

Single Center, Randomized Prospective Comparative Effectiveness Study of Dorsal Column Spinal Cord Stimulation to Dorsal Root Ganglion Stimulation in the Treatment of Complex Regional Pain Syndrome

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Protocol Synopsis

Title:	Single Center, Randomized Prospective Comparative Effectiveness Study of Dorsal Column Spinal Cord Stimulation to Dorsal Root Ganglion Stimulation in the Treatment of Complex Regional Pain Syndrome of the Lower Extremity
Investigational Products	<ol style="list-style-type: none"> 1. Nuvectra Algovita Dorsal Column Spinal Cord Stimulation System 2. Abbot Proclaim Dorsal Root Ganglion Spinal Cord Stimulation System
Regulatory Status	Post-market evaluation. The indications for both dorsal column and dorsal root ganglion neurostimulation utilized in this study are cleared by the FDA.
Study Objective:	To compare the outcomes of dorsal column stimulation with Dorsal Root Ganglion stimulation in patients with Complex Regional Pain Syndrome that persist despite a course of conservative management including physical therapy and analgesic pharmacotherapy.
Study Design:	Prospective, randomized single center study. Patients will be randomized in a 1:1 ratio to Dorsal Column or Dorsal Root Ganglion stimulation after they have failed conservative treatment.
Patient Population:	Patients with Budapest criteria (research diagnostic definition) of Complex Regional Pain Syndrome occurring below the umbilicus who have not had an adequate response to conservative management including analgesic and physical therapies.
Enrollment Size and Number of Sites:	A total of 62 patients will be recruited from a single center
Primary Outcome:	50% change in index pain using a Numerical Rating Scale (NRS) at 6 months
Secondary Outcome:	30% change in function based on Oswestry Disability Index (ODI)
Additional Assessments:	<ul style="list-style-type: none"> • Change in Quality of Life as measured by EQ-5D • Change in Health Status measured by Short Form-36 (SF-36) • Pre and Post Procedure Pain medication usage • Global Improvement Impression of Change (PGIC) • Satisfaction with the pain relief, therapy in general, and likelihood of undergoing the therapy again for a similar outcome • Neurological assessment • Additional intervention(s)

	<ul style="list-style-type: none"> • Safety defined as adverse events related to the procedure or devices
Inclusion Criteria	<p>All patients must meet all of the following Inclusion Criteria to be eligible to be enrolled into the study:</p> <ul style="list-style-type: none"> • Patient is greater than 18 years of age • An infraumbilical location of the index pain • Symptoms have been present for greater than 6 months • Continuing pain which is disproportionate to any inciting event • Report hyperesthesia and/or allodynia • Report vasomotor changes including temperature asymmetry and/or skin color changes and/or skin color asymmetry • Report edema and/or sweating changes and/or sweating asymmetry • Report decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) • Display at least one sign in two or more of the following categories: <ul style="list-style-type: none"> ○ Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) ○ Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry ○ Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry ○ Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) • Patient failed to have resolution of symptoms despite at least 4 weeks of conservative management including analgesic pharmacotherapy and physical therapy • Patient has index site pain \geq spine pain • The subject is physically and mentally able to participate in the study • Patient is willing and able to provide informed consent • Patient is willing and able to comply with the study protocol
Exclusion Criteria	<p>All patients who meet any of the following Exclusion Criteria should not be enrolled into the study:</p> <ul style="list-style-type: none"> • Previous surgery to the spine which could compromise placement of the study device

	<ul style="list-style-type: none"> • Anatomical spinal abnormality including severe central canal stenosis or bony foraminal impingement which could preclude device placement • Foreseen need for MRI to monitor or evaluate another chronic condition • Previous experience with an implanted or trial neuromodulation system (spinal cord stimulation, peripheral nerve stimulation) for the treatment of pain at the index location • Active local or systemic infection • Actively in litigation for pain symptoms • Currently on Workman’s Compensation • Women who are pregnant or intend to become pregnant during the study duration
Study Duration / Follow-up Period	Patients will be followed for an additional 6 months after device implant, with visits at 10 and 30 days, and 3 and 6 months post-procedure. Interim visits for device programming visits will be considered routine.
Baseline Visit	<ul style="list-style-type: none"> • Demographics: gender, age, height, weight • History • Characterization of the inciting event including duration of pain symptoms • Previous treatments including conservative management and physical therapy • Diagnosis and review of the inclusion and exclusion criteria • Neurological assessment • NRS for the index pain location • Pain medication usage (dosage and frequency)
Psychological Assessment	Psychological assessment will consider appropriateness for a neuromodulation system and for participation in a clinical device study.
Pre Trial Visit	<ul style="list-style-type: none"> • Neurological assessment • NRS for the index pain location • ODI • EQ-5D • SF-36 • Satisfaction with baseline management strategy • Pain medication usage (dosage and frequency)

	<ul style="list-style-type: none"> • Presurgical trial evaluation as stratified by the investigator including advanced imaging if necessary • Randomization
Trial Procedure	<ul style="list-style-type: none"> • Neurological assessment • NRS for the index pain location • Pain medication usage (dosage and frequency) • Trial of the study device
Trial Device Removal (7 days postop +/- 3 days)	<ul style="list-style-type: none"> • Wound check, trial device removal • NRS for index site pain • Neurological assessment • Additional intervention(s) • Complications / Adverse events
Pre Implant Visit	<ul style="list-style-type: none"> • Neurological assessment • NRS for the index pain location • ODI • EQ-5D • SF-36 • Satisfaction with present management strategy • Pain medication usage (dosage and frequency) • Presurgical medical evaluation, history and physical examination, and additional special tests as stratified by the investigator including laboratory analysis, EKG, infectious screening, and/or advanced imaging
Implant Procedure	<ul style="list-style-type: none"> • Neurological assessment • NRS for the index pain location • Pain medication usage (dosage and frequency) • Implantation of the study device
Post-Operative Follow-up Visit (10 days postop +/- 3 days)	<ul style="list-style-type: none"> • Wound check, suture removal • NRS for index site pain • Neurological assessment • Additional intervention(s) • Complications / Adverse events
Follow-up Visit (30 days +/- 7 days)	<ul style="list-style-type: none"> • NRS for index site pain • Neurological assessment • ODI • EQ-5D

	<ul style="list-style-type: none"> • SF-36 • Pain medication usage (dosage and frequency) • PGIC • Additional intervention(s) • Complications / Adverse events • Radiograph to evaluate lead(s) position
Follow-up Visit (3 month +/- 14 days)	<ul style="list-style-type: none"> • NRS for index site pain • Neurological assessment • ODI • EQ-5D • SF-36 • Pain medication usage (dosage and frequency) • PGIC • Satisfaction questionnaire • Additional intervention(s) • Complications / Adverse events
Follow-up Visit (6 month +/- 14 days)	<ul style="list-style-type: none"> • NRS for index site pain • Neurological assessment • ODI • EQ-5D • SF-36 • Pain medication usage (dosage and frequency) • PGIC • Satisfaction questionnaire • Additional intervention(s) • Complications / Adverse events
Anticipated Unscheduled Visits	<ol style="list-style-type: none"> 1. Radiograph to evaluate device positioning 2. <i>Ad hoc</i> programming of the study device
Site	Department of Evidence Based Pain Research Cleveland Clinic 9500 Euclid Ave / C25 Cleveland, Ohio 44195

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1 INTRODUCTION

1.1 Background and Rationale

Complex Regional Pain Syndrome (CRPS) is a constellation of pain symptoms which are associated with impairment in mood, social and physical function (Harden, et al. 2007) (Deer, Levy and Kramer 2017) (Banks and Kerns 1996) (Modovan, et al. 2009). Spinal Cord Stimulation (SCS), a technique of placing electrodes into the epidural space is a validated treatment for Complex Regional Pain Syndrome (Deer, et al. 2014). Treatment of CRPS with SCS, in combination with physical therapy, reduced pain to a greater degree than physical therapy alone (Kemler, et al. 2000). 40%-50% of CRPS patients achieve >50% pain relief with SCS using dorsal column stimulation (Kemler, et al. 2000) (Geurts, et al. 2013). Dorsal Root Ganglion (DRG) SCS has also recently demonstrated clinical efficacy in patients with CRPS and peripheral causalgia (Deer, Levy and Kramer 2017) (Van Buyten, et al. 2015). We hypothesize that DRG stimulation is non-inferior to dorsal column SCS in patients with CRPS who have failed to respond to a course of analgesics and physical therapy. Additionally, we aim to assess functional, quality of life, patient satisfaction and medication requirements in subjects treated with neuromodulation for CRPS and contrast outcomes amongst subjects treated with DRG SCS and dorsal column SCS.

2 Device Indications for Use

DEVICE DESCRIPTIONS

See the manufacturer's Instructions for Use and Surgical Technique Manual for more detailed information.

The Nuvectra Algovita Dorsal Column Spinal Cord Stimulator is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back pain and leg pain.

The Axiom Neurostimulator System is indicated for spinal column stimulation via epidural and intra-spinal lead access to the dorsal root ganglion as an aid in the management of moderate to severe chronic intractable pain of the lower limbs in adult patients with Complex Regional Pain Syndrome Types I and II

Systems that will be utilized in this study are indicated for use in this condition and have already been cleared for marketing by the FDA.

3 STUDY PURPOSE AND OBJECTIVE

The purpose of this study is to compare outcomes between dorsal column spinal cord stimulation and dorsal root ganglion spinal cord stimulation in patients with Complex Regional Pain Syndrome at an infraumbilical location who have failed a course of conservative management including analgesic pharmacotherapy and physical therapy.

4 STUDY ENDPOINTS

The following endpoints will be evaluated in all patients enrolled in the study.

4.1 Primary Endpoint

- The primary endpoint in this study is 50% change in index pain using a Numerical Rating Scale (NRS) at 6 months

4.2 Additional Assessments

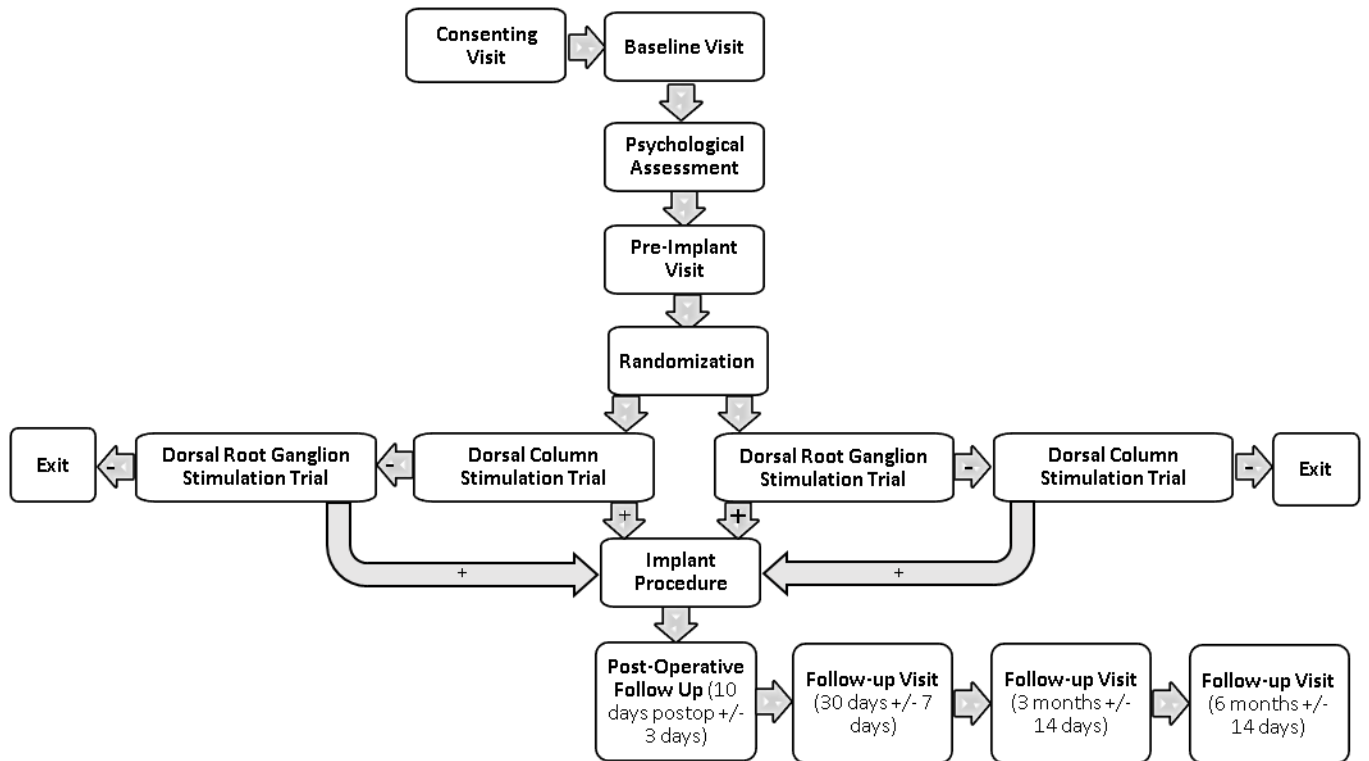
- Change in function based on Oswestry Disability Index (ODI)
- Global Improvement Impression of Change (PGIC)
- Change in Quality of Life as measured by EQ-5D
- Pre and Post Procedure Pain medication usage (dosage and frequency)
- Patient Satisfaction
- Procedure time
- Neurological assessment
- Additional intervention(s)
- Safety defined as adverse events related to the procedure or device

5 STUDY DESIGN

5.1 Overview

This is a prospective randomized post-marketing clinical study. Patients will be randomized in a 1:1 ratio to Dorsal Column or Dorsal Root Ganglion Spinal Cord Stimulation if they have failed a course of conservative management including analgesics and physical therapy. All patients are expected to undergo clinical, neurological, and imaging assessments, if appropriate, at selected follow-up visits.

Figure 1. Study Design Flow Chart



5.2 Sample Size and Number of Centers

The study will be conducted a single center with a target maximum of 62 patients (31 randomized to each group).

5.3 Study Duration

Enrollment of subjects in this study is anticipated to take 24 months. Clinical follow-up evaluations will be conducted at 10 days, 1, 3 and 6 months post-implant. The total study duration is expected to be at least 30 months.

6 STUDY PROCEDURES

6.1 Patient Eligibility, Pre-Screening and Exclusions

All patients presenting to the Investigators with Budapest criteria, research subset¹, for the diagnosis of Complex Regional Pain Syndrome at an infraumbilical location who have not had an adequate response to a course of conservative management including analgesics and physical therapy will be screened for eligibility. A Screening/Enrollment Log will be utilized in order to maintain a cumulative tracking of all screened patients.

Patients must meet all inclusion/exclusion criteria for enrollment in the clinical study. Reasons for screening failure(s) will be documented.

6.1.1 Inclusion Criteria

Patients must meet ALL of the following criteria to be eligible for participation in the study:

- Patient is greater than 18 years of age
- An infraumbilical location of the index pain
- Symptoms have been present for greater than 6 months
- Continuing pain which is disproportionate to any inciting event
- Report hyperesthesia and/or allodynia
- Report vasomotor changes including temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Report edema and/or sweating changes and/or sweating asymmetry
- Report decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

¹ To make the clinical diagnosis of CRPS using the “research subset” patients must have at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom in three of the four following categories:

- Sensory: Reports of hyperesthesia and/or allodynia
- Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
- Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in two or more of the following categories:

- Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
- Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
- Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
- Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms (Harden, et al. 2007)

- Display at least one sign in two or more of the following categories:
 - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
 - Vasomotor: Evidence of temperature asymmetry ($>1^{\circ}\text{C}$) and/or skin color changes and/or asymmetry
 - Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
 - Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- Patient failed to have resolution of symptoms despite at least 4 weeks of conservative management including analgesic pharmacotherapy and physical therapy
- Patient has index site pain \geq spine pain
- The subject is physically and mentally able and willing to participate in the study
- Patient is willing and able to provide informed consent

6.1.2 Exclusion Criteria

All patients who meet any of the following Exclusion Criteria should not be enrolled into the study:

- Previous surgery to the spine which could compromise placement of the study device
- Anatomical abnormality including severe central canal stenosis or bony foraminal impingement which could preclude device placement
- Foreseen need for MRI to monitor or evaluate another chronic condition
- Previous experience with neuromodulation (spinal cord stimulation, peripheral nerve stimulation) for the treatment of pain at the index location
- Active local or systemic infection
- Actively in litigation for pain symptoms
- Currently on Workman's Compensation for a pain complaint at the index site
- Women who are pregnant or intend to become pregnant during the study duration

6.2 Enrollment and Written Informed Consent

Patients who pass the initial pre-screening will be asked to sign the study-specific IRB - approved Informed Consent form before any study-specific tests or procedures are performed. The investigator will inform the potential subject of the elements of the clinical

study including, risks, potential benefits and required follow-up procedures prior to obtaining the potential subject's informed consent.

6.3 Randomization

After informed consent has been obtained, patients will be randomized in a 1:1 ratio to one of two treatment groups: Dorsal Column Stimulation or Dorsal Root Ganglion Spinal Cord Stimulation. The investigator will be given numbered, sealed envelopes with a slip inside that discloses the patient assignment.

If a patient randomized to either group refuses the proposed treatment plan, they will be removed as a study participant. Patients withdrawing from the study due to randomization assignment will receive standard care with a new randomization code being assigned to the next enrolled study patient.

Investigators, their study staff, as well as study subjects will not be masked to the assigned study device. Observers will record sensory deficits to touch, pain, temperature, motor strength of major muscle groups, patient reflexes (0-4 scale), analgesics doses and frequency, and radiographic assessments if necessary. Subjects will complete the patient questionnaires at each follow-up visit.

6.4 Baseline Evaluation

The following evaluations are required at the time of patient screening/baseline.

- Demographic Information: gender, age, weight, height, and smoking status.
- Medical / Surgical History / Previous conservative treatment(s)
- Physical/Neurological Exam
 - Sensory Function/Deficit - Evaluated by the subject's response to light touch and/ or pinprick at infraumbilical dermatome areas.
 - Motor Strength - Evaluated by the subject's ability to contract various muscle groups. Strength will be measured pre-operatively and at each follow-up visit as either:
 - 0 - absent, total paralysis
 - 1 - trace, palpable or visible contraction
 - 2 - poor, active movement through full range of motion (ROM) with gravity eliminated
 - 3 - fair, active movement through full ROM against gravity
 - 4 - good, active movement through full ROM against resistance
 - 5 - normal
- Local tissue temperature asymmetry in the index pain location compared to the contralateral side.

- Pain Assessment: intensity of index pain using a Numerical Rating Scale (NRS)
- Functional Assessment: Oswestry Disability Index (ODI)
- Quality of Life Assessment: EQ-5D
- Health Status Assessment: SF-36
- Pain medication usage (dosage and frequency)
- Patient satisfaction with present treatment strategy

6.5 Procedure

The appropriate procedure will be performed based on the randomization assignment for each patient. Patients randomized to either group will have the device trialed, then implanted according to the standard procedures and practices at our institution.

Those who fail to respond to a trial of the randomized device will have the opportunity to cross over, and retriage the alternative device. Should they have favorable response to the second device, they will proceed to implant of the alternative system.

Any female patient of child bearing age who does not have a documented history of surgical sterilization will have a urine pregnancy test performed within two hours before the device is trialed or implanted.

Pain medications may be administered at the investigator's or prescriber's discretion. A pain medication log will be given to the patient. Continuous pain medication usage will be documented. The treating physician may continue to pharmaceutically manage the patient's pain through the length of the study as clinically indicated. Use of pain medications after either intervention, when compared to pre-intervention dosing, will be considered. The investigator or research coordinator will review the study requirements with the patient in order to maximize compliance with the follow-up schedule and the concomitant medical regimen.

The following parameters for both groups will be noted on the case report forms:

- Index pain location
- Procedure time
- Physical/Neurological Exam
- Complications / Adverse events
- Radiographic Assessment confirming appropriate device placement
- Pain medications

6.6 Post Procedures and Outcomes

Follow-up visits are scheduled for appointed times after the date of the procedure. It is important that this schedule is adhered to as closely as possible for all subjects. Study visits not completed within these time periods will be regarded as deviations. A study visit should be scheduled as closely as possible to the earlier part of the time period to allow for possible re-scheduling, thereby preventing a deviation. All subjects will be asked to return to the clinic at intervals described in **Table 1**. Device programming and radiographic lead positioning confirmation visits are anticipated unscheduled visits and do not represent protocol deviations, and may occur *ad hoc*.

The following post-operative data will be collected:

- NRS for the index site pain
- ODI
- EQ-5D
- Global Improvement Impression of Change (PGIC)
- SF-36
- Pain medication usage (dosage and frequency)
- Neurological assessment
- Patient Satisfaction
- Additional intervention(s)
- Complications / Adverse events

Table 1: Schedule of Assessments

Assessment									
	Pre-op	Trial Procedure	Trial Removal Follow-up 7 (+/- 3 days)	Implant Procedure	Post-Operative Follow-up 10 (+/- 3 days)	Follow-up Visit (30 days +/- 7 days)	Follow-up Visit (3 months +/- 14 days)	Follow-up Visit (6 months +/- 14 days)	Unscheduled Visit
Informed Consent	X								
Medical & Interval History	X	X	X	X	X	X	X	X	X
Demographics	X								
Physical Exam / Neurological Assessment	X	X	X	X	X	X	X	X	X
Pain Scales (NRS) & Pain Medication Usage	X	X	X	X	X	X	X	X	X
Oswestry Disability Index (ODI)	X					X	X	X	
EQ-5D	X					X	X	X	
Global Improvement Impression of Change (PGIC)			X		X	X	X	X	
SF-36						X	X	X	
Patient Satisfaction	X		X		X	X	X	X	
Adverse Events*	X	X	X	X	X	X	X	X	X
Other Interventions		X	X	X	X	X	X	X	X

*Adverse events should be recorded at any time during the course of the study

6.7 Patient Early Discontinuation / Withdrawal and Replacement of Patients

All subjects are informed of their right to withdraw from the clinical study at any time. Additionally, the investigator may prematurely discontinue any patient's participation in the study if the investigator feels that the patient can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the patient. However, it is anticipated that such withdrawals will be infrequent to ensure the integrity of the study. The reason for early discontinuation will be documented in the source documents and case report forms.

6.8 Lost to Follow-up Patients

Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information will include three attempts to make contact via telephone and if unsuccessful, then a certified letter from the investigator will be sent to the subject's last known address. In general, the study site coordinator should attempt to contact the subject after each missed visit to re-schedule the visit or collect patient-reported outcomes via phone interview.

7 Risk / Benefit Analysis

7.1 Benefits

Possible benefits of neuromodulation with either device may include the reduction of pain.

7.2 Risks

Possible risks associated with neuromodulation in either arm include:

- Failure to relieve pain
- Unable to place the device due to anatomical abnormality
- Infection
- Dural tear / CSF leak
- Nerve root irritation or nerve root injury with or without neurological deficit
- Seroma / Hematoma
- Vascular injury
- Bowel / bladder incontinence
- Bleeding
- Epidural fibrosis

Mean radiation exposure with spinal cord stimulation has been estimated at 13.9mGy, range: 1.8mGy-43.7mGy (Wininger, Deshpande and Deshpande 2010).

8 STATISTICAL SECTION

8.1 Statistical Considerations

A binary responder rate for spinal cord stimulation is defined as those subjects who achieved $\geq 50\%$ diminution in pain intensity. Historical responder rates with legacy spinal cord stimulation arrays were nearly 50% (North, et al. 2005). Contemporary responder rates utilizing novel programming algorithms and targeted placement now exceed 80% (Kapural, et al. 2015) (Deer, Levy and Kramer 2017) (Russo, et al. 2018).

8.2 Statistical Software

All statistical analysis will be performed using R Statistical Software Version 3.4.1.

8.3 Determination of the Sample Size

Sample size was determined based on the planned noninferiority test for effectiveness to primary end point of treatment success and contemporary responder rates. Treatment success was defined as $\geq 50\%$ reduction in the Numerical Rating Scale (NRS) score in the index area of pain. Previous data indicated that the success rate of DRG, defined as a 50% reduction in pain intensity, was 81%, and 56% for SCS (Deer, Levy and Kramer 2017). Assuming 15% attrition, an estimated 62 subjects (31 subjects in each arm) would provide greater than 70% power to test the primary end point hypothesis with a noninferiority margin of 5% at the 95% confidence interval.

8.4 Analysis of the Primary Endpoint

Descriptive statistics for all continuous variables will be presented as number of subjects, mean with SD and median with range and for the categorical variables, number and percentage of subjects will be used. DRG stimulation and SCS will be compared using a 2-sample t test (or Wilcoxon rank-sum test) for continuous outcomes and Pearson χ^2 test (or Fisher exact test) for categorical outcomes. Choice of parametric or alternative tests will be determined based on the data distributions for each measure. Two-sided confidence intervals will be also provided for certain outcome measures of interest to assess differences between the two different treatment arms. The primary end point analyzes the success rate between the two treatment arms using Blackwelder method for testing noninferiority between 2 proportions at a one-sided significance of 0.05 with setting the noninferiority margin at 5 %.

9 DATA MANAGEMENT

9.1 Data Collection

Data will be collected on paper case report forms (CRF). A unique study number will be assigned to each patient. All information recorded on the CRF about the patient will be recorded with the study number on it. The main database will contain only the study number to identify the patient. The code with patient name and study number will be maintained in a locked file cabinet in the secured designated location at the site. Any computerized data is password protected.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

Adverse events (AE) are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in which subjects, users or other persons, whether or not related to the investigational medical device.

All adverse events, regardless of relationship to the device, must be recorded, as applicable, on the case report forms provided. Adverse events that occur during this study should be treated by established standards of care, which will protect the life and safety of the patients.

Adverse events shall be assessed and documented at the time of the procedure and at all study follow-up visits.

10.1.2 Serious Adverse Events

An adverse event is considered a Serious Adverse Event (SAE) that

- a) led to death
- b) led to a serious deterioration in the health of the subject, that either resulted in
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function, or
 - 3) in-patient hospitalization or prolongation of existing hospitalization, or
 - 4) a medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to body structure or a body function.
- c) led to fetal distress, fetal death or a congenital abnormality

10.1.3 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death were not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2 Adverse Event Reporting

Any adverse event that occurs during the course of the study must be reported using the appropriate forms. The Investigator must determine whether the adverse event is serious or unanticipated, its intensity, and the relationship of each adverse event to the study device and/or procedure.

For any adverse event that is ongoing at the time of the initial report, periodic follow-up information is required until the adverse event is resolved or is judged to be chronically stable.

The Investigator will report all serious adverse events, including unanticipated adverse device effects, to the IRB according to the IRB requirements.

11 STUDY ADMINISTRATION

11.1 Statement of Compliance

The clinical investigations will be in accordance with the ethical principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil October 2013), ISO 14155:2011 and ICH-GCP Guidelines.

The clinical investigation shall not commence until approval by the IRB.

Any additional requirements imposed by the IRB or regulatory authority shall be followed.

11.2 Investigational Review Board Approval (IRB)

The study protocol shall be reviewed and approved by the IRB prior to patient enrollment. Significant changes to the investigational plan must be approved in writing by the IRB prior to implementation. A significant change is one which may increase the risk or present a new risk to a patient, or which may adversely affect the scientific validity of the study.

11.3 Informed Consent

Informed consent must be obtained from all subjects as per regulations, prior to participation in the study.

It is the responsibility of the Investigator to ensure written informed consent from each subject, or the legally authorized representative of the subject, is obtained prior to the initiation of any study-related procedures.

Patients who agree to participate in this study will do so voluntarily. They will be treated on an equal basis with all other patients. Choosing not to participate will not affect their care in any way.

Study personnel fully knowledgeable in the purposes and procedures of the study will approach all prospective study participants. The facilities and settings in which prospective participants will be presented with the opportunity to learn about and consent to participation in the study will provide them sufficient quiet and unhurried time to be informed of the study, to ask questions, and between consent being given and the initiation of study procedures. Study personnel will, after presenting the study to prospective participants, assess the subject's understanding and autonomy by asking the subject to explain the study in his/her own words.

Once that step is completed, consent will be able to be given by the subject's signing the consent form. A copy of the consent form will be given to all consented participants.

Signed subject consent forms must be retained in the study files by the Investigator, and available for review by the IRB and/or regulatory agencies, as applicable.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available, or if there is an amendment to the protocol which necessitates a change to the content of subject information and/or to the consent form. The Investigator will inform the subject of changes in a timely manner, and will ask the subject/patient to confirm his/her continuation in the study by signing a revised consent form.

Any revised informed consent form and other written information provided to subjects must receive IRB approval, as applicable

11.4 Amending the Protocol

This protocol is to be followed exactly, and will only be altered by written amendments. Amendments must be approved by all parties responsible for approving the Protocol including the IRB prior to implementation. However, in situations where the amendment is regarding safety issues and there is an immediate hazard to patients, the amendment will be submitted as an urgent amendment and can be implemented in the study prior to approval. The Informed Consent and CRFs will be reviewed to ensure these are amended if necessary.

Administrative changes that do not affect the patient benefit/risk ratio (e.g., editorial changes for clarity) may be made without any further approvals.

11.5 Protocol Deviations/Violations and Medical Emergencies

A protocol deviation or violation is a failure to comply with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed. An example of a protocol violation includes enrollment of a study subject who fails to meet inclusion/exclusion criteria as specified in the protocol. Each investigator shall conduct this clinical study in accordance with the study protocol and any conditions required by the IRB.

11.6 Criteria for Terminating Study

The investigator reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. The IRB will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.

In the event that the study is discontinued, study patients will be contacted by phone and registered mail. Study patients contacted will be asked to come into to clinic, to have their questions and concerns addressed, as well as discuss a continued plan of care.

12 References

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