Clinical Characterization of Burst Spinal Cord Stimulation for Chronic Pain Management

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PROTOCOL

1. STUDY SYNOPSIS

Study Title	Clinical characterization of burst spinal cord stimulation for chronic pain management.
Study Sponsor	Michigan Institute for Clinical & Health Research Education and Mentoring Group (MICHR-EMG)
Study Objective	To clinically characterize the new burst spinal cord stimulation (Burst-SCS) therapy for chronic pain management. We will investigate the **treatment effects of Burst-SCS** and its underlying **therapeutic mechanisms of action** in chronic pain patients who have been deemed candidates for Burst-SCS therapy, and who have already been selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care.
Study Design	**Randomized, double-blind, placebo-controlled, crossover study**. Subjects will participate in up to five research visits. During the first visit, we will screen chronic pain patients who have already been selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care. During the second visit, we will perform pre-operative baseline assessment prior to implantation of the spinal cord stimulation (SCS) electrode arrays. Following lead implantation, and during the externalized **"trial phase**" of Burst-SCS, we will randomize subjects to receive either 24 hours of clinically-effective Burst-SCS followed by 24 hours of sham SCS or vice versa (crossover design). We will perform assessments before the start of the randomization (visit 3), and at the end of each 24-hour period (visits 4 and 5). We will have two research teams. One team will be unblinded and will perform stimulator programming/adjustment, and the other team will be blinded and will perform clinical testing and collect study outcome measures.
Study Interventions	Burst-SCS and Sham SCS.
Study Duration	Subjects will participate in up to 5 research visits and each visit is expected to last about 2 hours. Therefore, the total time committment for each subject is **approximately 10 hours over 2-3 months**.
Sample Size and Population	We will recruit **20 chronic pain patients** who have been deemed candidates for Burst-SCS therapy, and who have already been selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care.
Statistical Analyses	We will perform appropriate statistical tests to look for **significant differences between treatment effects** on primary and secondary outcomes.

2. SCHEDULE OF EVALUATIONS

	Screening/ enrollment visit	**Pre-implantation visit[a]**	**First trial-phase visit**	**Second trial-phase visit**	**Third trial-phase visit**
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*
Informed Consent	X				
Hospital Anxiety and Depression Scale (HADS)	X	X	X		
EQ-5D Health Questionnaire	X	X	X		
Demographics	X				
Concomitant Medications	X	X	X	X	X
Socio-demographics	X				
Brief Pain Inventory (BPI)	X	X	X	X	X
Coping Strategies Questionnaire (CSQ)	X	X	X	X	X
Michigan Body Map (MBM)	X	X	X	X	X
PainDETECT	X	X	X	X	X
Pain Disability Index (PDI)	X	X	X	X	X
Fibromyalgia Survey Questionnaire (FSQ)	X	X	X	X	X
Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form Questionnaire (PROMIS-SD)	X	X	X	X	X
Short Form McGill Pain Questionnaire (SFMPQ)	X	X	X	X	X
Visual Analog Scale (VAS) – included in SFMPQ	X	X	X	X	X
Vitals (heartrate, blood pressure, respiration rate, blood temperature), height and weight	X	X	X	X	X
Multimodal Automated Sensory Test (MAST)	*b*	X	X	X	X
Vibrometer Test	*b*	X	X	X	X
Algometer Test	*b*	X	X	X	X
PinPrick Test	*b*	X	X	X	X
Conditioned Pain Modulation (CPM) Test	*b*	X	X	X	X
Randomization			*c*		
Treatment (Burst-SCS/Sham SCS)			*d*	X	X
Adverse Events	X	X	X	X	X

[a]Pre-implantation visit may also occur on the same day as the screening/enrollment visit
[b]Familiarization only
[c]Randomization will occur at the end of Visit 3
[d]Treatment will begin at the end of Visit 3

3. STUDY BACKGROUND

Chronic pain is a major health problem in the United States and affects ~100 million American adults.[1] Patients with chronic pain have ~3 times higher healthcare costs as compared to healthy individuals.[2] Chronic pain is debilitating as it impacts most aspects of a person's life, including physical inability, emotional distress and/or psychological impairment. Due to its debilitating nature and widespread impact, chronic pain is complex and often challenging to treat. Unfortunately, conventional treatments (e.g. pharmacological therapies, surgery) have limited effectiveness for many people with severe chronic pain.[2] Therefore, less conventional forms of therapy, such as neurostimulation are often considered for these patients.[3,4] **Spinal cord stimulation (SCS)** is one such popular neurostimulation therapy frequently utilized for patients with chronic pain conditions that are often refractory to conventional treatments (e.g. failed back surgery syndrome and complex regional pain syndrome).[3,5,6] Typically, the procedure of SCS involves implanting an electrode array in the epidural space dorsal to the spinal cord via a percutaneous needle or through the performance of a laminectomy.[7,8] The electrode array is connected to an implantable pulse generator that produces an electrical stimulus. The success of SCS is determined by its ability to deliver electrical stimulation to the dorsal columns of the spinal cord in an attempt to create analgesia (or inability to feel pain).[9,10] However, SCS has shown only limited success rates in treating patients with refractory chronic pain.[5,11] The success rate of SCS, defined as the proportion of patients receiving 50% or greater pain relief, is approximately 58%.[11] Furthermore, the success rate of SCS varies widely across studies, often declines over treatment time, and significant pain relief does not necessarily translate to improvements in quality of life (e.g. patients can't go back to work).[6,11-13] Therefore, there is a growing need for the development of improved neurostimulation treatments in chronic pain.

Burst spinal cord stimulation (Burst-SCS) is an exciting new SCS therapy that has the potential to transform neurostimulation treatments in chronic pain. **Burst-SCS was approved by the United States Food and Drug Administration (FDA) in 2016 to treat chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any one of the following: failed back surgery syndrome and intractable low back and leg pain.** Burst-SCS system delivers packets of high-frequency electrical pulses (500 Hz) periodically to the spinal cord (40 times a second) as compared to conventional SCS that deliver a constant stream of low-frequency pulses (~50 Hz).[14,15] A recent large clinical trial (SUNBURST; Success Using Neuromodulation with BURST) reported Burst-SCS to be more effective than conventional SCS in relieving pain.[16] Although findings of this trial suggest the potential superiority of Burst-SCS over conventional SCS, other studies have reported variable outcomes.[14,15,17-21] Furthermore, a majority of these clinical studies were performed in an unblinded manner.[14,17,18,21] Therefore, we believe that a "placebo" effect likely confounded the findings of these studies and the resulting variability in outcomes. Comparing the effects of Burst-SCS to sham (no) SCS in a randomized, double-blind, placebo-controlled, crossover fashion will help systematically control for placebo effects and will help identify the true pain-relieving effects of the therapy. We also believe the variable outcomes with Burst-SCS is attributed to our poor understanding of its mechanisms of action. Currently, there is minimal scientific understanding of how Burst-SCS works to relieve pain. Preliminary evidence suggests that Burst-SCS may provide improved pain relief via different therapeutic mechanisms of action relative to conventional SCS.[22] However, such claims are anecdotal and remain to be validated. To better understand the mechanisms of action of Burst-SCS, we will adopt a mechanistic approach to Burst-SCS.

As such, the proposed study will determine the treatment effects of Burst-SCS and its associated therapeutic mechanisms of action by systematically controlling for placebo effects. Understanding the treatment effects of Burst-SCS and its associated therapeutic mechanisms can provide useful information to help conduct larger clinical studies in the future. Because Burst-SCS

therapy and its clinical implementation are in their infancy, we believe our results will be directly applicable to improving clinical care.

4. STUDY OBJECTIVE

To clinically characterize the new Burst-SCS therapy for chronic pain management. We will investigate the **treatment effects of Burst-SCS** and its underlying **therapeutic mechanisms of action** in chronic pain patients who have been deemed candidates for Burst-SCS therapy, and who have already been selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care.

5. SPECIFIC AIMS/HYPOTHESES

5.1 To identify the treatment effects of Burst-SCS (Aim 1).

The goal of this aim is to determine the **pain-relieving effects of Burst-SCS**. In a randomized, double-blind, placebo-controlled, crossover study, we will compare the pain-relieving effects of Burst-SCS to sham (no) SCS in patients receiving Burst-SCS as part of their standard clinical care for chronic pain management. The primary outcome measure will be the change in patient-reported ratings of pain intensity (measured by the Visual Analog Scale, VAS).[14] Secondary outcome measures will be related to the change in patient-reported ratings of pain quality [(measured by Pain Disability Index (PDI)[23] and Short Form McGill Pain Questionnaire (SFMPQ)],[24] pain severity (measured by Brief Pain Inventory, BPI),[25] pain spread (measured by Michigan Body Map, MBM),[26] and pain centralization (measured by Fibromyalgia Survey Criteria, FSQ).[27] Exploratory outcome measures will be related to the change in patient-reported ratings of affect (depression, anxiety), fatigue, sleep interference, catastrophizing, physical function, and overall quality of life. **We hypothesize that Burst-SCS will provide superior pain relief in patients as compared to sham SCS.**

5.2 To identify the therapeutic mechanisms of Burst-SCS (Aim 2).

The goal of this aim is to determine the **potential therapeutic mechanisms of action of Burst-SCS.** We will perform detailed clinical testing in the patients from Aim 1 using a series of quantitative sensory testing (QST) measures. We will assess sensitivity to non-painful vibratory stimuli and painful pressure stimuli. We will assess pain perception in response to sequential stimuli of equal physical strength (temporal summation or TS).[28] We will also determine the efficiency of (supraspinal) descending pain inhibition by measuring pain thresholds subsequent to the application of an acute conditioning stimulus (conditioned pain modulation or CPM).[29,30] **We hypothesize that patients who respond to Burst-SCS will show decreased vibration and decreased pressure-pain sensitivity, reduced TS, and improved inhibitory CPM. Alternatively, patients who do not respond to Burst-SCS will demonstrate no changes or worsening of QST outcomes**.

6. PROPOSED STUDY METHODS

6.1 Study Design

The study design is a **randomized, double-blind, placebo-controlled, crossover study design.** Subjects will participate in up to five research visits ***(Figure 1)***. During the first visit, we will screen chronic pain patients who have already been selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care. During the second visit, we will perform pre-operative baseline assessment in the subjects prior to implantation of their SCS electrode arrays. Following lead implantation, and during the externalized "**trial phase**" of Burst-SCS, we will randomize subjects to receive either 24 hours of clinically-effective Burst-SCS followed by 24 hours of sham SCS or vice versa (crossover design). We will perform assessments before the start of the

randomization (visit 3), and at the end of each 24-hour period (visits 4 and 5). **Note:** Empirical evidence suggests that maximal pain relief can be measured within 24 hours.[31-34] Patients also clearly state that their pain returns within a matter of seconds to a maximum of few hours when the stimulation is switched off.[19] Therefore, the plan for the crossover to occur after 24 hours of the initial treatment should not only be sufficient to detect significant differences in pain relief, but should also allow sufficient wash-out time for the initial treatment. Furthermore, the 24-hour stimulation window will allow us to complete the experiment within a reasonable timeframe. On the contrary, increasing the crossover period to longer than 24 hours could lead to potential confounds, such as patients increasing their medications and/or patient withdrawal because sham SCS may not provide adequate pain relief.

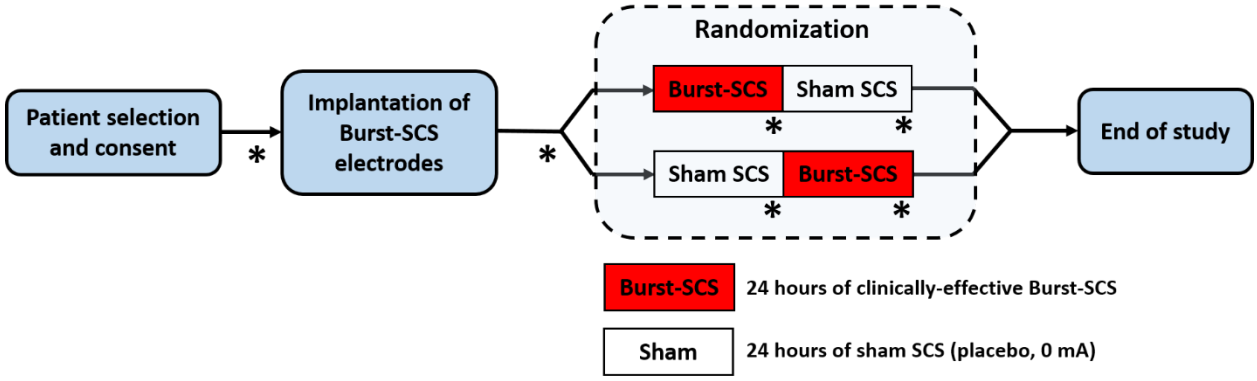

Figure 1. *Schematic of the study design. Testing time-points are denoted by* *

6.2 Study Participants and Recruitment

Patients will be recruited actively and passively. We will actively recruit patients from clinics at the University of Michigan (UM), such as clinics in the Department of Anesthesiology and the Department of Neurosurgery at University of Michigan (UM). These departments will have access to the purpose of the study, intended patient population, and inclusion/exclusion criteria. Chronic pain patients who have been deemed candidates for Burst-SCS therapy, and who are selected to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care will be considered suitable candidates for this study. For active recruitment, our team of pain specialists (e.g. anesthesiologists and/or neurosurgeons) and other study personnel at UM will identify potential candidates and inform them about the study. The study coordinator or a person from the study team will contact these candidates (e.g. via telephone) to discuss details about the study (e.g. eligibility determination) and/or to verify interest. The necessary contact information (e.g. telephone number) of the candidates will be obtained by searching appointment logs or medical records. We may also email candidates the consent forms to study and think about participation. For interested and eligible candidates, we will schedule enrollment visit and/or other subsequent visits.

For passive recruitment, we will post publicly accessible flyers and brochures throughout UM Clinics, and also in various locations around Michigan Medicine (e.g. University Hospital). We will also post flyers and brochures across various other Pain Clinics and Hospitals in Livingston, Washtenaw, and/or Wayne County. IRB-approved flyers and brochures will be hung in several locations (e.g. waiting areas) in these clinics and hospitals. These flyers will have contact information of the study team (e.g. email, phone) and will also have a description of the study **(resource included in section 8-1.8 of the IRB application).** Interested candidates may initiate contact with the study team. Screening will be done over phone to verify eligibility. For eligible candidates, we will schedule enrollment visit and/or other subsequent visits.

Note: We will provide all candidates the option of choosing to receive their appointment details by phone or text **(texting template included in section 44 of the IRB application).** Candidates traveling from more than 1.5 hours away may be offered lodging or transportation as needed.

6.3 Inclusion and Exclusion Criteria

6.3.1 Inclusion criteria

- Chronic pain patients: Men or women with chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome and intractable low back and leg pain, and who are scheduled to receive a temporary externalized trial of Burst-SCS from their own doctors as part of their standard clinical care for chronic pain management.
- Candidates who are 18 years or older and can speak, read, and understand English.

6.3.2 Exclusion criteria

- Subjects who are pregnant- as determined by verbal report or chart review.
- Subjects with current, habitual, or previous use within the last 12 months of artificial nails, nail enhancements, or nail extensions that cover any portion of either thumbnail. Exceptions, including brief and/or occasional use, may be permissible at the discretion of the principal investigator (PI).
- Subjects who are unable or unwilling to cooperate with clinical testing.
- Subjects having any impairment, activity or situation that, in the judgement of the study coordinator or PI, would prevent satisfactory completion of the study protocol.

If patients meet eligibility criteria, we will ask them (during the screening visit) if they would like to enroll in the study. If they enroll, we will ask them to sign an informed consent form/document, and invite them to be part of various study visits (included in **2. Schedule of Evaluations**). We will also ask patients about their medical, social and psychiatric history. We will additionally assess patients' psychological status (e.g. anxiety, depression) using self-reported patient questionnaires/surveys (e.g. EuroQol questionnaire, EQ-5D[35] and Hospital Anxiety and Depression Scale, HADS– **resource included in section 29 of the IRB application**).[36] If patients meet criteria for extreme anxiousness or depression (as indicated in the EQ-5D questionnaire or an equivalent score of 11-21 on HADS) we will offer/provide them with a "Depression Resource Handout" (**resource included in section 44 of the IRB application**). However, patients can still continue their participation in the study. We will also collect patients' vital signs (heart rate, blood pressure, respiration rate, and body temperature), height, and weight during the screening visit, and also during each subsequent visit. Furthermore, we will collect other additional information (e.g. demographics, sociodemographics, concomitant medications- **resource included in section 29 of the IRB application**) from the patients during enrollment and during each subsequent visit (e.g. change in medications, post-QST VAS, post-QST survey- **resource included in section 29 of the IRB application**).

6.4 Randomization

We will perform randomization using **TATUM** (Treatment Assignment Tool University of Michigan), a web-based tool developed by the Michigan Institute for Clinical & Health Research (MICHR). A MICHR biostatistician (included in our study team) will develop the randomization plan, and will create the blinded randomization list to be uploaded by a study team member in TATUM. This will enable study personnel to obtain treatment allocations and will provide functionality to manage the treatment allocation process and ensure the randomizer will not be able to retrieve a treatment assignment until a patient is ready to be enrolled in the study. TATUM will also track study treatment-allocation progress and provide documentation of the treatment assignment.

6.5 Blinding

We will have **two** research teams. **One team will be unblinded** (e.g. clinical care provider/company representative, study coordinator) and will perform stimulator programming/adjustment, and the **other team will be blinded** (e.g. research personnel) and will perform clinical testing and collect study outcome measures.

6.6 Stimulator programming

During the stimulator programming session, subjects will receive either 24 hours of clinically-effective Burst-SCS (i.e. active treatment phase) followed by 24 hours of sham SCS (i.e. no treatment phase/placebo control phase) or vice versa. Patients will be blinded during programming. Before patients participate in this study, clinicians will have determined which stimulation parameters provide the best pain relief as part of a patient's standard clinical care. For this study, we will use these clinically-effective stimulation parameters during the active treatment phase.[14] During the placebo control phase or no treatment phase of stimulation, we will use the same parameters as in the active treatment phase, except that we will set the stimulation amplitude to 0 mA.[14] We will use the **St Jude Medical™ Invisible Trial System** to apply stimulation via externalized extension wires (**this device is listed in section 16 of the IRB application**).[14,15] Patients will not be able to change the stimulation settings during either treatment phase, as they will not receive the patient programmer. However, we will instruct patients to use the magnet, if needed, in the case of emergency. The magnet can be used to turn the stimulation on or off, in the absence of the programmer.

7. PROPOSED STUDY PROCEDURES

We will conduct the proposed study in accordance with the requirements of the University of Michigan Medical School Institutional Review Board (IRBMED). **All study visits will be conducted at UM**.

7.1 Assessing the treatment effects of Burst-SCS (Aim 1).

7.1.1 Primary Outcomes

We will measure primary outcomes using patient-reported VAS ratings. VAS ratings are the most commonly-used clinical outcome measure in SCS.[14,37] Operationally, a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, such as "no pain" and "worst possible pain" (description included in SFMPQ and in Post-QST VAS – **both resource included in section 29 of the IRB application**). The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks. The main advantage of using VAS ratings is that it will allow us to compare our outcomes to other clinical results available in the literature.[14,15,17-21]

7.1.2 Secondary Outcomes

We will measure secondary outcomes using several self-reported patient questionnaires (**all included in section 29 of the IRB application**). We will use the SFMPQ[24] and PDI[23] to assess the patient's description of the quality of pain. The main component of the SFMPQ consists of 15 descriptors (11 sensory and 4 affective) rated on a 4-point intensity scale (0=none to 3=severe). Three pain scores are derived from the intensity rank values of the words chosen for sensory, affective and total descriptors. The SFMPQ also includes the present pain intensity index (i.e. the VAS), and an evaluative overall intensity of total pain experience. The PDI is a 6-question survey regarding daily living activity. Range is 0 (completely able to function) to 10 (totally unable to function), with higher number indicating greater diability. We will use the BPI to assess the severity of pain and its impact on daily functioning.[25] The BPI is a 9-question survey with scores ranging from 0 to 10, with higher scores indicating more severe pain and greater interference with functioning. We will use the MBM to assess body areas where chronic pain is experienced, and specifically quantify the degree of widespread body pain in the patient (i.e. pain

centralization).[26] We will also use the FSQ in combination with the MBM to assess pain centralization.[27] We will administer these questionnaires on paper and/or using the Qualtrics survey platform.

7.1.3 Exploratory Outcomes

We will measure other or exploratory outcomes using several self-reported patient questionnaires (**all included in section 29 of the IRB application**) and using various QST methods (all described in section 7.2.1). We will use the PainDETECT to detect neuropathic pain components in patients.[38] We will use the HADS to assess anxiety and depression,[36] Patient Reported Outcomes Information System Sleep Disturbance Short Form questionnaire (PROMIS SD) to assess sleep interference, and Coping Strategies Questionnaire (CSQ) to assess catastrophizing in patients.[39] We will use the EQ-5D to characterize the patient's quality of life.[35] We will administer these questionnaires on paper and/or using the Qualtrics survey platform.

7.2 Assessing the therapeutic mechanisms of Burst-SCS (Aim 2).

7.2.1 Quantitative Sensory Testing (QST)

We will perform a battery of psychophysical pain tests in the patients from Aim 1. The overall objective of the tests is to evaluate pain processing at different levels of the neuraxis. We will assess generalized mechanical sensitivity using the Multimodal Automated Sensory Testing (MAST) device. We will assess spinal segmental sensitivity using a vibrometer and a pressure algometer. We will assess temporal summation (TS) using a pointed skin probe. We will assess descending pain inhibition using the test of conditioned pain modulation (CPM). We will conduct all tests, including patient familiarization and training. For each test, we will read scripted instructions to the patients, and we will advise them that they can stop testing at any time without penalty if the sensations become intolerable.

7.2.1.1 Generalized Mechanical Sensitivity. We will assess generalized mechanical sensitivity using the MAST device.[40] The device consists of: 1) a wireless, hand-held thumbnail pressure stimulator with a circular 10 mm^2 rubber tip, 2) client interface displaying a pain-rating scale, and 3) a clinician interface used to design and control testing paradigms and generate data reports ***(Figure 2A).*** In this study, we will use the MAST device to deliver mechanical stimuli in the form of a series of automated (ascending) pressures onto the thumbnail bed ***(Figure 2B).***

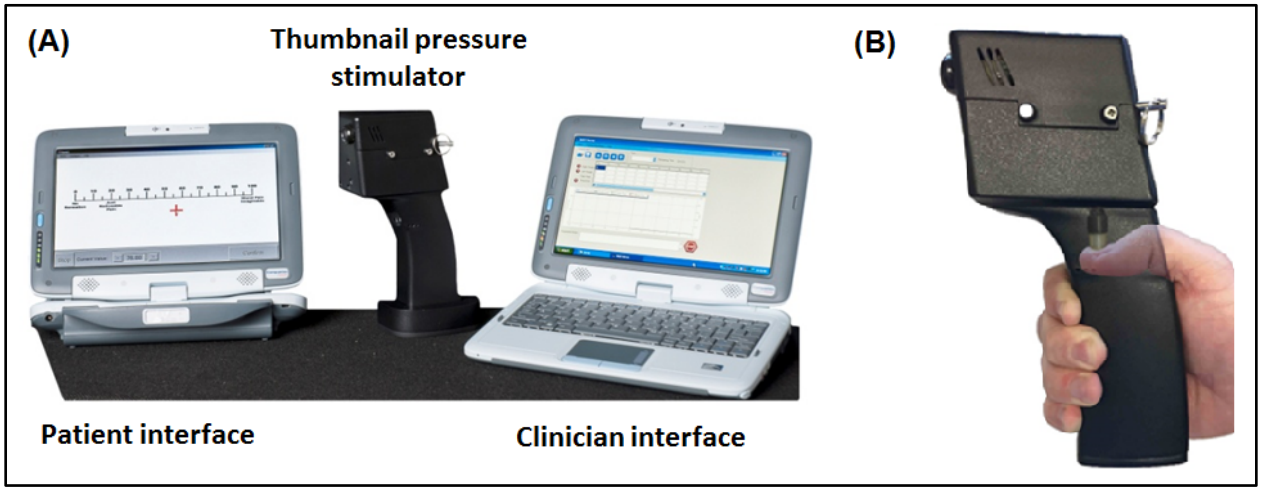

Figure 2. *Generalized mechanical sensitivity assessed using the MAST system. (A) MAST system components: thumbnail pressure stimulator, patient interface displaying a pain-rating scale, and clinician interface used to design and control testing paradigms and generate data reports. (B) Close-up view of the thumbnail pressure stimulator.*

First, we will apply 1-2 light "sample" pressures to the participant's thumbnail to ensure proper thumb positioning. Once the subject's thumbnail is in the proper position, we will conduct the familiarization procedure. We will apply a series of discrete pressure-pain stimuli to the subject's left or right thumbnail. After each pressure is released, we will ask the subjects to rate their pain on a VAS or a 0-100 numerical rating scale (NRS), with 0 representing "no pain" and 100 representing "worst possible pain". If any pressure is intolerable, subjects are allowed to let us know and the pressure will be released immediately. Subjects can also release the pressure themselves by pressing the 'STOP' button on their screen. Following familiarization, we will conduct the MAST ascending test, where we will apply an ascending series of discrete pressure stimuli with a duration of 2.5-5 s beginning at 0.25 kg/cm^2 and increasing in 0.25-0.50 kg/cm^2 steps to the subject's opposite thumbnail. We will ask the subjects to rate their pain using a VAS or a 0-100 NRS. Testing is completed when a pain rating >80 using a VAS or a 0-100 NRS is received or after 10 kg/cm^2 of pressure has been applied. The MAST system will calculate, in kg of force, the patient's pain detection threshold, tolerance, and moderate and high supra-threshold pain values. Following this test, a second series of tolerable pressures (as determined from the MAST ascending test) may be delivered in a random order. **Note:** This paradigm may require minor modifications during the execution of this protocol. These modifications will not exceed the parameters described above, i.e. maximum pressure intensity will never exceed 10 kg/cm^2.

7.2.1.2 Spinal Segmental Sensitivity. We will assess spinal segmental sensitivity using a manual vibrometer[41] and a pressure algometer[33,42] at the primary pain site ***(Figure 3).*** The primary pain site is defined as the area of maximum pain intensity (i.e. the area of worst possible pain) as reported by the patient. If severe hyperalgesia or allodynia prevents testing of the primary pain site, we will select an adjacent, less sensitive pain area. We will also perform testing at mirror sites (site directly opposite to the tested pain site) and/or bilaterally at several control sites (e.g. trapezius, lateral epicondyle, forearm). We will perform testing with the subject resting in a stationary position (e.g. sitting, supine, prone) to reduce the possibility of postural compression of the nerves being tested.

We will use a handheld vibrometer (VSA-3000, Medoc Inc., Ramat Yishai, Israel) with a 1 cm^2 circular probe ***(Figure 3 (A))*** to deliver vibratory, non-painful stimuli to determine sensitivity to vibration. We will apply an ascending series of vibratory stimuli. Subjects will report the first sensation of vibration (denoted as vibratory threshold). We will average the vibratory thresholds across two or three consecutive trials at each site separated by intervals of approximately 20 to 60 seconds. We may also apply a random sequence of fixed intensity vibratory stimuli, 1-3 times each, to the individual sites.

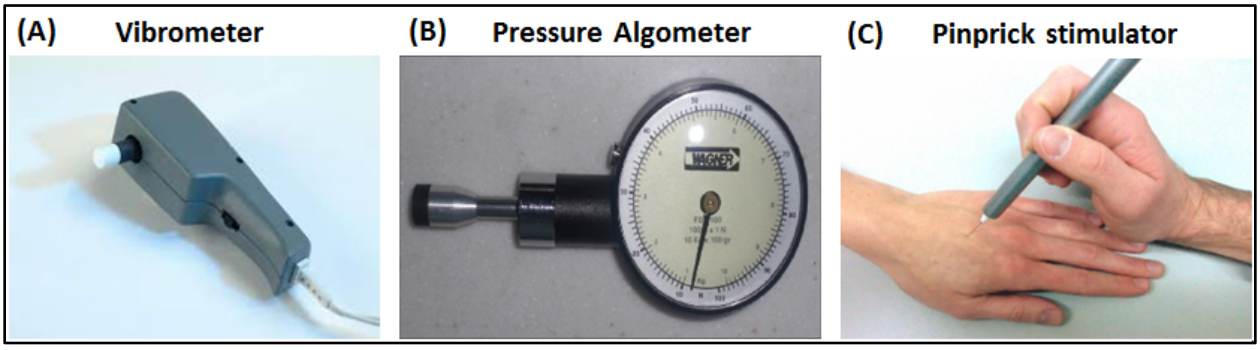

Figure 3. *Spinal segmental sensitivity assessed using a (A) Vibrometer and a (B) Algometer. TS is assessed using a (C) PinPrick stimulator.*

We will use a handheld, analog pressure algometer (FPK Algometer, Wagner Instruments, Greenwich, CT) with a 1 cm^2 flat rubber probe ***(Figure 3 (B))*** to deliver pressure-pain stimuli. We will increase the pressure at a rate of approximately 0.30 kg/cm^2 or 30-50 kPa/s (100 kPa/s maximum rate),

to a maximum of 10 kg/cm^2. Subjects will report their first sensation of pain (pressure-pain detection threshold) and pressure-pain tolerance. We will average the pressure-pain thresholds and pressure-pain tolerance across two or three consecutive trials at each site separated by intervals of approximately 20 to 60 seconds. We may also apply a random sequence of fixed intensity pressures, 1-3 times each, to the individual sites. We will ask the subjects to report the pain intensity of the pressure stimuli using a VAS or a 0-100 NRS.

7.2.1.3 Temporal Summation (TS). We will use a handheld, pointed skin probe (PinPrick Stimulator, MRC Systems, GmbH) to deliver a fixed intensity stimulus to evaluate TS ***(Figure 3 (C))***. TS refers to an increased perception of pain in response to sequential stimuli of equal physical strength. It is a QST model of neural plasticity and central hyper-excitability that is thought to reflect the progressive increase in neuronal firing of dorsal horn neurons in response to repetitive nociceptive C-fiber stimulation (i.e. windup).[28] We will apply a single fixed intensity stimulus (256 mN or 512 mN) using the pointed skin probe perpendicular to the subject's skin for approximately 0.5 seconds. Following a 5-second pause, we will apply a train of 10 identical stimuli (256 mN or 512 mN) with a frequency of 1 Hz within an area of 1 cm^2. Immediately following the single stimulus and the train of 10 stimuli, we will ask the subjects to report the pain intensity of the stimulus using a VAS or a 0-100 NRS. We will conduct this testing paradigm (a single stimulus followed by a train of 10 stimuli) 3 times with the same 256 mN or 512 mN stimulator, and each cycle will be separated by at least 10 seconds. For each testing site (pain site and control site), we will divide the mean pain rating of the 3 stimulus trains by the mean pain rating of the single stimuli to calculate a wind-up ratio (WUR); a WUR of >1 indicates temporal summation. At 15- and 30-seconds following the last train of 10 stimuli, we will ask subjects to rate any residual pain sensation in the testing area using the 0-100 NRS.

7.2.1.4 Conditioned Pain Modulation (CPM*).* We will use CPM to test the effect of a noxious "conditioning" stimulus on a "test" stimulus to determine the efficiency of (supraspinal) descending pain inhibition. We will use pressure delivered by the algometer as the test stimulus, and a contralateral thumbnail pressure (using MAST) as the conditioning stimulus. We will determine pressure-pain thresholds before and after application of a conditioning stimulus. The conditioning stimulus is a 60-second continuous pressure to the contralateral thumbnail at the exact or similar pain intensity as the test stimulus. During the first 30-s, subjects will rate the intensity of the thumbnail pressure alone on a VAS or a 0-100 NRS. Parallel to the last 30-seconds of CPM conditioning while the subjects' thumb is still in the MAST device, we will reapply the test stimulus and determine pressure-pain thresholds. We will conduct the CPM test separately on the pain site and the control site. We will evaluate CPM as the mean difference in pressure-pain thresholds before and after application of a conditioning stimulus. If the difference in pressure-pain threshold is found to be negative, the subject is considered to have achieved an inhibitory CPM response; if the difference in pressure-pain threshold is found to be zero or positive, it is concluded that the subject did not exhibit a CPM response.

7.2.1.5 Other important considerations*.* If the participant has been diagnosed with peripheral neuropathy in the upper extremity that could potentially interfere with the MAST results, we will skip the MAST and thumb-based CPM procedures. However, the participant will complete the other tests. If the participant has a missing, severely malformed, or injured thumb on which testing is to be performed, we will conduct MAST testing on the opposite thumb, provided it is not missing nor injured. For example, we would conduct both familiarization and testing on the dominant thumb if the non-dominant thumb was abnormal, or vice-versa. To permit sufficient tissue recovery, we will provide a rest interval of 5-10 minutes between the MAST familiarization protocol and the MAST test, if we conduct testing on the same thumb. We will record the thumb on which familiarization and testing occurred. If

both thumbs are missing and/or injured, we will skip the MAST and the thumb-based CPM tests. However, the participant will complete the other tests.

8. STUDY STATISTICS AND DATA ANALYSIS PLAN

8.1 Sample Size

For this study, we will recruit **20 chronic pain patients** for whom Burst-SCS has been recommended as a treatment option as part of their standard clinical care.

8.2 Data Analysis Plan

8.2.1 Initial data screening.

Prior to any of the substantive analyses, we will evaluate the data to ensure that it has appropriate variability and distributional properties for the subsequent analyses. When necessary and sensible, we will consider data transformations, including the elimination of outliers and the reduction of non-linearity and non-normality, for variables with problematic properties.

8.2.2. Defining the variables of interest

Table 1. *Variables of interest*

Treatment Outcomes
Primary outcome: VAS ratings
Secondary outcomes: Self-reported patient questionnaires (SFMPQ, PDI, BPI, MBM, FSQ)
Exploratory outcomes: Self-reported patient questionnaires (PainDETECT, EQ-5D, HADS, CSQ, PROMIS SD), QST measures (generalized mechanical sensitivity, vibration sensitivity, pressure-pain sensitivity, TS and CPM)

8.3 Data analysis

8.3.1 Treatment outcomes

We will compute VAS scores at pre-implantation (visits 1 and 2) and post-implantation (visits 3,4 and 5) to help assess percentage change in pain scores due to the effects of stimulation (Burst-SCS and sham SCS). We will also compare our VAS ratings to other clinical results available in the literature. Similarly, we will assess outcomes of pain-specific questionnaires at pre-implantation and post-implantation, and compare across all patients using appropriate statistical tests.

8.3.2 QST

We will conduct appropriate statistical tests to compare the effects of stimulation (Burst-SCS and sham SCS) on the various QST measures. We will also look for potential correlations between pain intensity and QST measures.

9. STUDY SITES

We will conduct this study at UM, and therefore this is a single-center study. We will not perform this study at any UM Family Health Center, Regional Hospitals or any non-UM sites such as nursing homes, schools or community-based organizations.

10. INFORMED CONSENT

We will explain the study verbally and in writing. If interested, candidates will sign an informed consent, and will be given a copy. **We will withhold information regarding the type of treatment (active vs. sham), and the order of treatment (active/sham vs. sham/active) the subjects will receive during the study (concealment).** Instead, we will inform subjects that we are adjusting the settings on

their SCS device. We will inform candidates that the purpose of this study is to investigate the potential mechanisms of action of Burst-SCS. We will also explain to each candidate that there will be no expected benefit to him/her by participating in this research study. However, it is possible (although not anticipated) that during this research new stimulator settings may be found that could be beneficial. We will also explain that the knowledge gained from this research may be beneficial for others, society, and/or science. **Note:** We will debrief subjects at the conclusion of their last research visit (i.e. visit 5). Concealment is necessary to conduct this research study to avoid potential for altering subject behavior such that study results are biased.

The research team (e.g. PI or other study personnel) will conduct the consent interview and the interview will take place in a private setting (e.g. examination room, office), allowing sufficient time for prospective subjects to make an informed decision. Furthermore, we will also offer candidates the option of taking the informed consent form home to study and think about participation, with a follow up with one of the investigators or study personnel. We will only recruit subjects who can speak, read, and understand English.

11. WAIVER OR ALTERATION OF INFORMED CONSENT

Alteration of the informed consent is requested, since this research involves the deception or concealment of subjects.

12. CONFIDENTIALITY OF DATA

The study requires obtaining direct patient identifiers due to collecting standard of care data in addition to the research data for the project. We will assign subject numbers to patients and those numbers will be used in the research. We will maintain a password-protected file linking subject numbers to identifying information on a UM computer. Research personnel will store identified study data in accordance with standard regulations and will not be disclosed or shared with any outside third parties. Identifying information will be severed from study data that is reported. Only relevant research personnel listed in the institutional review board (IRB) study application will have access to study files and folders. We will protect the data on a laptop computer or on a removable device by encryption.

13. DATA SAFETY AND MONITORING

All research personnel involved in any way in this project will have completed training in the protection of human research participants per guidelines issued by the United States Department of Health and Human Services, Office for Human Research Protection. The protocol will undergo review and approval by the IRBMED and other necessary regulatory and oversight entities prior to implementation.

13.1 Causality

Events will be considered study related if classified by the PI or other study personnel as possible, probable, or definite. Association of events to the study will be made using the following definitions ***(Table 2).***

Table 2. *Definition of causality events.*

Term	Definition
Definitely Not	The event is definitely not associated with the study
Probably Not	The temporal association, patient history, or clinical condition is such that the study is not likely to have had an association with the observed event.

Possible	The event: a) follows a reasonable temporal association with the study procedures, but b) could have been produced by the patient's clinical condition or other therapy.
Probable	The event: a) follows a reasonable temporal association with the study conduct, b) abates upon discontinuation of study procedures, and c) cannot be reasonably explained by the patient's clinical condition or other therapy.
Definite	The event: a) follows a reasonable temporal association with the study, b) abates upon discontinuation of study procedures, c) cannot be reasonably explained by the patient's clinical condition or other therapy, and d) reappears on re-exposure to the study procedures.
Unknown	Not enough information exists for the assessment of causality at the time of occurrence.

13.2 Severity

The PI or other study personnel will grade the signs and symptoms as mild, moderate, severe, or life threatening according to the following definitions ***(Table 3).***

Table 3. *Adverse events severity scale.*

Grade	**Definition**
Mild	Causing no limitation of usual activity
Moderate	Causing some limitations of usual activities
Severe	Causing inability to carry out usual activities
Life Threatening	Patient was at immediate risk of death from the event

13.3 Serious Adverse Event (SAE)

Any adverse event (AE) that:

- Is fatal;
- Is life threatening, meaning the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
- Causes a persistent or significant disability or incapacity;
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization if it is longer than 24 hours or requires an intervention to treat emergent symptomatology (non-diagnostic);

Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed in this definition. We will report SAEs to the IRBMED per the IRBMED Standard AE Reporting Plan at https://az.research.umich.edu/file/864. If the SAEs are not related to the study, we will report them at Continuing Review. If the SAEs are related to the study, we will report them within 7 days or sooner to the IRB. We will also report AEs and SAE's to the PI. If there is any evidence of a pattern of unanticipated AEs (regardless of causality), or SAE, we will immediately have an independent third party review these data. Based on the conclusions of this individual, the PI will either terminate the study or convene a Data Safety and Monitoring Board to make recommendations.

13.4 Termination of Subjects

13.4.1 Subject Decision.

Subject participation is strictly voluntary and the research strictly knowledge driven; therefore, a subject may withdraw from further participation in the study without penalty or harm. Any reason(s) the subject may give for terminating his or her participation will be kept confidential. We will store the study documents according to the procedures outlined in the Confidentiality of Data section of this protocol (Section 12). We will require no further information of the subject and the subject will be compensated for their completed study visits prior to termination.

13.4.2 Investigator Decision.

Study personnel (PI, Co-Is, and study coordinator) will be authorized to release a subject from further study participation according to the following guidelines:

- The researcher believes that it is not in the subject's best interest to stay in the study.
- Subject becomes ineligible to participate.
- Subject's condition changes such that he or she needs treatment that is not allowed while taking part in the study.
- Subject does not follow instructions from the researchers.
- The study is suspended or canceled.

Upon termination of a subject, the investigators will ensure the subject is dismissed with any study documents to which he or she is entitled. Subjects will be compensated for their completed study visits prior to termination. Investigators will require no further obligation or participation from a terminated subject.

14. PROTECTION OF HUMAN SUBJECTS

14.1 Risks to Human Subjects

Potential risks include: risk related to Burst-SCS and lead placement, risk of completing surveys, risks related to QST, risks related to electrical stimulation, risk related to loss of confidentiality, and additional risks.

14.2 Potential Risks and Protection against Risk

14.2.1 Risk related to Burst-SCS therapy.

Subjects will be asked to sign a separate consent explaining the potential risks involved with Burst-SCS therapy by their own doctor(s) as part of their standard clinical care for chronic pain management.

14.2.2 Risk of completing surveys.

The risks associated with completing the personal symptom surveys, may cause some discomfort or personal distress. However, the subject may refuse to answer any question on the questionnaires or surveys that may be uncomfortable.

14.2.3 Risks related to QST.

The MAST testing may cause some temporary physical discomfort on the thumbnail. The MAST system includes multiple software, electrical, and mechanical safeguards to ensure that the amount of pressure applied does not exceed safe limits, including a safety release pin that the subject can turn to immediately release the pressure actuator from his or her thumb. The test is terminated at or before 10 kg/cm^2 of pressure which is a commonly-used maximum pressure level in human sensory testing and does not result in physical injury. Subjects can also stop the stimulus at any time or express instructions to stop the stimuli. The subjects can also withdraw their thumb from the device.

The vibrometer, pressure algometer and the pointed skin probe are commonly used in QST studies and will not cause any tissue injury at the maximum forces applied in this study. However, the instruments may cause minor physical discomfort in the areas of testing that is expected to resolve within minutes of test completion. We will halt these tests automatically if subjects report a pain rating of 100.

Overall, the QST procedures may cause minor but temporary physical discomfort. The comfort and well-being of the subjects are very important to us and we have designed the QST experiments following strict safety standards and to be as brief as possible. We will limit the intensity of each stimulus to levels that are deemed safe and acceptable. Furthermore, study personnel are trained by the investigators to be sensitive to participant discomfort and concerns. The patient can inform the person to stop the QST at any time that the pain or unpleasantness of the task becomes intolerable.

14.2.4 Risks related to electrical stimulation.

During the stimulator programming session, subjects will receive either 24 hours of clinically-effective Burst-SCS (i.e. active treatment phase) followed by 24 hours of sham SCS (i.e. no treatment phase/placebo control phase) or vice versa. For the active treatment phase, we will use clinically-effective stimulation parameters that provided the best pain relief as part of a patient's standard clinical care. Therefore, we do not anticipate any side-effects related to stimulation. However, stimulation-induced paresthesias may sometimes occur (usually as a tingling sensation) due to positional changes (e.g. bending, lifting) and/or extreme movement. We will instruct the subjects to avoid such movements during the 24-hour period. We will also ensure that we set the stimulation amplitude so that patients are unlikely to feel any stimulation-induced paresthesias. During the placebo control phase or no treatment phase of stimulation, we will use the same parameters as in the active treatment phase, except that we will set the stimulation amplitude to 0 mA. Therefore, patients may not get adequate pain relief, due to the absence of stimulation. To minimize this risk, we limit the duration of the placebo control phase to 24 hours.

Whenever using electricity to stimulate tissue, there is also the possibility of a shock hazard, including an electrical burn. However, we will use only electrical stimulators approved by the FDA for Burst-SCS. Therefore, the risk of tissue damage or electrical shock during the electrical stimulation is minimal.

14.2.5 Risks related to loss of confidentiality.

Physicians, engineers, and technicians participating in the necessary research procedures will each have initial access to the patient and his/her name. This is the case for any standard of care treatment. Collaborators in this research will acquire data that initially contains the patient's name and other identifiable information. However, we will assign subject numbers to patients and those numbers will be used in the research. We will maintain a password-protected file linking subject numbers to identifying information on a UM computer. Only relevant research personnel listed in the IRB study application will have access to study files and folders. We will protect the data on a laptop computer or on a removable device by encryption.

14.2.6 Additional risks

This research requires that subjects extend their Burst-SCS trial by an additional 2-3 days. This additional time may increase the likelihood of some risks, such as infection or other device-related complications. However, the total duration of the trial, including both the time for the standard of care (~5-10 days) and research procedures (~2-3 days), will be well within the 30-day trial period that is allowed for the approved indication of Burst-SCS. Therefore, the percentage chance that subjects incur these additional risks is negligible.

15. RESEARCH COSTS

We will use funds from the grant (MICHR-EMG) as well as internal discretionary funds to cover the costs of materials that are necessary for this research. These costs include (but are not limited to) patient incentives, patient room rental, testing material, and biostatistical support. This research project may also involve the use of a study coordinator whose effort will be covered with the grant funds and/or internal discretionary funds.

16. INVESTIGATIONAL DRUG

There is no involvement of any investigational drug in this study.

17. INVESTIGATIONAL DEVICE

We will be using an investigational device in this study (**St. Jude Medical Invisible Trial System**), but it is an FDA-approved device being used in accordance with the labeling.

18. MARKETED DRUGS/DEVICE

This study does not involve an approved device for an indication different from the approved labeling or instruction use. The study does not require an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) as it does not involve a route of administration or dosage level, use in a subject population, or other factors that significantly increase the risks associated with the use of a device.

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