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# 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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## 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.

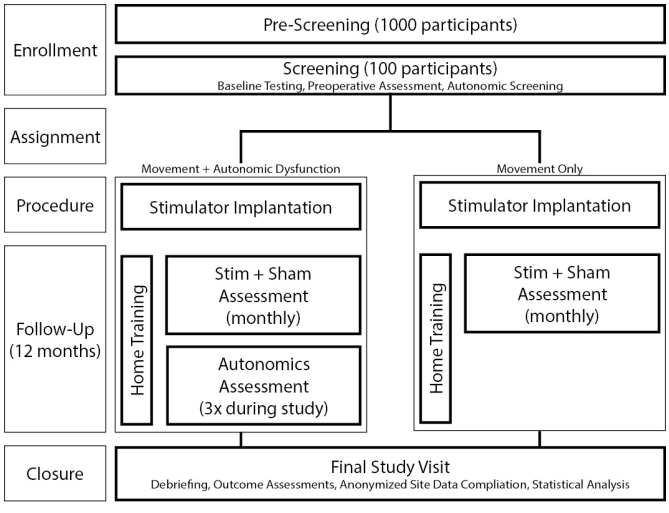


**Figure 1** Study schema. Participants are assigned a study group (autonomic+movement vs movement only) and followed for a total of 15 months including the screening and implantation periods.

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

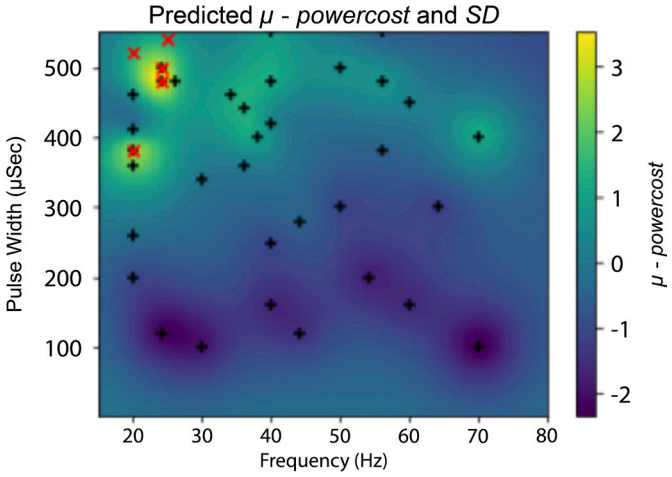


**Figure 2** Example preference response surface over frequency and pulse width. Black crosses denote settings evaluated and red crosses denote setting suggested by Bayesian optimisation.

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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**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.

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**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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