Clinical Study Protocol

ECAP Study: A prospective, multicenter, single-arm study examining ECAP-controlled, closed-loop stimulation with the Evoke Spinal Cord Stimulator (SCS) System to treat patients with chronic pain of the trunk and/or limbs.

Protocol Number: CLIN-PCL-006732

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Date: 27 May 2022

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NCT04319887

Sponsor:
Saluda Medical Americas, Inc.
[redacted]

TABLE OF CONTENTS

1 CLINICAL PROTOCOL SUMMARY

Title	**ECAP Study:** A prospective, multicenter, single-arm study examining ECAP-controlled, closed-loop stimulation with the Evoke Spinal Cord Stimulator (SCS) System to treat patients with chronic pain of the trunk and/or limbs.
Investigational Device	Evoke Spinal Cord Stimulator (SCS) System (Evoke System) The Evoke System measures and records spinal cord (SC) activation resulting from stimulation via evoked compound action potentials (ECAPs). The Evoke System can be programmed to provide ECAP-controlled, closed-loop SCS or open-loop, fixed-output SCS; ECAPs may be measured and recorded in either stimulation mode.
Target Indication for Use	The Evoke System 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 the following: failed back surgery syndrome, intractable low back pain and leg pain.
Purpose	The purpose of this study is to evaluate neurophysiological measures and clinical outcomes of the Evoke System to treat trunk and/or limb pain in a real-world population.
Study Design	This study is a prospective, multicenter, single-arm study. Data will be collected at baseline, time of procedure (trial and permanent), trial phase, and at 1, 3, 6, 12, 18, and 24 months post-implantation.
Primary Objective	The primary objective of this study is to collect data in a real-world population while further characterizing neurophysiological measures and clinical outcomes.
Statistical Analysis	A number of outcome variables of interest will be collected and assessed across study visits. No pre-planned formal statistical hypothesis tests will be performed. Multivariable regression modeling and descriptive statistics will be utilized.
Data Collection	The following data will be collected: • Baseline characteristics and demographics • Procedure characteristics • Medications • Study Pain Assessment • PROMIS-29+2 • PROMIS-10 Global • Profile of Mood States (POMS 2-A Short) • Patient Global Impression of Change (PGIC) and Patient Satisfaction • Stimulation characteristics • Posture change measurements • Neurophysiological measurements • Programming parameters and characteristics • Safety (adverse events, device deficiencies, protocol deviations)
Inclusion Criteria	Subjects enrolled in this study must meet all of the following inclusion criteria (based on investigator judgement): 1. Subject has chronic intractable pain of the trunk and/or limbs (VAS ≥6 cm in at least one of the regions intended to be treated with SCS). 2. Subject is willing and capable of giving informed consent and able to comply with study-related requirements, procedures, and visits. 3. Subject has trunk and/or limb pain such that lead placement will be in the lumbar to cervical region.
Exclusion Criteria	Subjects enrolled in this study must not meet any of the following exclusion criteria (based on investigator judgement): 1. Subject is unable to operate the system. 2. Subject is an unsuitable surgical candidate. 3. Subject has a condition currently requiring or likely to require the use of diathermy. 4. Subject has another implantable stimulator such as demand type pacemakers or cardioverter defibrillator. 5. Subject is <18 years old. 6. Subject is pregnant or nursing.

	7. Subject is allergic, or has shown hypersensitivity, to any materials of the neurostimulation system which come in contact with the body. 8. Subject is involved in an injury claim under current litigation or has pending/approved worker's compensation claim. 9. Subject has prior experience with SCS. 10. Subject is being treated with electroconvulsive therapy (ECT) or transcranial magnetic stimulation (rTMS).
Investigation Sites	Up to 25 US sites.
Enrollment	Up to 300 subjects (enrollment defined as trial procedure). Enrollment is anticipated to take 36 months.

2 BACKGROUND (REPORT OF PRIOR INVESTIGATIONS)

2.1 Disease Summary

Chronic pain is one of the most common reasons for medical care resulting in one of the largest and costliest medical health problems in the developed world and it is likely to worsen(1–3). Chronic pain persists well after the initial injury or illness that produced the initial pain has healed. The International Association for the Study of Pain (IASP) has defined chronic pain as pain that lasts more than three to six months beyond the normal time of healing(4). Chronic pain invariably is generated by physical, psychological, and environmental factors (bio-psycho-social concept of chronic pain). It is difficult to manage, and many afflicted patients have a florid medical history with multiple comorbidities. Chronic pain is also difficult to generally define beyond its chronicity. Chronic pain is routinely characterized by multiple aspects including: the nature of the pain as perceived and reported (e.g. nociceptive, neuropathic, ischemic), the pathophysiology causing the pain (e.g., painful diabetic neuropathy), or the anatomical location that the pain is perceived (e.g., chronic low back pain), or a combination of these (e.g., discogenic low back pain). The published *Classification of Chronic Pain, Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* from IASP lists around 100 separately identifiable chronic pain conditions(4).

2.2 Current Treatment Options

The multifaceted nature of chronic pain requires interdisciplinary assessment and multimodal treatment. First line treatment strategies are generally conservative treatments including: exercise programs, physical therapy (PT), occupational therapy, cognitive behavioral therapy (CBT), biofeedback, acupuncture, transcutaneous electrical nerve stimulation (TENS), and oral medications. Second line treatments become more intensive and involve the use of more extreme CBT, more powerful medications such as systemic opioids, and interventional techniques such as nerve blocks (local anesthetic or steroids) and spinal injections. The last line of treatment involves more advanced therapies that require surgical interventions. Systems such as intrathecal drug delivery (IDD) or spinal cord stimulators (SCS) may be implanted. Surgery to repair an anatomical issue responsible for the pain may be performed. Finally, surgical techniques that block pathways to the brain such as cordotomy, rhizotomy, and thalamotomy may be used rarely in extreme cases.

Recent guidelines and the literature on the treatment for chronic pain of the trunk and/or limbs demonstrate that each of the surgical interventions have the potential to be effective in managing pain, increasing patient activity, and to result in high patient satisfaction when conservative treatment modalities have failed. The risk profile for SCS therapy has advantages compared to surgical revision and neuroablation due to the fact it is reversible as the device can be surgically removed. Furthermore, typically patients undergo a trial period with SCS, in which leads are temporarily placed in the epidural space and connected to an external pulse generator, to assess tolerability and the degree of pain relief prior to being permanently implanted. The Neuromodulation Foundation recommends that an SCS trial precede major reconstructive procedures and ablative therapies (5). In addition, SCS therapy has the

advantage of not having drug side effects, including respiratory distress, as compared to IDD systems, or addictive properties, as compared to opioid usage, which is currently of epidemic proportions in the United States (US). There is consensus among national medical societies to recommend SCS as a treatment option in patients with chronic, severe pain for which conservative treatment modalities have failed or are contraindicated(5–13). SCS may be delivered in parallel with other therapies and should be used as part of an overall multimodal treatment strategy.

2.3 Rationale for the Proposed Treatment

SCS is a well-established therapy with a long history of use in treating chronic intractable pain of the trunk and/or limbs. SCS consists of applying an electrical stimulus to the spinal cord which causes the activated fibers (e.g., Aβ-fibers) to generate action potentials. Aβ-fibers are the low-threshold sensory fibers in the dorsal column that contribute to inhibition of pain signals in the dorsal horn (14). The action potentials summed together form the electrically evoked compound action potential (ECAP). Therefore, ECAPs are a direct measure of spinal cord fiber activation that generates pain inhibition for an individual.

The original SCS device consisted of an implanted radiofrequency-controlled power source connected to two electrodes (Shealy et al. 1967). Over the last 50 years there have been many advances in SCS therapy, including a better understanding of the target patient population and improvements in device technology and reliability. The technology has evolved from large profile, single channel, non-rechargeable implantable pulse generators (IPG) and monopolar leads, to smaller profile, multichannel, rechargeable IPGs with new programming parameters and multiple contact leads with various electrode arrays.

A significant challenge that still remains in SCS, however, is the ever-changing distance between the stimulating electrodes relative to their spinal cord target. The electrode is fixed in the epidural space, while the spinal cord changes position within the cerebrospinal fluid with every movement, including the cardiorespiratory cycle (e.g., breathing, heartbeat), coughing, or changes in body position (e.g., standing, sitting, lying). Small changes in distance between the electrode and spinal cord result in large changes in the current reaching the spinal cord, as the current density with SCS varies with the inverse of the distance between the electrode and spinal cord squared (15). Thus, at a fixed SCS output level, the degree of spinal cord (SC) activation varies widely.

Currently available SCS systems, regardless of the stimulation parameters, are open-loop systems and incapable of measuring SC activation or varying stimulation output based upon such measurement. For these systems, the stimulation is fixed based on in-clinic programmed settings. There is a feed-forward system (16) with an accelerometer located in the pulse generator, distant from the electrode to spinal cord interface, that utilizes pre-programmed, fixed output stimulation programs based on gross postural changes (17). In all cases, however, the stimulation output does not vary based upon how much current is reaching the spinal cord, which can result in significant variation in SC activation. To manage variance in stimulation, patients generally reduce the stimulation amplitude using a remote control, which improves tolerability of stimulation and reduces the incidence of overstimulation, but also reduces the amount of analgesia that can be achieved (18).

To address these limitations, the Evoke System has been developed that is able to record in vivo human spinal cord electrophysiology continuously in real time (19,20). An ECAP is measured for each stimulation pulse delivered; this reflects the degree of SC activation elicited by SCS. The system may operate in fixed-output, open-loop (plus ECAP measurement) or ECAP-controlled, closed-loop mode. In open-loop SCS, the system measures ECAPs, which may be used to determine optimal stimulation settings, but are not used to automatically adjust stimulation current to maintain a target response. In closed-loop SCS, the difference between the measured ECAP and the target ECAP amplitude is minimized by automatically adjusting the stimulation current to maintain consistent SC activation within the individuals' therapeutic window. By real-time modulation of the output current, the closed-loop system

maintains consistent SC activation with corresponding inhibition of pain processing pathways, and thus maximizes the therapeutic effect.

The Evoke System has been designed to ensure that there are no additional risks to patients compared other commercially available SCS systems, which have a long history of safety and effectiveness. The Evoke System is the same or functionally similar to other SCS devices already on the market in terms of intended use, and with respect to their biological and technical characteristics with the primary difference being that it measures and records ECAPs, and in addition to open-loop stimulation (equivalent to other commercially available SCS systems), it offers closed-loop stimulation using ECAPs as the feedback mechanism. Importantly, the Evoke System stimulation parameters associated with patient safety and actual product use for both stimulation modes (i.e., open- and closed-loop) fall within the range of currently approved SCS systems.

2.4 Summary of Prior Preclinical and Clinical Experience

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2.5 Rationale for Clinical Study

The clinical experience with the Evoke System to date suggests that the device performs as intended and is safe and effective. Additionally, the unique ability of the Evoke System to measure neurophysiological data and operate in closed-loop mode has the potential to advance the science of pain management. This study has been developed to further understand the clinical utility of the neurophysiological measurements that the Evoke System is capable of measuring, as well as provide ongoing evidence in support of safety of the device. In alignment with IMMPACT recommendations (24), data collected in this study will be used to interrogate and analyze the underlying neurophysiological mechanisms of chronic pain with the goal of furthering a mechanism-based treatment approach to improve the efficacy of neuromodulation therapies.

3 DEVICE DESCRIPTION AND INDICATION FOR USE

3.1 Device Description

3.1.1 Investigational Device

The Investigational device is the Evoke Spinal Cord Stimulator (SCS) System. It consists of a stimulator (implantable and external), leads, programming system, accessories, and surgical tools. Please refer to the current Instructions for Use (IFU) for the most up-to-date description of the System and Accessory Components.

The Evoke System can measure ECAPs following every stimulation pulse, and can use ECAPs in a feedback mechanism to deliver closed-loop stimulation. The Evoke System records ECAPs following every stimulation pulse from two electrodes not involved in stimulation. The recorded ECAP signal is sampled by the stimulator and processed to allow measurement of the ECAP amplitude. The feedback mechanism minimizes the difference between the measured ECAP amplitude and the ECAP amplitude target (set by the clinician and adjusted by the patient using the pocket console) by automatically

adjusting the stimulation current for every stimulus. In doing so, it maintains spinal cord activation near the target level (Figure 1). The system is designed to operate in either ECAP-controlled, closed-loop stimulation mode, or open-loop (fixed-output) stimulation mode equivalent to other commercially available SCS systems. ECAPs may be measured and recorded in either stimulation mode.

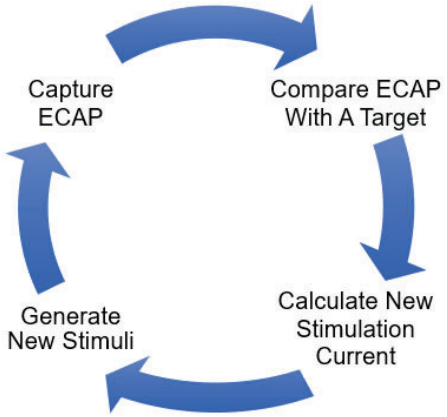

Figure 1: Feedback Mechanism – ECAP-Controlled, Closed-Loop SCS

3.2 Target Indication for Use

The Evoke System 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 the following: failed back surgery syndrome, intractable low back pain and leg pain.

4 STUDY PURPOSE AND OBJECTIVES

4.1 Study Purpose

The purpose of this study is to evaluate neurophysiological measures and clinical outcomes of the Evoke System to treat trunk and/or limb pain in a real-world population.

4.2 Primary Objectives

The primary objective of this study is to collect data in a real-world population while further characterizing neurophysiological measures and clinical outcomes.

5 STUDY DESIGN

This study is a prospective, multicenter, single-arm study designed to examine ECAP-controlled, closed-loop stimulation with the Evoke System to treat patients with chronic pain of the trunk and/or limbs.

Subjects with chronic, intractable pain of the trunk and/or limbs will be screened for participation in this study. Subjects who provide informed consent and meet the study eligibility criteria undergo a trial procedure and will be enrolled. Following the trial phase subjects may receive a permanent implant and be followed up at 1-, 3-, 6-, 12-, 18-, and 24-months following the permanent implant.

6 STUDY POPULATION

6.1 Study Sites

Study subjects will be enrolled at up to 25 US sites.

6.2 Inclusion Criteria

Subjects enrolled in this study must meet the following inclusion criteria, as determined by the Investigator:

1. Subject has chronic intractable pain of the trunk and/or limbs (VAS ≥6 cm in at least one of the regions intended to be treated with SCS).

2. Subject is willing and capable of giving informed consent and able to comply with study-related requirements, procedures, and visits.

3. Subject has trunk and/or limb pain such that lead placement will be in the lumbar to cervical region.

6.3 Exclusion Criteria

Subjects enrolled in this study must not meet the following exclusion criteria, as determined by the Investigator:

1. Subject is unable to operate the system.

2. Subject is an unsuitable surgical candidate.

3. Subject has a condition currently requiring or likely to require the use of diathermy.

4. Subject has another implantable stimulator such as demand type pacemakers or cardioverter defibrillator.

5. Subject is <18 years old.

6. Subject is pregnant or nursing.

7. Subject is allergic, or has shown hypersensitivity, to any materials of the neurostimulation system which come in contact with the body.

8. Subject is involved in an injury claim under current litigation or has pending/approved worker's compensation claim.

9. Subject has prior experience with SCS.

10. Subject is being treated with electroconvulsive therapy (ECT) or transcranial magnetic stimulation (rTMS).

7 STUDY ASSESSMENTS

7.1 Study Pain Assessment

The Study Pain Assessment includes the following:

- A body map drawing for subjects to shade in the areas of the subject's pain that are intended to be treated with SCS (i.e., "study pain"). The Investigator will review the pain map with the subject and identify which are the pain locations intended to be treated with SCS and which are not.

- A Visual Analogue Scale (VAS) to rate study pain intensity for each region shaded as having study pain on the body map. The VAS consists of a 10 cm line with two end-points representing "no pain" and "worst pain imaginable". Subjects are asked to rate their pain by placing a mark

on the line corresponding to their level of pain. The distance along the line from the “no pain” end to the subject’s mark is measured.

- Questions regarding the quality and nature of the subjects’ study pain and sleep.
- At Baseline only:
    - Douleur Neuropathique 4 Questions (DN4), which is a screening tool for neuropathic pain with 10 items split across four questions regarding the subjects’ study indication pain. Seven items related to pain quality (i.e. sensory and pain descriptors) are based on an interview with the patient and 3 items are based on the clinical examination.
    - Questions regarding the study pain etiology and pathophysiology.

7.2 Patient Global Impression of Change (PGIC) and Patient Satisfaction

Patient Global Impression of Change (PGIC) is a single item measure of global improvement with treatment. The subject is presented with a 7-point rating scale containing the options “very much improved”, “much improved”, “minimally improved”, “no change”, “minimally worse”, “much worse”, and “very much worse”.

Subject recommendation of and satisfaction with the stimulation therapy and study pain relief will also be collected. Recommendation options include “strongly recommend,” “recommend,” “neutral,” “not recommend,” and “definitely not recommend.” Satisfaction options include “very satisfied,” “satisfied,” “neither satisfied nor unsatisfied,” “unsatisfied,” and “very unsatisfied.”

7.3 PROMIS-29+2

The PROMIS-29+2 consist of the PROMIS-29 profile (v2.1) and two PROMIS Cognitive Function Abilities items. The PROMIS-29 is a 29-item profile instrument that assesses 8 universal domains (not disease-specific): Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to Participate in Social Roles and Activities, Pain Interference, and Pain Intensity. The first seven domains are assessed with 4 questions each; Pain Intensity is measured with a single 11-point numeric rating scale (NRS) from 0 (no pain) to 10 (worst imaginable pain). High scores represent more of the domain being measured. Thus, on symptom-oriented (negatively-worded) domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented (positively-worded) domains (physical functioning and social role) higher scores represent better functioning. The addition of the two items from the PROMIS Cognitive Function Abilities, for a total of 31 questions, allows for incorporation of the PROMIS Preference Scoring System (PROPr), which is a generic societal, preference-based summary score (also called a health utility score). The PROPr is measured on scale where 0 is the utility of being dead and 1 the utility of “full health.” The lowest possible score is –0.022 (for a state viewed as worse than dead), and the highest possible score is 1.

7.4 PROMIS-10 Global

The PROMIS Global Health measure produces two scores: Physical Health and Mental Health. PROMIS Global includes 10 items: four items that reflect different aspects of physical health (e.g., fatigue, physical function, pain) contribute to a Global Physical Health score, and four items that reflect different aspects of mental health (e.g., mood, cognition, social activities/role) contribute to a Global Mental Health score. A change in Global Physical Health may be the result of a change in fatigue, physical function, or other domain of physical health. The scores present a summary of multiple aspects of health. Higher PROMIS T-score represents more of the concept being measured. Thus, a person who has T- scores of 60 for the Global Physical Health or Global Mental Health scales is one standard deviation better (more healthy) than the general population.

7.5 Profile of Mood States 2nd Edition – Adult Short (POMS 2-A Short)

The Profile of Mood States 2nd Edition – Adult Short (POMS 2-A Short) is a 35 item, 5-point Likert scale that measures mood states overall (Total Mood Disturbance) as well as for six mood clusters: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. A scale score is also calculated for Friendliness, which is considered separately as a mood state that may influence the severity of the mood disturbance through interpersonal functioning. Higher scores indicate more negative mood states except for Vigor-Activity where higher scores indicate increased Vigor.

7.6 Stimulation Characteristics

Subjects will be asked questions about stimulation sensation and to shade in the areas where they typically experience stimulation sensation on a body map drawing.

7.7 Posture Change Measurements

Data on stimulation intensity and ECAP amplitude at various stimulation levels (i.e., activation plot) and in different postures will be collected in both stimulation modes. Subjects will rate the stimulation intensity on an 11-point numeric rating scale (0 equals “no feeling” and 10 equals “very intense”). All data will be recorded on device logs, except subject ratings, which will be recorded on the CRF.

7.8 Neurophysiological Measurements

Neurophysiological measurements of the stimulated fibers (e.g., ECAP features, conduction velocity, chronaxie, rheobase, late responses) will be collected. Data is automatically recorded on the device logs.

7.9 Programming Parameters and Characteristics

Program parameters (e.g., frequency, pulse width, stimulation amplitude) and characteristics (e.g., usage) will be collected. Data is automatically recorded on the device logs.

7.10 Additional Optional Assessments

Optional assessments to collect additional data may be requested that subjects can elect to participate in. Potential assessments include (but are not limited to):

- Medication interaction: Additional neurophysiological data may be collected during changes in medication to measure the effect of medications on spinal cord activation. Subjects may be requested to return to original doses of medications temporarily during this time. For example, if a subject is tapering medications, they may be asked to record their daily intake and return to the clinic for additional visits to collect neurophysiological measurements and optimize their stimulation therapy during the taper.
- Programming algorithms and dose: Various programming parameter algorithms and/or various levels of therapy or spinal cord activation “dose” may be evaluated.
- Usability: As new or modified products becomes available during the study, questions that pertain to the technical capability/performance (usability) of the product(s) may be asked of subjects.
- Pain signs/symptoms with stimulation on and/or off (e.g., Neuropathic Pain Symptom Inventory (NPSI), Complex Regional Pain Syndrome (CRPS)-specific questions, bedside-Quantitative Sensory Testing (bedside-QST))

These assessments may occur anytime during the study. These optional assessments are in addition to the required protocol data collection and there are no foreseeable additional risks to the subject. If additional testing is deemed to have additional risks, the investigator will obtain a separate consent.

Data will be collected on a CRF and/or the device log files based on the specific requirements.

8 STUDY PROCEDURES

8.1 Visit Schedule

Table 4. Required Protocol Assessments

	Screening	Temporary SCS Trial Phase		Permanent SCS Implant Phase						
Protocol Assessments	Baseline	Trial Procedure/ Post-procedure	Trial End (≤30 days)	Implant Procedure (Day 0)/ Post-procedure	1 Month (30 days -14 days, +21 days)	3 Month (90 days ± 21 days)	6 Month (180 days ± 30 days)	12 Month (365 days ± 60 days)	18 Month (545 days ± 90 days)	24 Month (730 days ± 90 days)
Informed Consent & Inclusion/Exclusion	X									
Baseline Evaluation	X									
Procedure[1]		X	X	X						
Imaging[2]		X	X	X						
Investigator Evaluation										
Study Pain Assessment	X		X		X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X	X
Safety[3]	X	X	X	X	X	X	X	X	X	X
Subject Questionnaires										
PROMIS-29+2	X		X		X	X	X	X	X	X
PROMIS-10 Global	X		X		X	X	X	X	X	X
POMS 2-A Short	X		X		X	X	X	X	X	X
PGIC & Patient Satisfaction			X		X	X	X	X	X	X
Stimulation Characteristics			X		X	X	X	X	X	X
Neurophysiological Data										
Posture Change Measurements		X			X	X	X	X	X	X
Neurophysiological Measurements[4]		X		O	X	X	X	X	X	X
Programming[5]		X		X	O	O	O	O	O	O

Additional Optional Assessments[6]	O	O	O	O	O	O	O	O	O	O

X = Required; O = Optional

[1] Trial procedure, trial end lead pull procedure, or permanent implant procedure.

[2] X-rays (AP and lateral) will be taken during the trial, implant, and revision/replacement procedures per standard of care. Additionally, X-rays (AP and lateral) are required prior to lead pull at Trial End and prior to the 1-month visit post-permanent implant. Fluoroscopy may substitute for X-ray. Additionally, imaging (e.g., X-ray, CT) may be taken at any time during the study in order to evaluate potential AEs, as needed and determined by the physician.

[3] Includes evaluation for potential adverse events, device deficiencies, and protocol deviations.

[4] Neurophysiological measurements may occur over more than one visit. Neurophysiological measurements for the trial and implant procedure need not be collected on the procedure date; they may be collected prior to and including trial end or the 1-month visit window; respectively. At follow-up, activation plots must be collected on the follow-up visit date; however, other neurophysiological measurements (e.g., conduction velocity, chronaxie, rheobase) may be collected any time within the visit window.

[5] Initial programming will occur following the trial procedure and following the permanent implant procedure (prior to the day of the 1-month follow-up visit); it need not occur on the procedure date. Reprogramming may occur as needed for optimization throughout the study.

[6] Additional optional assessments may be requested any time during the study that subjects can elect to participate in.

8.2 Screening/Baseline Evaluation

Potential study subjects will be identified and informed of the study. Subjects who provide informed consent for study participation (refer to section 13.2.2) will complete the study-specific baseline assessments. Medical records documenting the condition of the subject, including relevant previous medical history and results of diagnostic tests, will be obtained. Data collected during screening/baseline include:

- Determination of subject study eligibility (inclusion/exclusion criteria)
- Demographics, medical history, and physical examination
- Study Pain Assessment (including DN4 and pain etiology/pathophysiology)
- PROMIS-29+2
- PROMIS-10 Global
- POMS 2-A Short

8.3 Enrollment

Subjects who provide informed consent and meet eligibility criteria will be considered enrolled at the time of the trial procedure.

8.4 Temporary SCS Trial Phase

Before permanent implant of the Evoke System, subjects will undergo a trial stimulation phase with the external stimulator attached to one or two Evoke leads. The procedure will be performed in accordance with standard of care and the Evoke IFU. The device will be programmed for pain coverage in accordance with the Evoke IFU. Timing of post-procedure programming will occur at the discretion of the Investigator.

The trial will last up to 30 days (typically 1 week) to determine if the subject will proceed to the permanent implant. Subjects may have multiple visits during the trial phase in order to optimize stimulation settings. The following data will be collected during the trial phase:

Trial Procedure/Post-procedure:

- Trial procedure data
- X-rays (AP and lateral) during the procedure
- Posture change measurements (to be collected at least once post-procedure through Trial End)
- Neurophysiological measurements (to be collected at least once post-procedure through Trial End)
- Device programming

Trial End:

- Study Pain Assessment
- PROMIS-29+2
- PROMIS-10 Global
- POMS 2-A Short
- PGIC & Patient Satisfaction
- Stimulation characteristics
- Posture change measurements (to be collected at least once post-procedure through Trial End)
- Neurophysiological measurements (to be collected at least once post-procedure through Trial End)
- X-rays (AP and lateral) prior to lead pull
- Lead pull procedure

8.5 Implant Procedure/Post-procedure

Subjects will be approved to undergo implantation of the Evoke System if the subjects' trial was successful based on physician and subject determination.

The permanent implant will involve the implantation of the Evoke stimulator and one or two Evoke leads. The implant procedure will be performed in accordance with standard of care and the IFU, and programming will be performed in accordance with the IFU. Timing of post-procedure programming will occur at the discretion of the Investigator, prior to the 1-month follow-up visit.

The following data will be collected during the implant procedure/post-procedure:

- Implant procedure data
- X-rays (AP and lateral) during the procedure
- X-rays (AP and lateral) post-procedure, prior to 1-month follow-up
- Neurophysiological measurements (optional)
- Device programming

8.6 Follow-up Visits

Subjects will be followed-up at 1 month (30, -14 days, +21days), 3 months (90±21 days), 6 months (180±30 days), 12 months (365±60 days), 18 months (545±90 days), 24 months (730±90 days). Subjects may have their device reprogrammed throughout follow-up. The following data will be collected during follow-up:

- Study Pain Assessment
- PROMIS-29+2
- PROMIS-10 Global
- POMS 2-A Short
  PGIC & Patient Satisfaction
- Stimulation characteristics
- Posture change measurements
- Neurophysiologic measurements
- Device programming (as needed)

8.7 Programming Sessions

Device programming will initially occur following the trial and implant procedures. Programming adjustments may occur as many times as needed after initial programming (for either the trial or the permanent implant) to optimize treatment. Programming will be performed in accordance with the IFU by the Sponsor representative.

8.8 Revisions, Replacements, and Explants

During the study subjects may require a device revision, replacement or explant. The following data will be collected for revisions, replacements, and explants:

- Revision/replacement/explant procedure data
- Adverse Events
- Device deficiencies
- X-rays (as needed)
- Neurophysiologic measurements (optional)

8.9 Study Exit – Completion and Withdrawal

At the end of the subjects' study participation, either due to study completion or early withdrawal, a study exit form will be completed documenting the date and reason for study exit. The study exit form

is only required for enrolled subjects. For those subjects who miss a scheduled study visit, the site shall attempt to contact the subject at least three times, with at least one attempt being a certified letter, prior to considering the subject lost to follow-up (LTF). For subjects who withdraw from the study early, all attempts will be made to collect safety data.

8.10 Concomitant Medications

Medications will be collected at baseline and changes will be tracked throughout the subjects' participation in the study.

9 ADVERSE EVENTS

9.1 Adverse Event Definitions

9.1.1 Adverse Event

An **adverse event (AE)** is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational medical device.

9.1.2 Serious Adverse Event

A **serious adverse event (SAE)** is defined as an AE that

- Led to death,
- Led to serious deterioration in the health of the subject, and 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. prolonged hospitalization, or
  4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death, or congenital anomaly or birth defect.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol (e.g., the index implant procedure, or device replacement due to normal battery depletion or lead migration), or a hospitalization without serious deterioration in health, is not considered an SAE.

9.1.3 Unanticipated Adverse Device Effects

An **unanticipated adverse device effect (UADE)** means 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 was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An event will not be considered a UADE if it is a known consequence of the underlying disease or condition under investigation, surgery, or other events that commonly occur in the study population independent of the investigational device.

The final determination of whether an AE meets the definition of a UADE will be made by the independent adjudication committee for this study.

9.2 Adverse Event Recording and Reporting

9.2.1 Adverse Event Recording

Investigators are responsible for providing a description of all AEs, including the clinical outcome for the subject. Investigators will evaluate each event for seriousness, severity, and relatedness to the procedure, device, or stimulation therapy. Investigators must supply the Sponsor with any additional information related to safety reporting of a particular event.

9.2.2 Adverse Event Reporting

Investigators are required to report all AEs from the time of consent (except as outlined below). If an AE leads to multiple outcomes that sequentially worsen, only the worst AE will be reported.

Investigators shall report AEs to the Sponsor, and to their reviewing IRB per the IRB's reporting requirements. Investigators are required to report UADEs to the Sponsor and their reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect, per 21 CFR 812.150 (refer to section 13.7.2 for Investigator reporting requirements).

AE reporting exceptions:

- AEs that would be reasonably expected to be associated with any surgical procedure (e.g., anesthesia associated symptoms, surgical site pain, post-procedure pain) will not be required to be reported as AEs unless, in the opinion of the Investigator, the nature and/or severity is outside of what is typical for SCS procedures and recovery.

- Lack of efficacy, by itself, does not constitute an AE since failure to receive therapeutic benefit is an issue of efficacy, not safety.

- Loss of therapy/stimulation does not constitute an AE unless an untoward medical occurrence results.

- A subject's perception of the stimulation induced feeling of stimulation sensation is called paresthesia. There are well-known challenges associated with optimizing SCS such as changes in stimulation intensity and stimulation in unwanted areas. These will not be reported as AEs unless the Investigator determines the nature and/or severity is outside what is typical for neurostimulation.

- Temporary changes in symptoms and stimulation that are alleviated with programming will not be reported as AEs unless the Investigator determines the nature and/or severity is outside what is typical for neurostimulation.

9.3 Independent Medical Reviewer and/or Adjudication Committee

Independent medical reviewer and/or adjudication committee will be responsible for the review, evaluation, categorization, and adjudication of all AEs that occur during the clinical study. AEs will be reported based on this adjudication.

10 DEVICE DEFICIENCIES

10.1 Device Deficiency Definitions

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

10.2 Device Deficiency Reporting

The Investigator shall report all suspected device deficiencies to the Sponsor. Device deficiencies will not necessarily result in an AE. However, if an AE is associated with a device deficiency, the AE shall be documented and reported.

11 STATISTICAL ANALYSIS

11.1 Sample Size

A sample size of 300 will provide a precision (defined as the half-width of the two-sided 95% exact binomial confidence interval) of approximately ±6% or smaller for any event based on an incidence of 50%; an observed lower or higher incidence will produce a more precise (i.e. narrower) interval (25).

11.2 Study Outcomes

A number of outcome variables of interest will be collected and assessed across study visits to characterize neurophysiological measures and clinical outcomes with the Evoke System.

11.3 General Statistical Procedures

The following general statistical methods will be employed to assess the study data:

- There are no pre-planned formal statistical hypothesis tests.
- Standard summary statistics will be used to summarize key study variables. Categorical variables will be summarized via incidence and percent. Continuous variables will be summarized via mean, median, standard deviation, and range.
- Findings of significance may be presented and include p-values and/or 95% confidence intervals as appropriate.
- Standard tests for significance will be employed, including one sample t-tests. Additional exploratory analyses may be performed and include correlation analysis, linear and logistic regression analyses, repeated measures analyses, and generalized estimating equation (GEE) analyses as appropriate.
- Unless stated otherwise, statistical significance is defined as achieving a p-value less than 0.05. P-values will be nominal and not adjusted for multiplicity.
- In the event planned parametric methods are found to be inappropriate based upon observed distributions of individual variables, appropriate non-parametric methods will be employed.
- The incidence of all distinct AEs will be presented. AEs will also be summarized by seriousness, severity, and relatedness to the procedure, device, and/or stimulation. AEs will be reported based on the adjudication committee determination.

11.4 Timing of Analyses

As there are no formal pre-planned hypothesis tests, statistical analyses may be completed at any time. Reporting will be completed as required per the regulations and governing IRBs.

12 RISK ANALYSIS

12.1 Potential Risks

Risks associated with the Evoke System are similar to those of other open-loop SCS systems, which are generally minor. All medical procedures involve some risk of injury, including death. Other anticipated risks associated with the Evoke System are listed in this protocol or found in the literature, post-market surveillance data (e.g., FDA Manufacturer and User Facility Device Experience (MAUDE) database), and device labeling for SCS systems. Please refer to the current Evoke IFUs for the most up-to-date risks associated with the Evoke System.

In addition to the general surgical risks, potential risks to subjects associated with implantation and use of the Evoke System include, but are not limited to:

- Undesirable changes in stimulation sensation and/or location
- Uncomfortable changes in stimulation (over and/or under stimulation)
- Persistent post-surgical pain at hardware implantation sites
- CLS migration, which may result in pain or difficulty in charging
- Seroma or hematoma at surgery sites
- Epidural hemorrhage, spinal cord injury and possible paralysis
- Lead migration from the location chosen at initial implantation resulting in stimulation changes
- Breakage of the lead or failure of other system components, which may result in loss of stimulation
- Rejection of, or allergic reaction to, the implanted components
- Infection that may require hospitalization with intravenous antibiotic therapy
- Cerebrospinal fluid (CSF) leakage
- Inadequate pain relief following system implantation
- Erosion of the lead or CLS through the skin
- Weakness, clumsiness, numbness or pain

Subjects may require surgery (including revision, explant, and replacement) as a result of any of the above.

12.2 Minimization of Risks

All known and foreseeable risks associated with the Evoke System have been identified and mitigated with appropriate risk controls to reduce the risk as far as possible.

Risks in this study will be minimized by strict compliance with this protocol, and adherence to the guidelines for subject selection, site training, and close monitoring of the subject status. In addition, the product labeling details instructions for device use, risks, warnings and precautions, which must be followed to minimize risk to subjects. Additionally, only licensed and qualified physicians trained on the Evoke System will implant the device, and device programming will be performed by a trained Sponsor representative with the oversight of the Investigator.

12.3 Potential Benefits

There are several potential benefits of the Evoke System, and specifically with regard to ECAP-controlled closed-loop stimulation, to participating study subjects suffering from chronic, intractable pain of the trunk and/or limbs. These include:

- The Evoke System may provide insight into the neurophysiological mechanisms of chronic pain and SCS.
- The Evoke System may provide significant pain relief.
- The Evoke System may allow patients to reduce their pain medications.
- The Evoke System may improve patients' quality of life, sleep quality, emotional and/or physical functioning.
- The Evoke closed-loop stimulation mode may reduce variation in electrical field strengths reaching the spinal cord due to normal physiological activity and movement.
- The Evoke closed-loop stimulation mode may be more effective in providing pain relief compared to open-loop stimulation.

12.4 Benefit-Risk Conclusions

SCS has been used for over 50 years to aid in the management of chronic, intractable pain of the trunk and limbs. The risks associated with participation in this study are outweighed by the potential benefits and value of the research. The evidence clearly indicates that although there are risks associated with the procedure and the device, the incidence rates are very low, and the majority of complications that can result can be treated. In addition, the procedure itself is completely reversible as the device,

including the leads, can be removed. The Evoke System has the added benefit compared to other SCS systems in that it can measure spinal cord activation resulting from stimulation and use this measure to automatically adjust stimulation current to maintain a target response. By real-time modulation of the output current, the closed-loop system maintains consistent SC activation and thus may maximize the therapeutic effect through the corresponding inhibition of pain processing pathways.

13 STUDY ADMINISTRATION

13.1 Study Materials

13.1.1 Packaging and Labeling

In accordance with 21 CFR Part 812, the study device or its immediate package will bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 21 CFR Part 801), the quantity of contents, if appropriate, and the following statement: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." Labeling describing all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions are provided in the IFU.

13.1.2 Handling and Storage

The Investigator must ensure that the study devices are controlled and stored according to the IFU. All supplies are to be used only for this study protocol and not for any other purpose. Products are not to be used after the expiration date indicated on the label. The Investigator must not destroy any unused supply unless instructed by the Sponsor.

13.1.3 Product Accountability

The Investigator is responsible for study device accountability, reconciliation, and record maintenance. The Investigator must maintain study device accountability records throughout the course of the study.

13.2 Ethics

13.2.1 Institutional Review Board Approval

The protocol, informed consent form (ICF) and authorization for the use and disclosure of health information per the Health Insurance Portability Accountability Act (HIPAA) must be approved by the investigation site's Institutional Review Board (IRB) before subject enrollment. Changes to the protocol must be approved in writing by the Sponsor and the IRB (as applicable) before the change is implemented.

A copy of the IRB approval letter (and approved ICF and subject materials) must be submitted to the Sponsor. Investigators are responsible for submitting and obtaining initial approval and continuing approval of the study from the IRB and forwarding copies of the approval documentation to the Sponsor.

13.2.2 Informed Consent

The Investigator will prepare an ICF in accordance with this study protocol, regulatory requirements (21 CFR Part 50), Good Clinical Practices (GCP), and the ethical principles that have their origin in the Declaration of Helsinki using the sample ICF provided in Appendix A of this study protocol.

As part of the consent process, the subject will have ample time and opportunity to ask questions of, and receive answers from the personnel conducting the study, and to decide whether to participate in the study. The information that is given to the subject shall be in language understandable to them.

Neither the Investigator nor the investigation site personnel shall coerce or unduly influence the subject to participate or continue to participate in the study.

All subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the IRB-approved ICF. The Investigator will retain the original ICF signed by the subject and a copy of the ICF will be provided to the subject.

The Sponsor will inform the Investigator whenever information becomes available that may be relevant to the subject's consent, and will revise the ICF accordingly and provide it to the Investigator for approval by the IRB. The Investigator or his/her authorized designee shall inform the subject of this information. After approval by the IRB, a copy of this ICF must be provided to the participating subjects, and the informed consent process as described above repeated, in accordance with the IRB requirements.

13.2.3 Subject Confidentiality

The Sponsor and its designees will make every reasonable effort to protect the confidentiality of the subjects participating in the study. Only Sponsor personnel or contracted agents of the Sponsor will have access to these confidential files and will act in accordance with applicable regulations as required by HIPAA. The IRBs and FDA also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of the study will eliminate any identifiable reference to the subjects.

13.3 Data and Quality Management

This study will be conducted in accordance with the regulatory requirements, GCP, and the ethical principles that have their origin in the Declaration of Helsinki. The study shall not begin until receipt of the required approval from the FDA and reviewing IRB. Any additional requirements imposed by the FDA or the IRB shall be followed as appropriate.

13.3.1 Data Collection and Management

Subject data will be collected and entered in an electronic data capture (EDC) system specifically created for this study in accordance with this study protocol, regulatory requirements (21 CFR Part 11), and GCP. Data from other external sources (e.g., device logs) may also be entered into the EDC system. Data may be reviewed by the Sponsor using programmed or manual queries to ensure accuracy of the data entered and minimize the occurrence of missing data. Data management activities will be specified in the Data Management Plan.

13.3.2 Monitoring

The study will be monitored to ensure the rights and well-being of human subjects are protected; the reported study data are accurate, complete, and verifiable from source documents; and the conduct of the study is in compliance with the study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA. Monitors will be qualified by training and experience to monitor the study in accordance with these requirements. Monitoring activities will be conducted in accordance with the Monitoring Plan.

13.3.3 Audits/Inspections

Audits of the investigation sites may be performed by the Sponsor or designee, independent of and separate from routine monitoring or quality control functions, to evaluate study conduct and compliance with the study protocol, applicable regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA.

The FDA or other regulatory agencies may perform inspections of the investigation sites before, during, or after the conclusion of the study. The Investigator shall contact the Sponsor immediately upon

notification of inspection, and must fully cooperate with the regulatory agency by permitting inspections at reasonable times and in a reasonable manner.

13.4 Access to Study Records

The Investigator must permit monitoring and auditing by the Sponsor or designee, and inspection by the appropriate regulatory authorities, and provide direct access to all requested study-related records.

13.5 Investigation Site and Subject Training

All implanting Investigators will be trained on the device. All primary site personnel (Investigator(s) and core site staff) will be trained on the study protocol and the applicable Code of Federal Regulations (CFRs). Support staff may be trained minimally based on delegated tasks.

13.5.1 Pain Assessment Training

Despite having validated methods for collecting pain measures, chronic pain clinical studies have been plagued by large variability in subjects' perception of pain and inconsistent reporting of these measurements. For example, a subject may give substantially differing pain scores at different follow-up time points but describe their pain as not having changed. For this reason, subject and Investigator/investigation site staff training on properly completing pain assessments will be performed to provide reliable and useful data. The training is two-fold, 1) train on the scale being used, and 2) train on the pain that is intended to be treated with SCS (to set expectations appropriately). As described by IMMPACT recommendations (26), this protocol requires Investigators (preferably the implanting Investigators) to perform a thorough training with the potential subject as part of the baseline assessment to set and manage appropriate expectations and increase subject understanding of the study indication pain (i.e., pain intended to be treated with SCS), as well as, differentiate comorbid pain conditions (non-index/non-study indication pain) to increase the likelihood of conscientious subject reporting of pain that is intended to be treated in the study. To obtain accurate reporting at follow-up, re-training will utilize the baseline pain map to remind the subject of the pain identified at baseline in which the Investigator intended to treat. Re-training of subjects on the proper completion of pain assessments to provide reliable and useful data may be conducted at any time during the study as the Investigator and site staff deem necessary.

13.6 Investigator Responsibilities

The Investigator is responsible for ensuring the study is conducted according to the signed Clinical Trial Agreement (CTA)/Investigator Agreement (IA), study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of devices under investigation.

13.7 Investigator Agreement and Financial Disclosure

The Principal Investigator (PI) at each site will be required to sign the Investigator's Agreement, as per 21 CFR Part 812.

In addition, in accordance with 21 CFR Part 54, all Investigators will be required to sign a Financial Disclosure form, which certifies or discloses the Investigator's and his/her immediate family's financial interests and arrangements with Saluda Medical. Investigators must inform the Sponsor of any changes to the information within the financial disclosure throughout the course of the study and for a period of two years after the device is approved by the FDA or the study is terminated, whichever is later.

13.7.1 Investigator Records

Records to be maintained by the Investigator in the investigation site's essential study files for this study include, but are not limited to:

- Study protocol and all amendments
- Signed IA for the PI
- Signed Financial Disclosure for all Investigators
- IRB approval letter(s) including approved consent and HIPAA authorization form(s), and subject materials
- IRB Membership list(s) or Letter of Assurance
- All relevant correspondence relating to the study between the site and Sponsor, the site and IRB
- Curriculum Vitae (CV) for all Investigators
- Training documentation
- Delegation of Authority
- Investigational device accountability records including: date, quantity, lot/serial numbers of all devices, identification of all persons the device was used on and final disposition.

The following records must be maintained for each subject enrolled in the study:

- Signed ICF and Authorization for the Use and Disclosure of Health Information
- AEs and any supporting documentation
- Protocol deviations
- Source documentation: complete medical records, including procedure reports, professional notes, etc.

13.7.2 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate, and timely reports:

- An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any **UADE** occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

- An Investigator shall report to the Sponsor, within 5 working days, a **withdrawal of approval by the reviewing IRB** of the Investigator's part of an investigation.

- An Investigator shall submit **progress reports** on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

- An Investigator shall notify the Sponsor and the reviewing IRB of any **deviation from the investigational plan** to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

- If an **Investigator uses a device without obtaining informed consent**, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.

- An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a **final report** to the Sponsor and the reviewing IRB.

- An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

13.8 Sponsor Responsibilities

Saluda Medical Americas, Inc., a fully owned subsidiary of Saluda Medical Pty. Ltd., will serve as Sponsor of this clinical investigation and is responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation, as required in 21 CFR 812 Subpart C, and for Sponsor records and reports outlined in 21 CFR Part 812 Subpart G.

13.8.1 Sponsor Representatives

Sponsor representatives may participate in the conduct of the trial to the extent described in this protocol. Participation in the study will be limited to Sponsor personnel who are appropriately trained. Sponsor representatives will operate equipment during the procedures and follow-up, and interact with the subject to accomplish procedure and programming activities. Typical tasks may include:

- Interrogating and downloading the device data
- Programming device parameters
- Clarifying device behavior, operation, or diagnostic output
- Assisting with the collection of study data from the device
- Entering data on study worksheets for procedures and programming
- Recording any device deficiencies

The Sponsor representatives may contact the subject at any time to check on their stimulation therapy and device functionality. Based on this interaction, additional training or troubleshooting may be provided or the subject may be asked to come into the clinic for reprogramming or troubleshooting. If unsolicited information is reported by the subject that is outside the technical nature of the device, the subject will be advised to contact the Investigator.

At no point shall personnel from the Sponsor:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's medical condition or treatment with a subject without the oversight of a healthcare professional

13.9 Deviations to the Protocol

An Investigator is required to conduct this study in accordance with the signed CTA/IA, study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA.

In accordance with FDA regulation 21 CFR Part 812.150(a)(4), the Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred.

All deviations from the study protocol must be reported to the Sponsor. Except in an emergency, prior approval by the Sponsor is required for an anticipated change in or deviation from the plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, prior FDA and IRB approval is also required in accordance with 21 CFR Part 812.35(a).

13.10 Amendments to the Protocol

Any amendments to the study protocol will be clearly documented and approved by the Sponsor and the IRB prior to implementation.

13.11 Completion, Early Termination, or Suspension of the Study

The Sponsor reserves the right to suspend or terminate the study at an individual investigation site or entirely at any time. Suspension or early termination of an investigation site may occur due to serious or repeated noncompliance on the part of an Investigator. Reasons for suspension or early termination of the entire study may include, but are not limited to, the following:

- The incidence and seriousness of AEs in this or other studies indicates a potential health hazard to subjects;
- New information on efficacy from this or other studies;
- The investigational product receives regulatory approval.

Subjects may continue to use the device following study closure, unless notified otherwise by the Sponsor (e.g., device does not receive regulatory approval). They will be followed by their physician in accordance with established practice for SCS systems.

13.12 Record Retention

The Investigator and Sponsor shall maintain the required records during the investigation and for a period of two years after the latter of either the completion/termination of the study or the date the Evoke System receives regulatory approval for the indication being studied. An Investigator or Sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them.

The Investigator's study records may be discarded only upon approval from the Sponsor. The PI must contact the Sponsor before destroying any records pertaining to the study to ensure that they no longer need to be retained.

13.13 Clinical Trials Registry/Database (ClinicalTrials.gov)

This clinical study will be registered on www.ClinicalTrials.gov. Study results will be submitted as required. Per the requirements of 21 CFR Part 50, the ICF will contain a statement that clinical trial information will be entered into this clinical trials registry/database.

13.14 Publication

Publication of clinical data from this trial will be in accordance with the fully executed CTAs. Publication of all data will conform to standards set forth in peer-reviewed journals and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (ICMJE).

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ABBREVIATIONS AND ACRONYMS

Abbreviation/Acronym	Term
AE	Adverse Event
BPI	Brief Pain Inventory
BWS	Body-Worn System
CFR	Code of Federal Regulations
CL	Closed-Loop
CLS	Closed Loop Stimulator
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
ECAP	Evoked Compound Action Potential
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol 5-Dimensional, 5-level quality of life instrument
ETS	External Trial System
FBSS	Failed Back Surgery Syndrome
FDA	Food and Drug Administration
GCP	Good Clinical Practice (For the purposes of this study, this means compliance with FDA regulations for IDEs and ISO 14155.)
HIPAA	Health Insurance Portability Accountability Act
IA	Investigator Agreement
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDD	Intrathecal Drug Delivery
IDE	Investigational Device Exemption
IFU	Instructions for Use (e.g., Surgical Guide, User Manual, Clinical Manual, Clinical Data Viewer Manual, and supporting materials)
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
LTF	Lost to Follow-up
MRI	Magnetic Resonance Imaging
MCS	Multi-Channel System
ODI	Oswestry Disability Index
OL	Open-Loop
PGIC	Patient Global Impression of Change
PI	Principal Investigator
POMS	Profile of Mood States
PRO	Patient-Reported Outcome
PSQI	Pittsburgh Sleep Quality Index
SAE	Serious Adverse Event
SC	Spinal Cord
SCS	Spinal Cord Stimulator, or Spinal Cord Stimulation
SF-12	Short Form Health Survey
TGA	Therapeutic Goods Administration
UADE	Unanticipated Adverse Device Effect

US	United States
VAS	Visual Analog Scale

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