Comparing Long-Term Effectiveness of High Frequency and Burst Spinal Cord Stimulation

Study Protocol and Statistical Analysis Plan

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No Funding is necessary considering the pragmatic nature of the study.

Specific Aims:

We are proposing to compare the effectiveness of high frequency and burst spinal cord stimulation in patients with chronic back and/or leg pain.

More than one hundred million Americans suffer from chronic pain with estimated annual cost of $635 billion.[1] To better characterize these patients, Stanford Pain Management Center has implemented a patient reported registry, Collaborative Health Outcomes Information Registry (CHOIR), since 2012. CHOIR surveys include National Institute of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) item banks, a body map, questions about pain intensity, pain catastrophizing scale, and questions about patients' pain experience and healthcare utilization. This learning healthcare system also has the capability of point-of-care randomization.

Spinal cord stimulation is one of the most effective treatments for patients with intractable trunk and limb pain. Traditional tonic spinal cord stimulation resulted in at least 50% pain reduction in about half of the patients.[2,3] Newer waveforms – high frequency and burst – achieve 50% pain reduction in 60-75% of the patients in comparison.[4-6] However, more studies are needed to compare effectiveness of these two new waveforms.

We are proposing to use patient reported outcomes to conduct a pragmatic clinical trial that integrates with patients' clinical care; thus, allowing faster recruitment of a larger patient cohort. The patient's provider will use CHOIR point-of-care randomization to randomly assign patients to either receive high frequency or burst spinal cord stimulation. The patients will then complete online CHOIR surveys sent out to them at baseline and then 1, 3, 6, 12, 18, 24 and 36 months after their device implant. These surveys will include PROMIS item banks for pain interference, function, depression and anxiety; questions about pain intensity; and questions about any potential side effects. We will include patients with chronic (pain for at least 6 months) back and/or leg pain refractory to conventional management.

Specific Aim 1: Comparing effectiveness of high frequency and burst spinal cord stimulation in improving pain, function and pain interference in patients with chronic low back and/or leg pain persistent more than 6 months.

We hypothesize that high frequency spinal cord stimulation is more effective than burst spinal cord stimulation in decreasing chronic low back and/or leg pain.
Our primary outcome is change from baseline in pain intensity at 12 months. We will also compare improvement in function and pain interreference at all follow up time points. We will plot the trend of all these measures and study change from baseline at 12 months. We will use repeated measure linear regression to compare these measures between the groups at follow up time points with time as the fixed effect and treatment as random effect.

Specific Aim 2: Comparing effectiveness of high frequency and burst spinal cord stimulation in improving depression and anxiety in patients with chronic low back and/or leg pain persistent more than 6 months.

We hypothesize that high frequency spinal cord stimulation is more effective than burst spinal cord stimulation in decreasing stress and anxiety in patients with chronic low back and/or leg pain.
Burst stimulation modulates medial thalamic pathway, which attributes adverse emotions to pain. We will therefore compare emotional response to these waveforms. We will compare change from baseline of depression and anxiety at 12 months. We will also plot depression and anxiety trend at all follow up time points between two groups using repeated measure linear regression. We will then perform a similar stratified analysis in responders (patients with 50% or more pain reduction at 1 year) and non-responders to these treatments; this analysis is to asses if pain reduction is an effect measure modifier in this relationship.

Research Strategy

(a) Background and Significance:

Chronic pain is a major healthcare problem affecting more than 100 million Americans. Chronic pain is a devastating disease entity that can significantly compromise patients' quality of life and cause disability. It imposes an annual cost of around $635 billion on United States healthcare system. The number of treatment modalities available for this condition is disproportionately low; the quality of data available for these modalities is not optimal either.[1]

A well-recognized and serious problem with current literature is the generalizability of the data. Large clinical trials usually have stringent inclusion and exclusion criteria. By restricting enrollment of patients with more serious comorbidities and psychological conditions, researchers can attribute the observed differences to the interventions studied. But we cannot easily generalize the results to a large population of patients with more serious comorbidities and psychological conditions; these patients are usually more difficult to treat. Better evidence and solutions are essential for this cohort of patients in particular.[7] Our current literature lacks high quality data to guide clinicians providing care to these patients. A simple example is the implant to trial ratio in patients undergoing trial of spinal cord stimulation. While most large clinical trials show that approximately 90% of patients have a successful trial of spinal cord stimulation and proceed with implantation,[4,6,8] large case series reporting experience of academic centers report that only 70% of the patients undergoing trial of spinal cord stimulation proceed to receiving an implanted device.[9,10] This example illustrates the disparity between results of well-designed, well-performed clinical trials and what we can realistically achieve in daily clinical care.

Pragmatic trials integrated with patient care is one of the solutions to the current problem. These trials have a less stringent inclusion and exclusion criteria targeting all patients who receive clinical care. Thus, the participants of these studies better represent our target population: *patients with chronic pain*. Embedding research in patient care will allow enrollment of larger number of patients with minimal disruption of patient care. This will enable the researchers to analyze known and unknown effects of treatments in the whole sample as well as in specific subgroups.[11]

Pragmatic trials focus more on effectiveness rather than efficacy. An initial explanatory clinical trial usually proves the efficacy of a certain treatment in experimental settings. However, such trials do not typically acquire enough information to assess long term effectiveness of the treatment in the setting of clinical care. In addition to efficacy, other factors affect effectiveness of a treatment including compliance, accessibility, ease of administration, etc. Ideal experimental settings of a traditional explanatory clinical trial differ from usual conditions of clinical care. In chronic diseases in particular, studying long term *effectiveness* of a treatment modality in usual conditions of clinical care directs care to achieve meaningful sustainable improvement for patients.[11-13]

Treatments available for patients with chronic pain are limited and do not offer remarkable changes in patients. Development of spinal cord stimulation in late 1960's changed this trend for select patient populations.[14] Very simply, spinal cord stimulation is based on gate control theory of pain: introducing different stimulus to spinal cord can modulate pain signal transit.[15] Initial trials showed that spinal cord stimulation results in at least 50% pain relief in about half of the patients compared to conventional medical management that could achieve the same pain decrease in about 10% of the patients.[2] Spinal cord stimulation is also superior to repeat surgery in patients with post-laminectomy syndrome.[3] Patients undergo surgical implantation of epidural leads and an internal pulse generator to get this therapy.

According to Food and Drug Administration labeling, patients with chronic pain (more than 6 months) in trunk or limbs refractory to conventional management are considered for receiving this treatment. Length and type of conventional treatment is not well-defined and can be interpreted by clinicians. Applying this therapy requires two steps:

1. Trial period: One to two percutaneous leads are inserted into the epidural space. The distal ends of the leads connect to an external pulse generator (outside the body) that delivers pulses of electricity to dorsal column of spinal cord. The patients live with this trial system for 5-10 days, testing its efficacy in reducing pain intensity and improving function. At the end of trial period, the physician removes the trial leads and discusses the outcome and further steps with the patient. The figure shows a trial system.
2. Implant of permanent device: If the patients experience more than 50% pain relief during trial period, they will undergo a surgery for implanting a permanent device. The permanent device consists of one to two epidural leads and an internal pulse generator. Patient can use a remote control to change between the programs of the device. They can also recharge the batter of the internal pulse generator. The figures show the components of spinal cord stimulator.

Traditional tonic spinal cord stimulation was the only available option for a few decades prior to introduction of newer waveforms in 2015 and 2016. Tonic stimulation delivers one pulse of electricity at frequency of 40-60 hertz. The pulse

width ranges from 200 to 450 microseconds. Patients usually need pulse amplitude of 3.5-8.5 milliamperes. High frequency stimulation increases the frequency to 10,000 hertz and the pulse width is the limited to 30 microseconds. The patients usually need amplitudes of 1.5-3.5 milliamperes. High frequency spinal cord stimulation results in more than 50% pain relief in about three quarters of the patients (vs. half of the patients with tonic stimulation).[4,5] Burst stimulation applies a train of five stacked pulses (without time to discharge between pulses) which is repeated at frequency of 40-60 Hertz. Burst spinal cord stimulation results in more than 50% pain relief in two third of patients.[6] The figure compares tonic and burst waveforms.

In addition to somatic pain pathway (lateral thalamic pathway), burst spinal cord stimulation also activates medial thalamic pathway as detected by increased EEG activation.[16] This pathway interprets emotional aspects of pain. Thus, clinicians have speculated that this waveform can improve patients' emotional status and mood; however, this is not verified in any clinical studies.

Availability of more diverse and efficacious waveforms and devices has remarkably advanced the field of neuromodulation but has created a dilemma for pain physicians: what is the best waveform and device for ***each*** patient? Overall superiority of the device as well as its appropriateness in individual patients is very important. We are thus proposing to compare effectiveness of these two new waveforms in patients with chronic back and lower extremity pain. The results of this study will help clinicians make more informed decisions choosing appropriate neuromodulation modality for patients with chronic pain.

(b) Innovation:

Comparing effectiveness of high frequency and burst spinal cord stimulation:

In comparison with conventional medical management (including medications, physical therapy, etc.), spinal cord stimulation results in more superior pain relief in a larger number of patients with chronic refractory pain in trunk and extremities. This treatment can achieve 50% pain relief in about half of the patients.[2,3] More novel waveforms – high frequency and burst – are even more effective by achieving 50% pain relief in 60-80% of patients.[4-6] However, it is unclear if either high frequency or burst spinal cord stimulation works better for all or a subgroup of patients. Our proposed research aims to compare effectiveness of these two novel waveforms in patients with chronic low back and/or leg pain. Moreover, the pragmatic nature of our proposed trial enables us to follow up these patients longer than currently published clinical trials.

Length of Follow-up:

Currently, data is available about safety and efficacy of high frequency and burst spinal cord stimulation for up to 24 months. However, more long-term effectiveness of these treatment modalities has to be established. Our proposed research aims to follow up the patients for 36 months (and possibly longer).

Pragmatic design using point-of-care randomization:

Stanford Pain Management Center enjoys the luxury of an established learning health system – Collaborative Health Outcomes Information Registry (CHOIR) – with capability of point-of-care randomization. This system is already integrated in patient care in our clinic; thus, enrollment, randomization and follow-up data collection will be achieved on the same platform with minimal intrusion in clinical care.

Preliminary Data:

Comparative effectiveness research compromises normal clinical operations when researchers add experimental manipulations. Integrating research with clinical care should aim at offering the strengths of experimental design while remaining minimally intrusive. At Stanford Pain Management Center, we developed a novel, integrated clinical and research environment to achieve this goal. Collaborative Health Outcomes Information Registry (CHOIR) is an open-source learning health care system developed to monitor patient progress in both perioperative and pain medicine settings. This platform is an innovative tool for both patient care and research. All patients referring to Stanford Pain Management Center are asked to complete these surveys at initial visit and each follow-up visit after that. Our clinicians use the data to monitor clinical progress. CHOIR uses the validated National Institute of Health (NIH) Patient Reported Outcomes Measurement and Information System (PROMIS) measures.[17] In addition, the patients answer questions about their pain experience, cause of pain, treatments received, current treatments, etc. CHOIR has built in computer adaptive testing to improve efficiency in data collection and reduce patient burden.

To date, we have more than 100,000 entries for around 30,000 patients in CHOIR (across all national and international sites) and this number is growing. There have been multiple retrospective and prospective studies performed using data from CHOIR.[18-25] Moreover, CHOIR is now being utilized in growing number of centers nationally and internationally (and in multiple clinical conditions), creating the opportunities for future multi-center pragmatic trials in perioperative and pain

medicine. We have successfully developed the software for our clinicians to perform point of care randomization without interrupting patient care. Patient-Centered Outcomes Research Institute (PCORI) recently awarded our center (Dr. Beth Darnall) an award for a multi-state study on "comparative effectiveness of pain cognitive behavioral therapy and chronic pain self-management within the context of opioid reduction". We are using CHOIR and the same point of care randomization tool for this study of over 1000 patients (https://www.pcori.org/research-results/2017/comparative-effectiveness-pain-cognitive-behavioral-therapy-and-chronic-pain). Similarly, American Society of Anesthesiologists Foundation for Anesthesia Education and Research awarded the principal investigator for another study using CHOIR for point-of-care randomization (comparative effectiveness of duloxetine and desipramine in patients with chronic pain).

(c) Approach:

Study Design: We are proposing to conduct a pragmatic randomized clinical trial to compare long-term effectiveness of two novel spinal cord stimulation waveforms: high frequency and burst. We are planning to study the superiority of high frequency spinal cord stimulation in improving pain and function, and superiority of burst spinal cord stimulation in improving depression and anxiety.

Patients: We will enroll chronic pain patients referring to Stanford Pain Management Center who meet the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Adult English-speaking patient 18 years old or above
2. Persistent pain in lower back and/or leg for more than six months
3. Candidate for spinal cord stimulation (with either high frequency or burst waveforms) based on recommendations from Stanford Pain Management Center Neuromodulation Multidisciplinary Team Conference.

Exclusion Criteria:

1. Motor weakness in neurological examination in lower body based on the assessment by treating pain physicians
2. Previous failed spinal cord stimulation trial with either high frequency or burst waveforms
3. Patient refusal

Randomization: After obtaining informed consent, the patients who meet the inclusion and exclusion criteria will be 1:1 randomized to undergoing treatment with spinal cord stimulation with either high frequency or burst waveforms. Treating pain physician will randomize the patient during clinic visit using CHOIR point-of-care randomization system. Randomization algorithm will be based on computer generated numbers in random blocks of four, six and eight.

Blinding: Two different competing manufacturing companies will be providing devices that deliver these two waveforms. Interacting with the manufacturer representative for programming and device maintenance will inform the patient of the type of waveform. Therefore, blinding will be challenging, and we will not attempt to blind the patients to the treatment they are receiving. The risk profile and maintenance of these devices are similar; they are novel to the patients with similar efficacy literature. Thus, we do not expect differences in either compliance or therapy expectation secondary to lack of blinding. The figure shows the process of the study up to randomization.

Intervention: At Stanford Pain Management Center, pain physicians identify candidates for spinal cord stimulation; thereafter, they refer these patients to our pain psychologists. A multidisciplinary neuromodulation team conference – which is attended by pain physicians and pain psychologists in our division – assesses appropriateness of spinal cord stimulation for these candidates based on their pain diagnosis, spinal anatomy, history of spine surgery, medical comorbidities, psychological comorbidities, expectations, cognitive status and mood stability. The team also recommends the choice of devices appropriate for each patient who is identified as an optimized candidate. With current evidence, the team does not distinguish between high frequency and burst waveforms. The checklist of items discussed during these team conferences is provided in Appendix 1. The treating physician will then obtain informed consent and randomize the patients who are identified as optimized candidates for spinal cord stimulation by multidisciplinary neuromodulation team conference. These participants will receive treatment with either high frequency or burst spinal cord stimulation.

High Frequency: After randomization, the patient will be scheduled for placement of trial system. We will use Senza® (Nevro Corp., Palo Alto, CA) trial and implant systems to deliver high frequency spinal cord stimulation. A trial system includes two trial leads, an external pulse generator, and a remote control. The permanent implant system includes two leads, an internal pulse generator, a remote control, and a charging device for internal pulse generator. We will use our routine process of trial and implant.

We will position the patients prone on the operating room table, minimizing the lordosis of lumbar spine. We will assist patient comfort and relaxation by nurse-administered moderate sedation titrating doses of midazolam and fentanyl. The patients will be conversing to communicate unusual pain to avoid accidental damage to any neural structures. After

appropriate skin preparation and draping, fluoroscopy will be used to identify and mark vertebral body levels from T8 to L2. After infiltrating skin and subcutaneous tissue with local anesthetic for analgesia, we will access epidural space at most convenient lumbar space using a 14-gauge Tuohy needle. Epidural access will be confirmed using loss of resistance technique to air with a pulsator syringe. We will then insert an 8-contact, styletted trial lead through the needle. We will advance the lead through posterior epidural space at midline using live fluoroscopy imaging. We will place the tip of the lead at the superior border of T8 vertebral body. We will then access the epidural space and insert a second lead in a similar fashion. The tip of the second lead will be in the middle of T9 vertebral body; the contacts will be staggered with the other lead. We will then check the impedance of the contacts. After confirming appropriate placement, we will remove the needles and lead stylets under live fluoroscopy imaging. We will secure the leads and apply transparent occlusive dressing. We will then transport the patient to post-anesthesia care unit. A representative from the manufacturer will connect the leads to an external pulse generator which will be secured in a small bag around patients' waist. The manufacturer representative will then program the device and will be communicating with the patient daily during the trial period. The trial period will be 5-10 days. We will instruct the patients to maintain the same routine end even try to be more active to test efficacy of the treatment. We will also instruct the patients to keep the dressing, the leads and external pulse generator completely dry. The external pulse generator will deliver the therapy continuously during the trial period. High frequency waveform will be delivered with following parameters: frequency of 10,000 hertz, pulse width of 20 microseconds, and amplitude of 0-15 milliamperes. The patients will return to our clinic at the end of the trial period to remove the trial leads and discuss the treatment outcome. If the patients report more than 50% pain relief and/or improvement in function, they will be scheduled for implant of permanent spinal cord stimulation system at least two weeks after removal of trial leads.

For implant, we will position the patient prone on the operating room table minimizing lumbar lordosis. An anesthesiologist will provide appropriate level of sedation during the surgery. After appropriate skin preparation and draping, fluoroscopy will be used to identify and mark vertebral body levels from T8 to L2. After infiltrating the skin and subcutaneous tissue with local anesthetic for analgesia, we will make a vertical midline incision for placement of leads and anchoring devices. After achieving hemostasis, epidural access will be achieved similarly to the trial. We will then use a similar approach to place the leads in the posterior midline epidural space. We will then thread the anchoring device over the leads, suture the anchoring devices to the fascia layer, and tighten the anchoring device around the lead using the provided torque screw-driver.

We will then make a horizontal incision between iliac crest and ischial tuberosity to create a pocket for internal pulse generator. After hemostasis, we will tunnel the leads from the midline incision to the lateral pocket incision. After appropriate irrigation, we will close both incisions in multiple layers. We will then apply an occlusive dressing and take the patient to post-anesthesia care unit. The manufacturer representative will then program the device. The parameters of the waveform will be similar to the trial.

Burst: After randomization, the patient will be scheduled for placement of trial system. We will use BusrtDR™ (Abbott Saint Jude Medical, St. Paul, MN) trial and implant systems to deliver burst spinal cord stimulation. A trial system includes two trial leads, an external pulse generator, and a remote control. The permanent implant system includes two leads, an internal pulse generator, a remote control, and a charging device for internal pulse generator. We will use our routine process of trial and implant.

The trial and implant process will be identical to high frequency with one difference: correct placement of the leads will be confirmed during the trial procedure by inducing paresthesia over the painful area (instead of standard anatomical placement with high frequency). The parameters of the stimulation are as below: each burst includes 5 pulses of electrical stimulation at intra-burst frequency of 500 hertz without time for discharge in between pulses. These bursts will be repeated at inter-burst frequency of 40-60 hertz. The amplitude will range between 0 and 15 milliamperes.

Data Collection: As a part of evaluation for spinal cord stimulation, patients in our clinic complete initial survey on Collaborative Health Outcomes Information Registry (CHOIR). The participants will receive electronic surveys via email at 1, 3, 6, 12, 18, 24 and 36 months after the operation for implant of spinal cord stimulator (or trial in case of failed trial). The participants will receive email reminders after three and five days if the surveys are not completed. If the participants do not complete the surveys within seven days of receipt of the survey link, they will be contacted to be reminded of the survey. These surveys will include average and worst Numerical Rating Scale (NRS) of pain; National Institute of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) measures for function, pain interference, depression and anxiety; patient global impression of change on a 7-point Likert scale; and questions about any adverse events related or unrelated to the therapy. Data about use of other analgesics and medications, and pain interventions

will also be recorded at these intervals from participants' electronic health records and California Prescription Drug Monitoring Program. We will also record participants' baseline characteristics including age, sex, main pain diagnosis, other pain diagnoses, psychological comorbidities, medical comorbidities, medication use, and education level.
Adverse events will be reported to the principal investigator either directly by the participants or through the treating pain physician at Stanford Pain management Center. The principal investigator is responsible for reporting the adverse events and deviations from the protocol appropriately to institutional review board and other authorities.
Mood instability will be monitored as a component of routine clinical care by treating physician.

Outcomes:

Primary Outcome:

- Change from baseline in pain intensity at 12 months. Baseline pain intensity is measured at last CHOIR completion before trial, and is based on patient reported outcome in CHOIR for average pain in the week prior to completion of questionnaire.

Secondary Outcomes:

1. Patient global impression of change at all follow up time points
2. Pain intensity at all follow up time points
3. Change from baseline in function at 12 months
4. Function at all follow up time points
5. Change from baseline in pain interference at 12 months
6. Pain Interference at all follow up time points
7. Change from baseline in depression at 12 months
8. Depression at all follow up time points
9. Change from baseline in anxiety at 12 months
10. Anxiety at all follow up time points
11. Daily opioid dose in morphine equivalent at all follow up time points

Analytic Plan: We will test the hypotheses that:

1. High frequency spinal cord stimulation is more effective than burst spinal cord stimulation in decreasing pain at 12 months in patients with chronic low back and/or leg pain.
2. High frequency spinal cord stimulation is more effective than burst spinal cord stimulation in improving pain, pain interference and function in patients with chronic low back and/or leg pain.

We will use repeated measure linear regression to compare these measures between the groups at follow up time points with time as the fixed effect and treatment as random effect. This method allows missing data subject to assumption of missing at random.

3. Burst spinal cord stimulation is more effective than high frequency spinal cord stimulation in improving depression and anxiety in patients with chronic low back and/or leg pain.

We will use repeated measure linear regression to compare these measures between the groups at follow up time points with time as the fixed effect and treatment as random effect. This method allows missing data subject to assumption of missing at random. Some improvement in depression and anxiety is expected to be the result of improvement in pain and function. We will also perform a stratified analysis in responders (patients who achieve >50% pain relief) and non-responders (patients who do not achieve 50% pain relief) to the treatments.

4. Patients receiving burst spinal cord stimulation will report higher satisfaction with treatment using patient global impression of change compared with patients receiving high frequency spinal cord stimulation.

We will use SAS Enterprise Guide (SAS Institute Inc., Cary, NC) for all analyses. Our null hypotheses are similarity of measures. We will perform a two-sided hypothesis testing with accepted type I error of 0.05. We will compare baseline characteristics using t-test for continuous variables and chi-square for categorical variables. We will adjust for the variables that are different between the groups in our final regression model. Our primary analysis will be based on modified intention-to-treat. We will only exclude patients with no follow up data from our final analysis. We will then perform a secondary analysis based on implants only (excluding patients who do not achieve appropriate pain control in trial period).
We will then perform the following subgroup analyses:

1. Patients who have undergone lumbar spine fusion versus patients who have not.
2. Patients with back pain only (based on baseline body map) versus patients with back and leg pain or leg pain only.

3. Patients with PROMIS depression measure of above 90th percentile in baseline evaluation.
4. Patients with PROMIS anxiety measure of above 90th percentile in baseline evaluation.

The rate of CHOIR survey completion is more than 60% in our routine clinical care. We expect a higher rate for our proposed study considering that these surveys are abbreviated, and participants will receive more frequent reminders as well as telephone reminders (currently patients receive only one email reminder to complete the survey). For our primary outcome we will try to minimize missing data by calling the patients who do not complete the surveys up to seven times; we will try to ask and record the pain intensity even if they are not willing to complete surveys. Our analysis model will allow for missing data in longitudinal variables, subject to assumption of missing at random.

Data and Safety Monitoring Plan: We will not perform any interim analyses for benefit, harm or futility. We will establish a data and safety monitoring board consisting of investigators, at least two independent clinicians in our clinic (not part of the study team), and at least one neurosurgeon subspecialized in spine surgery who will monitor the study quarterly for adverse events and patient safety, reporting of adverse events, enrollment pace and study timeline, quality of data, and deviations from the protocol.

Sample size: The highest standard deviation of NRS pain scale in our clinic is 2.25 based on prior publications.[19,21-25] Accepting type I error of 0.05 with 80% power, we will require 80 participants per group to detect one unit between-group difference in change from baseline in NRS pain scale. We are proposing a more conservative (larger) sample size to preserve power considering that some patients do not proceed from trial to implant and do not receive therapy. Currently more than 80% of patients who undergo a trial of spinal cord stimulation proceed to receiving an implant. We will therefore target 100 patients in each arm. Correlation between repeated measure will decrease variance and increase the power of the proposed study.

Timeline: Stanford Pain Management Center performed more than 120 trial of spinal cord stimulation in 2017 and this practice is increasing in our division. We expect a high consent rate considering the nature of our study. We believe we will be able to complete recruitment in two years; thus, last follow up of last recruited patient will be completed by five years.

Data Management: CHOIR will be the main tool for data collection and storage for the study. At completion of the study, the data from CHOIR, participants' electronic health records and California Prescription Drug Monitoring Program will be downloaded for analysis. After initial steps of data preparation, we will de-identify the dataset for further analysis. The principal investigator will save the de-identification code on a secure computer within Stanford University Network only.

Limitations:

1. One of the most important advantages of pragmatic clinical trial with less stringent inclusion/exclusion criteria is to improve the ability to generalize the results to a wider range of patients. However, considering that the current study is a single center study conducted in a tertiary pain management center, our sample might not be representative of chronic pain patients seen by community pain providers.
2. Our aim is to integrate our trial into patient care; thus, we are not blinding the provider and the participants. Method of data collection is similar in both groups and does not involve interaction with investigators. This will minimize, but not eliminate, the bias introduced by proceeding with an open label design.
3. Costs of treatment will be covered as part of usual care and paid by insurance. However, any patients for whom their insurance does not cover this therapy will be excluded. Fortunately, most insurers readily cover this therapy.
4. We allow treatment with all other modalities. Therefore, any benefit observed cannot be solely attributed to study interventions. However, this ambiguity is expected to be non-differential between the groups since the patients are randomized to these treatments. Moreover, our goal is to assess the effectiveness of these treatments in the setting of routine patient care where we allow other treatments and changes.
5. Because stimulation parameters are preset, outcome differences could be attributed either to the device (HF vs. burst) or to fixed parameters that might not necessarily elicit the optimal performance of the device.

Appendix 1. Checklist of items discussed during multidisciplinary team conference.

Patient's Name:

MRN:

Age and Gender:

1. Modality & Device chosen
2. Diagnostic indication
3. Relevant imaging
4. Conservative therapies trialed/failed
5. Medical comorbidities/medications
6. Relevant labs (ECG, A1C)
7. Secondary plan if patient fails trial
8. Significant social factors that should be considered (appropriate f/u, living circumstances, etc.)
9. The patient's coping status if the trial fails
10. Appropriate expectation from the treatment (this applies to interventionalist too)

Appendix 2. Process of patient selection for spinal cord stimulation at Stanford Pain Management Center

Appendix 3. Measurement tools (not including PROMIS item banks)

Patient Global Impression of Change (PGIC)
Since the start of the study, my overall status is:
□ Very Much Improved
□ Much Improved
□ Minimally Improved
□ No Change
□ Minimally Worse
□ Much Worse
□Very Much Worse

Pain Intensity:
In the past 7 days:
How intense was your average pain on a scale of 0-10 with zero indicating no pain and 10 indicating the worst imaginable pain?

In the past 7 days:
How intense was your pain at its worst on a scale of 0-10 with zero indicating no pain and 10 indicating the worst imaginable pain?

References

1. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC), Institute of Medcine, 2011
2. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB: Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007; 132: 179-88
3. North RB, Kidd DH, Farrokhi F, Piantadosi SA: Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery 2005; 56: 98-106; discussion 106-7
4. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH: Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology 2015; 123: 851-60
5. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Yearwood TL, Bundschu R, Yang T, Benyamin R, Burgher AH: Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery 2016; 79: 667-677
6. Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, Tavel E, Staats P, Falowski S, Pope J, Justiz R, Fabi AY, Taghva A, Paicius R, Houden T, Wilson D: Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation 2018; 21: 56-66
7. C. G, J. S, R. E: Large Simple Trials and Knowledge Generation in a Learning Health System, Learning Health System. Washington DC, Institute of Medicine, 2013
8. Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Obray J, Scowcroft J, Golovac S, Kapural L, Paicius R, Kim C, Pope J, Yearwood T, Samuel S, McRoberts WP, Cassim H, Netherton M, Miller N, Schaufele M, Tavel E, Davis T, Davis K, Johnson L, Mekhail N: Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain 2017; 158: 669-681
9. Hayek SM, Veizi E, Hanes M: Treatment-Limiting Complications of Percutaneous Spinal Cord Stimulator Implants: A Review of Eight Years of Experience From an Academic Center Database. Neuromodulation 2015; 18: 603-8; discussion 608-9
10. Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J: Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract 2011; 11: 148-53
11. Fiore LD, Lavori PW: Integrating Randomized Comparative Effectiveness Research with Patient Care. N Engl J Med 2016; 374: 2152-8
12. Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutical trials. J Clin Epidemiol 2009; 62: 499-505
13. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K: A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009; 62: 464-75
14. Shealy CN, Mortimer JT, Hagfors NR: Dorsal column electroanalgesia. J Neurosurg 1970; 32: 560-4
15. Melzack R, Wall PD: Pain mechanisms: a new theory. Science 1965; 150: 971-9
16. De Ridder D, Vanneste S: Burst and Tonic Spinal Cord Stimulation: Different and Common Brain Mechanisms. Neuromodulation 2016; 19: 47-59
17. Bevans M, Ross A, Cella D: Patient-Reported Outcomes Measurement Information System (PROMIS): efficient, standardized tools to measure self-reported health and quality of life. Nurs Outlook 2014; 62: 339-45
18. Bhandari RP, Feinstein AB, Huestis SE, Krane EJ, Dunn AL, Cohen LL, Kao MC, Darnall BD, Mackey SC: Pediatric-Collaborative Health Outcomes Information Registry (Peds-CHOIR): a learning health system to guide pediatric pain research and treatment. Pain 2016; 157: 2033-44

19. Carriere JS, Martel MO, Kao MC, Sullivan MJ, Darnall BD: Pain behavior mediates the relationship between perceived injustice and opioid prescription for chronic pain: a Collaborative Health Outcomes Information Registry study. J Pain Res 2017; 10: 557-566
20. Hah JM, Sturgeon JA, Zocca J, Sharifzadeh Y, Mackey SC: Factors associated with prescription opioid misuse in a cross-sectional cohort of patients with chronic non-cancer pain. J Pain Res 2017; 10: 979-987
21. Karayannis NV, Sturgeon JA, Chih-Kao M, Cooley C, Mackey SC: Pain interference and physical function demonstrate poor longitudinal association in people living with pain: a PROMIS investigation. Pain 2017; 158: 1063-1068
22. Sharifzadeh Y, Kao MC, Sturgeon JA, Rico TJ, Mackey S, Darnall BD: Pain Catastrophizing Moderates Relationships between Pain Intensity and Opioid Prescription: Nonlinear Sex Differences Revealed Using a Learning Health System. Anesthesiology 2017; 127: 136-146
23. Sturgeon JA, Carriere JS, Kao MJ, Rico T, Darnall BD, Mackey SC: Social Disruption Mediates the Relationship Between Perceived Injustice and Anger in Chronic Pain: a Collaborative Health Outcomes Information Registry Study. Ann Behav Med 2016; 50: 802-812
24. Sturgeon JA, Darnall BD, Kao MC, Mackey SC: Physical and psychological correlates of fatigue and physical function: a Collaborative Health Outcomes Information Registry (CHOIR) study. J Pain 2015; 16: 291-8.e1
25. Sturgeon JA, Dixon EA, Darnall BD, Mackey SC: Contributions of physical function and satisfaction with social roles to emotional distress in chronic pain: a Collaborative Health Outcomes Information Registry (CHOIR) study. Pain 2015; 156: 2627-33