jude Medical is also providing devices for use in this study.

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3. SITE OF THE RESEARCH STUDY

Where will this study be done?

This research study will be conducted at HCMC, University of Minnesota, and Minneapolis VA Health Care System. You will be participating in the study in the HCMC neurosurgery clinic for your non-procedure visits.

4. PURPOSE OF THIS RESEARCH STUDY

Why is this research study being done?

The purpose of the study is to investigate whether epidural spinal cord stimulators (devices that give an electrical boost to your spinal cord) can improve voluntary movement in the legs of patients with paraplegia (paralyzed legs). We will also investigate whether it can help with standing and how it affects your heart, circulation, mood, and urination. This is an experimental use of epidural spinal cord stimulation and is in no way guaranteed to work at all. Other studies have been done that show that it works in similar patients. Fifty people are expected to participate in this study over the course of this study.

5. ELIGIBILITY

Who is being asked to be part of this research study?

You have been asked to participate in this study because you have a non-progressive spinal cord injury between cord levels C6 and T11 (lower neck to lower back injury) classified ASIA A or B (you have no voluntary movement below the injury), you are in a stable medical condition, you have no medical condition that will interfere with standing/step training, you are negative for significant depression or drug abuse, you are not currently taking anti-spasticity medication, you have not received Botox injections in the previous 6 months, you are unable to stand, it has been one year since your injury, you are at least 22 years of age, and you are not pregnant.

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6. PROCEDURES

What procedures will be done for this research study?

If you agree to participate in the study, we would ask you to do the following: complete baseline neurologic testing, undergo surgery to implant the epidural spinal cord stimulator and the neurostimulator (a small machine that makes the electrical signal) in your back and a pocket under your skin, and return for monthly appointments to be tested and complete training. Each appointment will be 1-2 hours long. The following chart is a template of what will happen at each appointment. The epidural spinal cord stimulator placement procedure and the follow-up testing and training regimen are not part of the standard of care for your injury and are entirely experimental.

Procedures	Screening	Enrollment	Surgery	Post Op Visit	Follow up 1	Follow up 2	Follow up 3	Follow up 4	Follow up 5	Follow up 6	Follow up 7	Follow up 8	Follow up 9	Follow up 10	Follow up 11	Follow up 12	Closure
Spinal Cord Stimulator Implantation			**X**														
Questionnaires	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical Exam	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Radiology	**X**																
Electromyography	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Tilt Table Test	**X**																
Home Blood Pressure Test	**X**																
Autonomic Assessments					**O x 3**												
Falls Diary		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Home Training				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Note: All subjects do the **X** procedures. Only subjects selected by results from the Tilt Table Test and Home Blood Pressure test do the **O** procedures.

Here are the procedure categories explained in detail:

Spinal Cord Stimulator Implantation

The epidural spinal cord stimulator is a small device that generates a small electric current that will travel along a paddle electrode (a wire with a flat metal head encased in plastic) within your spinal canal right next to your spinal cord. A small incision will be made in the skin of the back over the spine, bone covering the

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spinal canal will be removed, and the paddle electrode will be positioned under x-ray guidance. A pocket under your skin will be made where the neurostimulator will be placed. After allowing the incision to heal, a small electric current will be sent through these wires to stimulate the spinal cord.

Questionnaires

You will be asked questions about your identity (such as name, race, gender, occupation) and physical and mental health (such as spinal cord injury history, other health conditions, sleep, and quality of life).

Physical Exam

We will obtain vital signs (such as blood pressure and weight) and perform a neurologic exam up to two times a session.

Radiology

We will try to get your most recent X-Ray and MRI (magnetic resonance imaging) spine scans from your medical record if possible. If we need additional scans, they will be obtained prior to surgery unless there are risks associated with performing them (such as excessive radiation from multiple CT scans or anything that prevents you from being exposed to magnets in the MRI), at which point you will be exempt. All imaging will be done at no cost to you.

Labs

We will try to get your most recent lipid profile bloodwork (fats in your blood) at the start of the study. If we need to obtain it at the start of the study, we will do so at no cost to you.

Electromyography

Surface electrodes will be placed on your skin (stickers with wires attached), which will be connected to a machine that reads electrical signals that come from your muscles. The electrical tests will only measure the electrical signals your muscles make by themselves and will not be painful. During these visits, you will be asked to move your limbs while a physician makes the stimulator runs several

stimulation programs. Some of these programs may not send any signals to your spine – these are called "sham trials." You will get stimulation that sends an electrical signal to your spinal cord during each visit, but you will not be told which of the programs are sham or experimental.

Tilt Table Test

This test determines whether the Autonomic Assessments are done. You will be secured to a flat table with a Velcro belt and blood pressure cuffs will be put on one arm and two fingers. The table will then tilt upwards until it is upright, ten it will tilt back to a flat position. We will monitor your blood pressure during this procedure. If your blood pressure decreases too much, or you feel faint, we will stop the procedure and assign you to the Autonomic Assessments group.

Home Blood Pressure Test

This is another test that determines whether the Autonomic Assessments are done. You will be given a blood pressure cuff you will wear for a full 24 hours. You can go home and do normal activities during this time. The next day, you will return the blood pressure cuff. If the cuff results are very high or very low, we will assign you to the Autonomic Assessments group.

Autonomic Assessments

You will only participate in these tests if you are assigned to them by the two previous tests. These tests consist of multiple parts. First, you'll have a sympathetic skin response test, in which we apply a small electrical signal to your arms and legs and measure the effect. This electrical signal is not painful. Then, we do an orthostatic sit up test. We will have you empty your bladder, then record your blood pressure while you lie down and sit up. If you can't sit up, we will use a special table that moves to help you into an upright position. We will also use an ultrasound machine (an imaging device that looks inside your body using sound waves) to look at your heart and blood vessels during these tests – the ultrasound probe will be placed on your chest and on your head. Finally, we will have you read words on a television screen during this assessment. You will receive a combination of sham or experimental stimulation programs during these tests.

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Falls Diary

You will be asked to keep a record of events where you fall or nearly fall on a supplied calendar.

Home Training

You will be expected to engage in very simple leg exercises regularly at home with the epidural stimulator on. None of the stimulator programs for home training are sham – all send an electrical signal to your spinal cord. The stimulator can be used for a maximum of 4 hours per day. You will also be given a urinary, bowel, and sexual function diary to record any changes in these habits during the study.

7. RISKS, DISCOMFORTS, AND INCONVENIENCES

What are the possible risks, side effects, discomforts, or inconveniences of this research study?

The study has the following risks. Most of the risks associated with this study have to do with surgery. The chances of these risks are listed here:

Likely (more than 10 out of 100 people):

- The electrical paddle that sends a signal to the spine moves and may have to be repositioned.
- The wire going to the paddle breaks and has to be replaced.

Less Likely (1 to 10 out of 100 people):

- Infection
- Problem with the stimulator device that causes it to be replaced.
- Too much or too little stimulation due to wrong stimulator settings.
- Dead battery
- Discomfort or pain at the paddle or surgery area
- Loose connection of stimulator wires that need to be resecured

Rare (less than 1 out of 100 people or never reported):

- Epidural hematoma: Bleeding into the surgery site

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- Leakage of fluid in your spinal cord (cerebrospinal fluid)
- Paralysis, weakness, clumsiness, or numbness below the implant
- Allergic reaction
- Skin sores

You may also require future surgery if the device malfunctions, you develop an infection, or you have cerebrospinal fluid leak. If you develop a severe infection you may become ineligible for future participation.

As part of the surgical planning process, you will undergo one thoracic spinal x-ray. This procedure involves exposure to ionizing radiation. The average amount of radiation that the average person would receive from this procedure is less than half of that received from natural sources of radiation (i.e. the sun, air, soil) by a Minnesota resident in one year (300 mrem).

Previous studies of epidural stimulation implantation in people with spinal cord injury have not resulted in major harm to subjects, but since this is a new application with few people tested so far, you must be informed of these theoretical risks of spinal cord stimulation. You may experience paresthesia (a buzzing or tingling sensation) that may feel uncomfortable and painful to you. You may experience involuntary movement. You may have an episode of autonomic dysreflexia (your blood pressure becomes really high). These events have not happened in previous similar studies, but we will closely monitor you for their occurrence should they happen to you.

You may be taken out of the study by the researchers if staying in the study would be harmful - such as if you develop an infection due to device insertion, you fail to follow instructions during follow up, the study is canceled, or the device fails.

In any research study, there may be risks we do not expect. You will be told about any important new information that may change your mind about your participation in this study.

8. REPRODUCTIVE AND PREGNANCY ISSUES

What is important to know about being a part of this study and pregnancy?

There are no known reproductive or pregnancy issues with being in the study.

9. HEALTH BENEFITS

What are the possible health benefits to you or to others from your being part of this research study?

The benefits to study participation are: You may be able to regain voluntary movement while the epidural stimulation is on. You may also be better able to stand. We are not sure if there will be improvements in cardiovascular function, mood, or depression and likely will need to study more patients in the future to know.

10. ALTERNATIVE TREATMENTS

What treatments or procedures are there for you if you decide not to be part of this research study?

You do not have to participate in this trial. Unfortunately, there are no other treatments similar to which we are offering in this trial.

11. CONFIDENTIALITY

Who will know that you are part of this research study?

Any information that could be used to identify you will be treated in strict confidence to the extent allowed by law. Nevertheless, some uses and disclosures of your information are necessary to conduct the study. If you agree to be part of this study, you will also be allowing the uses and disclosures of your private health information as needed for the purposes of this study as described in this consent.

"Private health information" means information that identifies you and is collected:

- during this study;
- from your past and current medical records maintained by your regular health care providers (including, if applicable, HCMC), to the extent the information is relevant to this study or to your eligibility for this study; or

- from any payment records relating to items or services furnished to you during this study.

By signing this consent, you are agreeing that your private health information may be disclosed to and used by:

- the doctors and other health care providers involved in this study;
- their staff;
- the research center (Minneapolis Medical Research Foundation);
- members of the HCMC Human Subjects Research Committee/Institutional Review Board;
- the sponsor of this study and its agents; and
- monitors from the United States Government and/or Food and Drug Administration (FDA).

The findings of this study may be used for scientific meetings, written reports, and publications, but no information that could be used to identify you will be disclosed for these purposes.

Once your private health information has been disclosed to a third party, federal privacy laws may no longer protect it from re-disclosure. However, anyone obtaining access to your private health information under this consent must agree to protect your information as required by this consent.

This consent to use your private health information as described above does not expire. However, if you later change your mind, you can revoke this consent by writing to Dr. David Darrow saying that you no longer wish to allow your private health information to be used for this study. If you revoke your consent, you may no longer be able to participate in the study. Moreover, we cannot undo uses or disclosures of your private health information that have already taken place in reliance on your prior consent.

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12. COSTS ASSOCIATED WITH THE RESEARCH STUDY

Will your insurance provider or you be billed for any costs of any treatments, medicines, or procedures done as part of this research study?

Your surgery and device will be paid for by this study. You are responsible for attending all appointments. You are also responsible for obtaining preoperative authorization with history and physical from your primary care provider. Medications after surgery will also not be paid for. If complications occur, you may be responsible for paying any additional medical bills.

The principal investigator of this study is paid to cover the costs of conducting the research.

13. COMPENSATION AND MEDICAL TREATMENT FOR ANY STUDY-RELATED INJURY

If you are injured from being part of this research study, what should you do and who will pay for it?

If you agree to be part of this study and believe you are sick or have been injured from being in this study, you should call the study doctor, Dr. David Darrow, (612) 873-8701, day or night. Medical care for any study-related sickness or injury will be available to you at Hennepin County Medical Center (HCMC). Financial compensation for lost wages, disability, and discomfort is not routinely available. The cost of this medical care will be billed to you or your insurance company.

14. COMPENSATION FOR PARTICIPATION

Will you be paid for being part of this research study?

You will not receive any payment for participating in this study.

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15. NEW FINDINGS

Will you be told of any new information or new risks that may be found while this study is going on?

In every research study, there may be risks we do not expect. You will be told about any important new information that may cause you to change your mind about being part of this study.

16. FREEDOM TO PARTICIPATE AND WITHDRAW

Is being part of this research study voluntary? Can you decide to stop being in this research study at any time?

Being part of this research study is your choice. You do not have to be part of this study. You can agree to be in the study now and change your mind later. Your decision to stop being in the study will not affect your regular care. Your doctor's attitude toward you will not change.

If you decide to stop being in the study, the study doctor may discuss with you a more limited participation in this study such as still collecting information from your medical records after you stop your direct participation. If you agree at that time, to such continued limited participation, that agreement will be noted in your records.

17. PROCEDURES FOR ORDERLY WITHDRAWAL OR REMOVAL FROM THE STUDY

What would happen if you decide to stop being part of this study or if you are removed from this study?

You may be taken out of the study by the researchers if:
- staying in the study would be harmful;
- you fail to follow instructions; or
- the study is canceled.

If you do decide to withdraw your consent, we ask that you contact Dr. David Darrow and let him know that you are withdrawing from the study. If you wish to

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withdraw your authorization as well you must contact Dr. David Darrow in writing.

Remember that withdrawing your authorization only affects the use and sharing of information after your written request has been received, and you may not withdraw your authorization for uses or disclosures that we have previously made or must continue to make to complete analyses or report data from the research. The Principal Investigator or another member of the study team will discuss with you any considerations involved in discontinuing your participation in the study. You will be told how to withdraw from the study.

You may choose to have the spinal cord stimulator and neurostimulator removed at any time and for any reason. If you want to have the device removed, please contact Dr. Darrow or the other investigators listed on this study. An appointment will be scheduled to perform the surgery necessary for removal. The cost for removal will be billed to your preferred payment / insurance method. The removal of the device may halt or withdraw your participation in the study.

18. CONTACT INFORMATION FOR QUESTIONS

Who should you contact if you have questions?

A description of this clinical trial will be available on http://www.ClinicalTrials.gov (NCT Number: NCT03026816), as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you have any problems, concerns, or questions about the study or your rights as a subject in this research study, want to obtain information, or want to offer input, and want to talk to someone other than the study doctor, you can call the Office of Human Subjects Research at Hennepin County Medical Center at (612) 873-6882.

If you have any questions before signing this consent, please be sure to ask them now. During the study, if you have any questions, concerns, or complaints for the study doctor, please call Dr. David Darrow at (612) 217-4290.

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19. EMPLOYEES AND STUDENTS

Are you affected from participating in this research?

All students or employees that wish to participate will not have their academic status or grades, or employment be affected by their decision to participate in this study. Record of their participation cannot be linked to an academic or employee record.

20. DECLARATION OF INTEREST

Are there any relevant relationships between the Investigators and this study?

St. Jude Medical has given Dr. Darrow's research team epidural spinal cord stimulator devices for use in this study. The agreement between Dr. Darrow and St. Jude Medical is limited to reporting study progress to St. Jude Medical. Dr. Darrow does not receive any financial benefit dependent on the results of the study.

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VOLUNTARY CONSENT FORM

- I have either read the attached consent or it has been read to me.
- By signing this form, I do not give up any of my legal rights or release anyone involved in this research study from their responsibility for negligence.
- By signing this form, I agree to be part of this research study and consent to the use of my private health information as described in Section 11 ("Confidentiality") of the attached consent.
- A signed copy of this consent will be given to me.

_____
Subject's / Legally Authorized Representative's Signature

_____
Subject's / Legally Authorized Representative's Printed Name

_____
Date

I certify that a copy of this form has been provided to the above-named subject.

_____
Explained by (Signature)

_____
Explained by: (Printed Name, Title)

_____
Date

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