Official Title: A Pilot Study of Spinal Cord Stimulation for the Symptomatic Treatment of Rigidity and Painful Spasm in Stiff Person Syndrome

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A Pilot Study Evaluating Spinal Cord Stimulation for Stiff Person Syndrome

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Background

Stiff person syndrome (SPS) is a progressive, autoimmune neurological disorder secondary to autoantibodies against glutamic acid decarboxylase 65-kilodalton isoform (GAD65), the rate-limiting enzyme in the synthesis of glutamate to γ-aminobutyric acid (GABA) (1). SPS is clinically characterized by muscular stiffness and painful spasm primarily affecting the thoracolumbar paraspinal, truncal, and proximal limb muscles (2). The clinical presentation of painful rigidity and muscle spasms results from impaired GABA inhibitory signaling within the spinal interneurons, which results in co-contraction of agonist-antagonist muscle groups (3). SPS spectrum disorders (SPS-SD) exhibit variable clinical presentations, symptom severity, and diagnostic criteria (3). Current treatments include intravenous immunoglobulin (IVIG) therapy, immunomodulatory agents, plasmapheresis, and symptomatic management with GABAergic medications (3,4). These current treatments have demonstrated variable efficacy (2,4).

Spinal cord stimulation (SCS) is a safe and effective therapy for numerous chronic painful conditions, including painful diabetic neuropathy and refractory angina pectoris (5). SCS therapy starts with a 7-10 day trial involving fluoroscopically-guided placement of temporary, percutaneous stimulation leads in the dorsal epidural space connected to an external pulse generator. A trial is commonly defined as successful if there is at least 50% pain reduction.

A recent pilot study demonstrated improvement in strength and functional movement using SCS therapy to treat two patients with post-stroke upper-limb paresis (6). Ughratdar, et al. reported the use of SCS to successfully abort painful lower extremity spasm in a case of seronegative atypical stiff limb syndrome (7). Furthermore, our recent case report describes the novel use of SCS to treat painful rigidity and spasm in a patient with anti-GAD65 antibody positive SPS (8). The patient demonstrated durable clinical improvement in multiple health domains following permanent SCS implantation. Through this pilot study, we aim to gather objective preliminary data to evaluate the clinical response in SPS patients.

Since Dr. C. Norman Shealy's first spinal cord stimulator implant in 1967, there have been numerous advances in SCS. In recent years, significant advances have been made in SCS technology and applications. SCS-mediated neuroimmune modulation is a topic of growing interest. Various SCS programming methodologies, including Burst and Differential Target Multiplexed Programming (DMTP-SCS), have been shown to modulate components involved in central immune responses and inflammatory homeostasis in animal models (9-13). Experimental evidence has established modulation of GABAergic inhibitory signaling as the primary mechanism of action of SCS via observed decreases in pre-synaptic intracellular GABA concentration and subsequent increases in extracellular GABA concentrations following short periods of stimulation (14,15). DTMP-SCS was utilized in our recent case report and will again be used in this pilot study due to experimental evidence demonstrating its ability to directly target various inhibitory signaling pathway components, many of which are autoimmune antigenic targets involved in the disease pathophysiology of SPS-SD (4,12).

DTM-SCS has been shown in animals to increase expression of proteins involved with inhibitory signaling. The following is the mechanistic theory as to why SCS may result in immediate and long-term clinical change in SPS patients.

1. Direct release of presynaptic GABA (18,19).

2. Increased expression of GAD65 (12,16).

3. Increased expression of GABA and glycine receptors (12,17).

4. Increased expression of accessory proteins involved in inhibitory signaling (12,18,19).

5. Increased expression of potassium ion channel subunits (5,12,20-23).

6. Modulation of vesicular function and neurotransmitter reuptake and recycling (12,16).

Our novel translational use of SCS may serve to further promote and advance continued growth in this specific area of neuromodulation. To our knowledge, there exists no description in the literature of a molecular biomarker that serves to quantify SCS mediated change in vivo. The measurement of CSF anti-GAD65 antibodies found in SPS patients holds the potential for discovery as the first biomarker used as a surrogate measure of SCS-induced change. Additionally, it may be the first biomarker to corroborate experimentally derived SCS mechanisms of action. This may have profound implications in the future trajectory of neuromodulation, autoimmune neurological disorders of the CNS, and our understanding of CNS immunology. Should this pilot prove successful, future studies involving SCS therapy in Stiff Person Syndrome will evaluate such antibodies.

Study Objectives

The purpose of this prospective pilot study is to gather preliminary evidence evaluating spinal cord stimulation (SCS) as a potential therapy for the treatment of rigidity and painful spasms in patients with stiff person syndrome (SPS), a rare autoimmune neurological condition. We hypothesize that SCS-mediated clinical improvement occurs through multi-modal mechanisms of action targeting several components of neuronal inhibitory signaling pathways in the spinal cord. Symptomatic clinical changes in pain, stiffness distribution, spasm frequency and severity, functionality, quality of sleep, fatigue, depression, anxiety, and quality of life will be evaluated via validated assessments. SCS-induced objective changes will be measured with functional assessment scales evaluating multiple domains and incentive spirometry. These assessments will be evaluated at the end of the 7-10-day SCS temporary trial period. We will also evaluate at 2 and 4 weeks after end of the trial period to determine when subject symptoms have returned to baseline. We aim to demonstrate proof-of-concept for a larger clinical trial evaluating the efficacy of SCS for the symptomatic treatment of stiff person syndrome.

Spinal Cord Stimulator Trial Lead Insertion Description

The insertion of SCS trial leads is done percutaneously and with fluoroscopic guidance. Only local anesthetic (1% lidocaine) is used, and the subjects remain conscious throughout the procedure. The site of needle entry is at the T12-L1 interlaminar space, identified with fluoroscopy. Then, a 14g epidural needle is used to gain entry via loss of resistance technique to the epidural space. Then, a SCS lead is

placed through the needle and confirmed with fluoroscopy to be within the dorsal midline epidural space. The lead is then advanced under live fluoroscopy to the intended vertebral levels, Approximately T7. Then, a second lead is placed in the same fashion as described above. At that time during the procedure, the leads will be connected to an external pulse generator and turned on such that the patient will feel paresthesia in certain areas. The optimal lead location is performed via paresthesia mapping. The location of paresthesia should overlay the areas of stiffness/pain. At that time, the lead may be advanced superiorly (~T5) or withdrawn (~T10) based on location of paresthesia. This process of paresthesia mapping is standard of care. Therefore, it cannot be pre-determined exactly where the final location of SCS leads can be, but they will likely be no more superior than T4 and no more inferior than T11. The SCS trial lead insertion procedure for our investigative purposes is no different than what would be performed during an SCS trial lead insertion procedure for standard use.

Once optimal lead placement is finalized, the needles are removed while leaving the SCS lead in place. The leads are sutures to the skin using 0-silk suture and covered with gauze and Tegaderm. The external leads tips are then connected to an external pulse generator which the subject will wear using a belt for the duration of the trial period. The subject will be placed on appropriate antibiotics for the first two days of the trial period. Example picture seen below.

No additional devices will be used for the procedure or SCS trial period. The subject will undergo SCS programming using Medtronic DTM programming methodology. Optimal programming parameters are shown in the table below, example based on assumed symptomatic regions.

Group	**Area of coverage**	**Cycle**	**DTM-based programming parameters**		
			Current (mA)	**Pulse Width (µs)**	**Rate (Hz)**
A	Cervical and upper thoracic	1	6.3	200	50
		2	4.8	170	300
		3	4.8	170	300
		4	4.8	170	300
B	Truncal/thoracic paraspinal	1	5.5	200	50
		2	6.0	170	300
		3	3.7	170	300
		4	3.7	170	300
C	Low back and proximal lower extremity	1	6.0	200	50
		2	4.7	170	300
		3	4.7	170	300

		4	4.7	170	300

The pulse width and Rate are fixed and standard to DTM therapy. They will not be changed during the trial period. The subject may toggle between present groups (A, B, C) based on anatomic location of spasm they wish to treat. The current is variable and can be patient controlled, with range being (0.5mA – 15mA). The subject may choose to increase current when they feel more spasm in a particular area.

Using a higher current may lead to a stronger sensation of paresthesia, however there is no increased risk to patient safety with patient controlled adjustment of current. If there are unforeseen events compromising patient safety due to SCS programming or control to the device, the subject may simply turn the SCS system OFF. They will be instructed to inform the study investigator immediately and will be evaluated.

During the trial period while the subject is at home, they will be contacted by a Medtronic clinical representative. The clinical representative can be though of as a patient coach, with the primary goal of optimizing therapy to its fullest potential by the end of the trial period. They are unable to remotely program the device parameters, and simply serve as a translator between the patient and their SCS system. For example, on day 2 of the trial the patient increases their current setting to a point where they are able to feel paresthesia sensation in a certain area of their body and are bothered by this feeling. The clinical representative would then inform and teach the patient that this is due to the current being increased, and they should try decreasing that setting to the point in which they cannot feel the undesirable sensation. There are no major adverse effects compromising patient safety that can occur based on any action performed by the clinical representative. Additionally, ALL actions performed by the clinical representative are under the direction of the primary investigator. Should a patient require re-programming of their system to better optimize therapy, this action can only be performed in person and would take place in the presence of the primary investigator. An example of this scenario is if a patient SCS trial lead inadvertently pulls out or moves. At that time, the patient would come into the clinic for evaluation of the lead, and if determined by the investigator that a re-programming is necessary to capture the intended anatomic area, that action is authorized and then performed by the clinical representative. The aforementioned scenarios and descriptions of the role of an industry clinical representative are standard of care. The use of clinical representatives during an SCS trial is paramount and their absence greatly effects patient care and outcomes. Their involvement does not compromise patient safety in any fashion as the device is designed and adheres to the limits of DTM programming methodology, which are commercially available for indicated uses.

The Medtronic clinical representatives that would be part of this study are irreplaceable for the off-label indication being studied. This is due to the fact that the only successful attempt at using SCS for SPS was conducted under my guidance and with the assistance of industry clinical representatives. The Medtronic clinical representative that would be participating in the care of our subjects are the only representatives with any experience with SCS for our proposed off-label use, as it has never been performed in the past with any other clinical representatives. See section 2.1.2, reference #8.

There is no difference in how the SCS trial lead insertion procedure would be performed for standard on-label use and the proposed investigational use. The risk profile and impact on patient safety remains equal compared to on-label use, with the only change being the indication in which the SCS trial is being performed.

There is no difference in how the SCS trial programming will be performed between on-label use and the proposed investigational use. Therefore, programming for the proposed investigational use should not impact patient safety.

SCS Trial Lead Removal: The removal of SCS trial leads is performed in office, without anesthesia, and done painlessly. Two sutures holding trial leads in place are cut and the leads are gently pulled out of the epidural space. A bandage can be applied to the two SCS lead puncture sites. Adverse events from SCS trial lead removal will be assessed with a phone call to the subject 48 hours after lead removal. There are no long-term adverse events from SCS trial lead removal that necessitate longer term follow up than what is planned with a 2 week virtual follow-up visit after trial lead removal

Study Endpoints

Primary Endpoint

The primary endpoint will include an assessment of symptomatic clinical changes in the domains of pain, stiffness distribution, spasm frequency and severity, functionality, quality of sleep, fatigue, depression, anxiety, and quality of life. The following outcomes will be evaluated at baseline, end of trial, and 2 weeks after removal of trial neurostimulation leads as well as at 4 weeks after removal:

- Visual Analogue Scale (VAS) pain scores
- Michigan Body Map outcomes
- Penn Spasm Frequency and Severity Scale (PSFS) scores
- Pain Disability Index (PDI) scores
- Pittsburgh Sleep Quality Index (PSQI) scores
- Fatigue Severity Scale (FSS) scores
- Depression assessment -PHQ-8 scores
- Anxiety Assessment -GAD-7 scores
- EuroQoL (EQ-5D-5L) scores

Changes in pain (VAS pain scores), spasm frequency and severity (PSFS scores), fatigue (FSS), and medication usage will be assessed daily for the duration of the SCS trial period until 1 week (7 days) following trial lead removal.

Secondary Endpoint

The secondary endpoint will include functional measures using the Timed Up and Go (TUG) test, Trunk Impairment Scale (TIS), and pulmonary function changes using which will be performed at baseline, end of SCS trial, and two and four weeks after removal of SCS trial leads.

- Timed Up and Go (TUG)
- Trunk Impairment Scale (TIS)
- Lung Capacity (Incentive Spirometry)

Outcome Measures

- Pain VAS
- Michigan Body Map
- Penn Spasm Frequency and Severity Scale
- Pain Disability Index
- Pittsburgh Sleep Quality Index
- Fatigue Severity Scale
- Depression assessment (PHQ-8)
- Anxiety assessment (GAD-7)
- EQ-5D-5L
- Patient Global Impression of Change (PGIC)
- Timed Up Go
- Trunk Impairment Scale
- Lung capacity

Some of these questions will be asking for sensitive information. Suicide screening will be performed using the Columbia-Suicide Severity Rating Scale by a research team member The follow-up plan of action should the potential subject screen positive for suicidal ideation includes first, an evaluation by the primary investigator and may include escorting or arranging for transportation for the participant to the local ED for further evaluation; contacting a family member or close friend to assist in monitoring the individual or transporting them to the hospital, calling the participant's outpatient treatment providers to alert them to the risk; calling local police to assist when a person is judged to be at imminent risk but is not accepting of help; and following up with the participant after several days to re-assess risk level.

Study Halting/Stopping rules

- Subject may choose to terminate at any time their participation in the study

- Procedure related adverse events that are minor (eg. local allergic reactions, local skin infection, lead migration or accidental removal) may warrant halting participation in the study until evaluation by investigators and treatment, if necessary.

- Serious procedure related adverse events that may impact the safety of the subject may be grounds to stop participation in the study, as determined by the investigator. (eg. Epidural hematoma requiring emergent surgical intervention)

- All hospitalizations for any purpose will be reported. If hospitalization is related to study or stiff person syndrome, this will be documented, and outcomes followed via CRF. The study participation may either be halted or stopped based on investigator clinical judgement with safety of the subject superseding all.

    - The entire trial may be halted or stopped early if:

- Lack of efficacy is observed
- Overwhelming Positive efficacy is observed
- Unforeseen increase in symptom severity due to SCS therapy administration compared to baseline is observed
- enrollment issues
- loss of funding
- regulatory decisions

Study Plan

Enrollment goal: up to 10 patients

Subject participation duration: 2 months consisting of a screening period, baseline assessments, SCS trial procedure, up to 10 days of trial stimulation when the trial leads will be removed, a 2-week post trial lead removal virtual follow-up period, and a 4 week post trial lead removal virtual follow-up evaluation. Entire study period for follow-up of all subjects is approximately 12 months until completion of the study in its entirety.

Study Visits: Total estimate study duration for an individual study subject is approximately 2 months. There are three in-person visits that will take place at High Point Premier Pain Clinic and three virtual visits. There is an initial virtual baseline visit, followed by an in-person assessment the day prior to the scheduled procedure visit. There is a procedure visit for insertion of SCS trial leads. There is a SCS trial lead removal visit. There is a virtual visit 2 weeks after trial lead removal, with a final virtual (or in-person) follow-up done at 4 weeks after trial lead removal.

Pre-screening: We will send out a MyChart message to the surrounding area as a method of recruitment. We will also take referrals that reach out to the study team via BeInvolved as well as clinicaltrials.gov. Upon contact, we can also then reach out to schedule an in-person (or virtual) screening visit. Further study procedures can be determined from that point forward. When the EMR is reported based on criteria of diagnosis, we can then also pre-screen potential candidates via EMR review. If determined to be a good candidate, we will contact them by phone to schedule an in-person screening/enrollment/baseline visit.

Eligibility Criteria

Inclusion Criteria

1. Is 18 years of age or older at the time that the Informed Consent Form (ICF) is signed.
2. Has been clinically diagnosed with stiff person syndrome
3. Has clinical symptoms of muscle rigidity and spasms in the truncal (including abdominal, thoracic paraspinal, and pectoral) or proximal lower limb musculature
4. Has CSF anti-GAD65 antibodies or serum anti-GAD65 antibodies present at any titer
5. Is currently trying or has tried in the past at least two conventional therapies with insufficient symptomatic relief or intolerable side effects (such as nonsteroidal anti-inflammatory drugs,

topical patches/creams/gels/ointments, physical therapy, acupuncture, bracing, assistive devices, and lifestyle modification).

6. If taking oral medications for specifically for stiff person syndrome symptoms relief, is willing to maintain a stable regimen of only stiff person syndrome related medications for the duration of the study period. (eg. diazepam, baclofen, gabapentin)
7. Is cleared for an implantable medical device by licensed mental health provider.
8. Is an appropriate candidate for the surgical procedures required in this study based on clinical judgement of the study physician.
9. Is willing to and capable of giving written informed consent.
10. Is willing and able to comply with study-related requirements and procedures and attend scheduled visits.

Exclusion criteria

1. Is less than 18 years of age at the time at the time that the Informed Consent Form (ICF) is signed.
2. Has a BMI > 45.
3. Has a history of spine surgery or is planning to receive a spinal injection or procedure while participating in the study, unless this procedure can be postponed until after study completion.
4. Has radiological findings or evidence of moderate to severe central spinal canal stenosis or neuroforaminal stenosis at any thoracic level or laterality.
5. Has radiological findings or evidence of moderate/severe central spinal canal stenosis at any cervical or lumbar level.
6. Has had an epidural steroid injection within 6 weeks of enrollment.
7. Has a history of infection of the spine within 6 months of enrollment.
8. Has received intravenous immunoglobulin therapy (IVIG) within 10-14 days prior to the trial procedure, or is unwilling to hold IVIG from lead placement through the entire SCS trial period until 48 hours after lead removal.
9. Has an active implanted intrathecal baclofen pump that masks Stiff Person Syndrome symptoms. **EXCEPTION: If patient has active intrathecal baclofen pump, they may participate in this pilot study if the infusion dose has been stable for 30 days prior to enrollment, and must have continued symptoms of SPS despite active treatment with intrathecal baclofen pump.
10. Has a history of opioid misuse or current chronic opioid therapy.
11. Has evidence of a coagulation abnormality or low platelet count (<120,000) indicated on Complete Blood Count test at screening, or has a history of abnormal bleeding, or if unable to pause anticoagulation therapy in accordance with accepted ASRA anticoagulation guidelines for a spinal cord stimulator trial. (Reg Anesth Pain Med 2018; 43: 263-309)
12. Has a current local infection at the anticipated surgical entry site, active systemic infection, or active malignancy.
13. Has a medical condition or pain in other area(s) not intended to be treated in this study, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator (such as radicular pain, post-herpetic neuralgia, central canal stenosis of the cervical, thoracic or lumbar spine, critical limb ischemia due to peripheral vascular disease, or small vessel disease).

14. Has a history of untreated major depressive disorder, or history of any mental health disorder with psychotic features, such as schizophrenia.
15. Is pregnant (confirmed via pregnancy test) or plans on becoming pregnant during the study period.
16. Has had, within six months of enrollment, a significant untreated addiction to dependency producing medications, alcohol or illicit drugs.
17. Is concomitantly participating in another interventional clinical trial.
18. Is involved in an injury claim for a study-related chronic pain that is under current litigation.
19. Is a recipient of temporary Social Security Disability Insurance (SSDI) benefits due to Stiff Person Syndrome related chronic pain or disabling symptoms.
20. Has a pending or approved worker's compensation claim for Stiff person syndrome-related pain or symptoms.
21. Has low English language literacy interfering with the ability to complete study requirements.

Screening/Enrollment/Baseline Visit (virtual and in-person):
Before any study related tests and procedures are performed, the subject will be asked to read and sign an informed consent form (ICF). The following screening tests and procedures will then be performed/collected to determine if the subject qualifies to take part in this study:

- Prior and concomitant medications and treatments
- Demographics (age, sex, race/ethnicity, height, weight, BMI)
- Medical, surgical, social, and family history
- Physical exam (including neurological exam, musculoskeletal exam, and inspection of the intended surgical site)
- Thoracic MRI or review of MRI completed within the last 5 years
- Psychiatric evaluation by a licensed mental health provider for clearance for the study procedure This also assesses suicide risk. Psychiatric evaluation and clearance is standard of care prior to spinal cord stimulation.
- Pregnancy test (if subject is of child-bearing potential)
- Complete the following questionnaires:
    - Visual Analog Scale (VAS) pain assessment
    - Penn Spasm Frequency and Severity Scale (PSFS)
    - Michigan Body Map
    - Pain Disability Index (PDI)
    - Pittsburg Sleep Quality Index (PSQI)
    - Fatigue Severity Scale (FSS)
    - Depression Assessment (PHQ-8)
    - Anxiety Assessment (GAD-7)
    - EuroQol (EQ-5D-5L)
    - Columbia Suicide Severity Rating Scale
- Complete the following functional measures:
    - Timed Up and Go (TUG)
    - Trunk Impairment Scale (TIS)
    - Lung Capacity (Incentive Spirometry)
- CBC test for platelet count

SCS Trial Procedure Visit (in-person):

Subjects will undergo the following **prior** to the SCS trial procedure:

- Review concomitant medications and treatments
- Complete SDQ daily for 7 days prior to the SCS Trial Procedure visit
- Review SDQ
- Document any adverse events (AEs)
- SPS Diary Questionnaire (SDQ) Training – subjects will be asked to complete daily pain assessments consisting of average daily pain intensity scores using the Pain VAS at bedtime in the PDQ. In addition to pain scores, PSFS scores, FSS scores, and changes in medications will be recorded daily in the PDQ during the SCS trial period and for 7 days after the End of Trial Visit.

Subjects will undergo the following **after** the SCS trial procedure:

- Michigan body map, VAS pain assessment, PSFS, FSS, and comments from the patient after device activation at hours 2, 4, 6, and 8 after insertion of trial leads.
- SCS system programming by the trial lead manufacturer (standard of care)
- Complete the SDQ daily at bedtime for the duration of the study period

End of Trial Visit (in-person): 7-10 days after the trial SCS lead insertion procedure to have them removed

- Review concomitant medications and treatments
- Review SDQ
- Document any AEs
- Physical exam (including neurological exam, musculoskeletal exam, and inspection of the surgical site)
- Complete the following questionnaires:
    - Visual Analog Scale (VAS) pain assessment
    - Penn Spasm Frequency and Severity Scale (PSFS)
    - Michigan Body Map
    - Pain Disability Index (PDI)
    - Pittsburg Sleep Quality Index (PSQI)
    - Fatigue Severity Scale (FSS)
    - Depression assessment (PHQ-8)
    - Anxiety assessment (GAD-7)
    - EuroQol (EQ-5D-5L)
    - Patient Global Impression of Change (PGIC)
- Complete the following assessments:
    - Timed Up and Go (TUG)
    - Trunk Impairment Scale (TIS)
    - Lung Capacity (Incentive Spirometry)
- Removal of SCS trial leads
- Complete the SDQ daily at bedtime for the next week
- A follow up phone call 48 hours after removal of SCS trial leads will be conducted to assess for any SCS lead removal related adverse events, such as skin redness, swelling, draining from puncture sites, new motor weakness, bleeding.

1 Week Follow-up Call : 1 week following removal of trial leads

- Review concomitant medications and treatments
- Review SDQ

- Document any AEs

2 Week and 4 Week Follow-up Visit (Virtual): Review concomitant medications and treatments

- Review SDQ
- Document any AEs
- Complete the following questionnaires:
    - Visual Analog Scale (VAS) pain assessment
    - Penn Spasm Frequency and Severity Scale (PSFS)
    - Michigan Body Map
    - Pain Disability Index (PDI)
    - Pittsburg Sleep Quality Index (PSQI)
    - Fatigue Severity Scale (FSS)
    - Anxiety assessment (GAD-7)
    - Depression assessment (PHQ-8)
    - EuroQol (EQ-5D-5L)
    - Patient Global Impression of Change (PGIC)
- Complete the following functional measures:
    - Timed Up and Go (TUG)
    - Trunk Impairment Scale (TIS)
    - Lung Capacity (Incentive Spirometry)

Recruitment Plan

- Send MyChart message directly to SPS patients referred by Wake Forest Neurology Group
- Contact those who have reached out to us directly via BeInvolved or via clinicaltrials.gov
- Recruit locally via MyChart message to patients within Atrium Health system using code searches (G25.82 and R76.0)
    - We can send out MyChart message within a certain radial distance from a specific zip code
- If not a large enough local recruitment pool, reach out to SPS Research Foundation for any assistance with recruitment

Schedule of Study Events

	Enrollment/Baseline	Trial Phase		Follow-up Phase		
Visit	Consent, Screening, & Baseline Assessment (virtual and in-person)	Trial Implant (in-person)	End of Trial (EoT) (in-person)	1 Week phone call	2 Week Visit (virtual)	4 Week Visit (virtual or In person)
Window	-	-	7-10 days from		2 weeks ⍰ 3 days from EoT	4 weeks =/- 7 days From EoT

			Trial Implant			
Informed Consent	X					
Inclusion/Exclusion criteria assessment	X					
Prior and Concomitant Medications and Treatments	X	X[f]	X	X	X	
Medical/Surgical/Social/Family History	X					
Demographics	X					
Physical Examination[a]	X		X			
Serum CBC test	X					
Columbia Suicide Severity Scale	X					
Thoracic MRI if none within 5 years)	X[c]					
Psychological Evaluation	X					
Pregnancy test-if indicated	X[d]					
Review SPS Diary Questionnaire (SDQ)			X	X		
Pain Visual Analog Scale Assessment (VAS)	X	X[e]	X		X	X
Penn Spasm Frequency and Severity Scale (PSFS)	X	X[e]	X		X	X
Michigan Body Map	X	X[e]	X		X	X
Pain Disability Index (PDI)	X	X[e]	X		X	X
Pittsburg Sleep Quality Index (PSQI)	X	X[e]	X		X	X
Fatigue Severity Scale (FSS)	X	X[e]	X		X	X
Anxiety assessment-GAD-7	X	X[e]	X		X	X
Depression Assessment-PHQ-8	X	X[e]	X		X	X
EuroQol (EQ-5D-5L)	X	X[e]	X		X	X
Patient Global Impression of Change (PGIC)			X		X	X
Timed Up and Go (TUG)	X		X		X	X
Trunk Impairment Scale (TIS)	X		X		X	X
Lung Capacity (Incentive Spirometry)	X		X		X	
Placement of SCS trial leads		X				
Device Programming[f]		X				
Removal of SCS trial leads[g]			X			
Adverse Event Monitoring		X	X	X	X	

[a]The physical examination includes neurological exam, musculoskeletal exam, and inspection of the surgical site prior to trial lead removal., [c]To be completed for subjects who do not have recent thoracic MRI within past five years without evidence of spinal stenosis. [d]To be completed only for subjects of child-bearing potential. [e]To be completed prior to the SCS trial procedure. [f]To be completed after the SCS trial procedure. [g]SCS trial leads will be removed at the end of the visit.	

Adverse events summary

The implantation of a spinal cord stimulation system involves risks that are similar to other spinal procedures. In addition to those risks associated with this procedure. Certain adverse events may necessitate surgical intervention. All study procedures will be conducted in a sterile manner in the procedural area of the ambulatory surgery pain clinic. Potential subjects would not be exposed to the risks listed below were it not for their study participation. This potential showed in a stiff person syndrome subject when being treated for their back pain relief from their stiff person syndrome symptoms which leads us to this pilot study to fully evaluate the treatment possibilities for this rare disease without a cure.

The following are potential adverse events that have been reported with the spinal cord stimulator trials that have been conducted to date in regards to the treatment of chronic low back pain in preparation for permanent spinal cord stimulator implants. Not all adverse events listed apply for this study as a permanent device will not be surgically implanted:

▪ Allergic or immune system response to the implanted materials

▪Bleeding

▪ Infection

▪ Leakage of cerebrospinal fluid

▪ Lack of effective therapy or loss of therapeutic effect resulting in return of baseline symptoms during the SCS trial period (treatment failure)

▪ Device malfunction of the spinal cord stimulator. Device malfunction will be analyzed for causality after interrogation of the SCS by the clinical representative and PI. During the trial, the pulse generator is external and powered by replaceable batteries. Therefore, replacing the batteries would solve the issue.

▪ Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis and may necessitate emergent surgical intervention

▪ Procedural pain at the neurostimulator lead insertion site (post procedure pain)

▪ Radicular chest wall stimulation

▪ Change in stimulation, possibly related to cellular changes around the electrode(s), shifts in electrode position, loose electrical connections, lead or extension fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation). (unintended movement or removal of the wires from where device is implanted)

▪ Formation of reactive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant. This is very low risk as a surgically implanted permanent SCS system will not be implanted as part of the study.

▪ Stimulation-dependent gastrointestinal symptoms such as nausea, diarrhea, incontinence, or constipation

▪ Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency

-Death

▪ Changes in blood glucose levels in response to any adverse event

Note: Diabetic patients may have increased risks of infection, problems healing around

the surgical site, and complications common to any surgical procedure. The severity of

any surgical complication may be greater in diabetic patients, particularly those with

inadequate pre-operative glycemic control. Again, the aforementioned risk is minimal to nil as there is no surgical implantation of a permanent SCS system in this study.

Mitigation Plan for Major/Minor Risks with SCS Trial

- Allergy to SCS trial leads is mitigated based on allergic severity and reaction. If unable to treat pharmacologically, the final treatment is removal of temporary SCS leads

- Infection – Risk is mitigated with sterile procedure conditions, antibiotics for SCS trial period, no bathing or showering during trial period, and final treatment is removal of temporary SCS trial leads.

- CSF leakage is mitigated by performance of procedure using fluoroscopy. If dural puncture is encountered during SCS trial lead placement with subsequent post-dural puncture headache, conservative treatment with adequate fluid intake and caffeine is first line treatment. Post dural puncture headache usually self resolves over 2 weeks.

- Epidural hematoma, bleeding – This risk is mitigated by pausing anticoagulation prior to and during the trial procedure and trial period. Epidural hematoma is an adverse event that would occur and be recognized during trial lead placement or removal, within hours, and within the time frame of planned physical examination of the subject while in-person.

Radicular chest wall stimulation, untoward GI symptoms, bladder symptoms are mitigated by withdrawing trial leads slightly or decreasing current of stimulation. Final treatment is removal of SCS trial leads.

- There is no risk from anesthesia as the procedure is performed using local anesthetic only

- SCS trial leads are MRI Unsafe/incompatible. Thus, if a subject requires an emergent MRI for any purpose, SCS trial leads will simply require removal. The subjects will be supplied with a contact sheet in which other caregivers or medical personnel can contact the study investigator for further information, as well as information regarding the MRI Incompatibility of their SCS trial leads. See attached patient information/contact card.

- The change in protocol study assessments include no physical examination at 2-week post trial lead removal. This revision does not impact data quality and does not affect safety monitoring as virtual visits are continued with the presence of any adverse events being evaluated at those contacts via self reporting. Should an event occur then it would be followed as described under adverse event management.

- Removal of lumbar puncture- the study procedure removed this procedure to mitigate the risk of infection. The lumbar puncture would have been occurring in close proximity to the implantation of the spinal cord stimulator trial leads. The investigator's decision to remove this decreased the risk of infection without affecting the methodology as study is evaluating return to functionality with the SCS placement (alleviating/improvement of SPS symptoms)

- Depression and anxiety questionnaires add to the scientific soundness of the investigational plan. All study assessments in this study can involve disclosing sensitive information which the subject has the option to refuse to answer. In this way we are able to preserve the rights, safety and welfare of our study subjects.

- Inclusion of those subjects who continue to exhibit stiff person syndrome symptomatology despite stable baclofen pump drug dosage has been added. The safety profile of this allowance has been established as under normal care of subjects who have a baclofen pump are also able to receive a spinal cord stimulator trial procedure. The following will discuss the risks and mitigation strategies in detail.

Potential risks of pump catheter fracture and/or displacement

The risk of intrathecal catheter fracture and/or displacement during spinal cord stimulation (SCS) trials in patients with intrathecal baclofen pumps is generally considered low, primarily because the SCS lead is placed in the epidural space while the baclofen catheter resides in the intrathecal space. The anatomical separation between the epidural and intrathecal spaces does provide a degree of protection, and several case series and retrospective studies—including those involving epidural procedures in patients with intrathecal pumps—report a low incidence of direct catheter injury when proper technique and imaging guidance are used (24).

Case series and retrospective studies of patients with both devices (SCS and intrathecal pump) confirm that dual implantation is feasible and does not appear to introduce unique or synergistic risks of

catheter migration or breakage beyond those already known for each device. (25-26) For example, a recent case series in para-athletes with both devices reported an electrode fracture (SCS lead), but did not report increased rates of catheter migration or breakage for the intrathecal pump.

Increased risks of pump malfunction and/or SCS malfunction

Potentially SCS trials may precipitate pump malfunction through inadvertent mechanical disruption, electromagnetic interference, or infection risk associated with additional procedures.(26-28) Malfunction can result in baclofen withdrawal, overdose, or loss of therapeutic effect, necessitating prompt recognition and intervention which is an essential part of the risk mitigation strategy.

Plans to ensure catheter location

We will perform preoperative imaging to map the catheter path, intraoperative fluoroscopy, and multidisciplinary coordination to further minimize risk.

Procedural strategies include:

• Careful selection of the entry level and trajectory for the SCS lead, based on preoperative imaging, to avoid the intrathecal catheter in total.

• Avoiding deep sedation or general anesthesia unless necessary, as patient feedback during lead placement can help prevent neural injury and ensure accurate positioning.

• Postoperative interrogation of the baclofen pump system to confirm catheter integrity and pump function before discharge. (24)

Monitoring protocol for pump function

Pre-Trial Assessment:

Review the patient's history of pump function, dosing regimen, and any prior device-related complications. Confirm pump and catheter integrity through device interrogation and, if indicated, imaging to ensure proper placement and function before initiating the SCS trial (29-31).

Peri-Procedural Monitoring:

Conduct the SCS trial in a medically supervised, fully equipped environment with resuscitative equipment readily available, as recommended by FDA labeling and expert consensus. Monitor closely for signs of baclofen overdose (drowsiness, respiratory depression, hypotonia, coma) and withdrawal (increased spasticity, autonomic instability), as these can occur if pump function is compromised. Regularly assess neurological status, vital signs, and mental status throughout the procedure and in the immediate post-procedural period. Should there be any suspicion of compromise of the intrathecal pump catheter, an intrathecal catheter dye-study (pump-o-gram) is warranted, and study investigators are credentialed in performing this diagnostic procedure (29-30).

Pump Function Surveillance:

Interrogate the pump before, during, and after the SCS trial to confirm proper function and reservoir volume. Be vigilant for electromagnetic interference or communication issues between the SCS system and the pump, particularly during stimulation, as these may affect device interrogation but not drug delivery.(32). Should there be an issue with pump or stimulator communication, the SCS system may be completely turned off to further ensure pump communication. Finally, and while highly unlikely, the SCS trial may be aborted in total if it is deemed that communication issues with the pump are being caused by concomitant use of an SCS trial system.

Patient and Caregiver Education:

Provide clear instructions regarding the signs and symptoms of overdose and withdrawal, emergency procedures, and proper pump care. Ensure all caregivers and medical personnel are informed about the risks and management protocols.

Patient instructions to maintain spatial separation between the baclofen pump and external neurostimulator

Instructions for Keeping Your Spinal Cord Stimulator and Baclofen Pump Safely Apart

• Be aware of where your devices are placed. Your SCS and baclofen pump are usually implanted in different areas (for example, the SCS generator may be in your upper buttock or abdomen, and the baclofen pump is often in your lower abdomen). Try to avoid pressing or lying directly on either device for long periods

• Avoid activities that could cause the devices to move closer together. Sudden twisting, heavy lifting, or contact sports can sometimes cause the leads or pump to shift. If you notice any new lumps, pain, or changes in the way your devices feel, contact your care team right away.

• Keep strong magnets and electronic devices away from your pump and stimulator. Items like tablets, smartphones with magnetic chargers, and some headphones can interfere with your pump if placed directly over it, possibly causing it to stop working for a short time. Always keep these items at least 6 inches away from your pump and stimulator.

• Do not place belts, tight clothing, or bags directly over your devices. Pressure from these items can move the devices or cause discomfort.

• Watch for warning signs. If you notice increased muscle stiffness, spasms, fever, confusion, or if your pump or stimulator alarms, contact your care team immediately

Post-Trial Follow-Up:

Continue close monitoring for delayed complications, including infection, catheter displacement, or intrathecal mass formation.

Adverse event management:

Adverse events that are encountered at any time will be reviewed by the investigators. If deemed to be procedure related or requiring hospitalization, the subject's participation in the study may be halted or stopped altogether based on the clinical judgement of the investigator. For example, if a patient develops new onset motor weakness and extreme back pain 4 hours after insertion of spinal cord stimulator leads, there is a potential for an epidural hematoma requiring emergent surgical intervention by spine surgery. In this case, the patient's safety supersedes any study related requirements. Their adverse event will be promptly worked up and appropriately treated, with their study participation halted, with continued monitoring of the subject and appropriate reporting of adverse events and associated outcomes.

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