Clinical Investigation Plan

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DISTINCT
Dorsal spInal cord STImulatioN vs mediCal management for the Treatment of low back pain

Version Number	[redacted]
Date	2022 April 6
National Coordinating Clinical Investigator/Study Principal Investigator:	James Yue, MD
Study Co-Principal Investigator	[redacted]
Steering Committee	[redacted]
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Clinical Investigation Type	Prospective, multi-center, randomized, controlled, post-market trial
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CIP Author of Current Version	[redacted]

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.).

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1.0 INTRODUCTION

Spinal cord stimulation (SCS) is effective for relieving chronic intractable pain after failed back surgery syndrome (FBSS). Small studies have shown it to be effective in patients with predominant axial low back pain who are not candidates for surgery. However, larger randomized studies are needed. The purpose of this study is to evaluate the effectiveness of SCS stimulation compared with conventional medical management (CMM) in the treatment of chronic low back pain (CLBP) for patients who have not undergone and are not candidates for lumbar spine surgery.

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

Low back pain affects over one billion people worldwide each year in all sociodemographic classes (1). It was the leading cause of years lived with disability in 2016 and was among the top 10 in 195 countries including the U.S. (2). While the majority of cases of low back pain resolve within six weeks, there are 35 million adults in the U.S. (13.1%) who have chronic low back pain (CLBP) (3). Prevalence increases with age and is higher in women, current and former smokers, and obese individuals with BMI over 30 (3). There is a negative impact on physical function and quality of life, and patients with CLBP are three times more likely to have 10 or more healthcare visits per year (4).

Most (95-98%) CLBP cases stem from a pathoanatomical diagnosis, but a minority (2-5%) stem from visceral causes such as cancer (3). Pathoanatomical diagnoses include spinal stenosis, spondylosis, spondylolisthesis, facet joint disease, disc herniation, and discogenic pain. While some of these are relatively straightforward to diagnose and have favorable treatment evidence, others require a complex diagnostic work-up. Additionally, most patients have more than one pain generator, making a singular and distinct pain-generating diagnosis difficult.

There are several factors (psychological, economic, comorbidities) that impact the course of the condition and an individual's response to treatment. It is likely that treatment success depends not only on reducing pain intensity, but also on improving functional capacity. In addition to the recognized psychological factors that impact the course of pain and response to treatment (e.g., pain catastrophizing, depression, anxiety), other factors such as smoking history, obesity, diabetes and financial/legal status also influence treatment outcomes.

The widely accepted treatment algorithm for low back pain in an acute state begins with conservative care consisting of physiotherapy and medication optimization. Low back pain persisting for more than three months is considered chronic. Patients with CLBP are likely to be offered non-operative interventions such as anesthetic or steroid injections, radiofrequency ablation, and opioid therapy. Those with a clear anatomic pain generator may be offered surgery. Even with successful surgery at the correct anatomical level, there is inconsistent clinical effectiveness, and significant pain can persist from the original cause or from the post-surgical healing process (5-7). This phenomenon is commonly referred to as Failed Back Surgery Syndrome (FBSS).

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Currently, SCS is used in patients who have failed other treatment options for CLBP and have reached the end of the treatment continuum. Unfortunately, this is despite evidence that a longer time to treatment predicts lower chance of therapeutic success, and poor outcomes of surgery in the absence of spinal instability (8).

Due to shortcomings in the current treatment algorithm, the economic burden of CLBP continues to rise. Recently, there has been a 300% increase in the number of low-back surgeries. The greatest proportion of overall health care expenditure in US hospitals is spent on spinal fusion, costing $12.8 billion in 2011. There was a 170% increase of primary lumbar fusions from 77,682 to 210,407 between 1998 and 2008 (9). Up to 25% of diagnostic and therapeutic spine surgeries are unnecessary or ineffective. Back pain is consistently ranked as one of the areas with the highest level of spending, in spite of inconsistent outcomes, with $134.5 Billion spent alone in the US in 2016 (10).For these reasons, providers, payers, and hospital systems aim to identify which patient-specific or surgery-specific factors play significant roles in postoperative outcomes (11).

1.1.2 Rationale for Conducting this Clinical Investigation

Spinal cord stimulation (SCS) has been used to treat chronic pain for more than 50 years and the mechanisms of its action are characterized in several publications (12-14). Recent advancements in neuromodulation, including BurstDR™ stimulation, have increased its overall effectiveness as a treatment modality for chronic pain (15, 16). To date, studies show that SCS is effective in the treatment of CLBP due to FBSS and is superior to conservative medical management and repeat surgery (17, 18).

Previous neuromodulation trials in patients with low back pain suggest the potential for improved effectiveness compared to conventional medical management. The PROMISE randomized controlled trial (tonic SCS vs optimal medical management) for FBSS showed that 39.2% of patients achieved at least 30% reduction in low back pain with SCS, compared to 12.0% in the medical management group (17). Tonic SCS brought about a decrease in Oswestry Disability Index of 12 points from baseline, and NRS scores for back and leg pain decreased by 2.0 and 1.6 vs baseline, respectively (17). A single-center study evaluating HF10 high-frequency SCS for axial low back pain with no previous spine surgery found that 75% of patients (15/20) had a reduction in VAS of more than 50% at six-month follow-up (19).

In addition to its clinical effectiveness, SCS was found to be more cost-effective over the long term than operation or re-operation procedures (20). Considering the conflicting evidence on efficacy of other treatment modalities and the poor benefit-risk ratio of opioid medication, it is reasonable to consider using SCS earlier in the treatment continuum ahead of surgery and before initiating or escalating opioid use for CLBP.

The reimbursement landscape in the U.S. requires patients to try several conservative treatments (including opioids) in a stepwise fashion in order of increasing invasiveness and cost before implantable technologies and surgery are covered. Moreover, the majority of commercial payors in the U.S. require a patient to have failed at least one spine surgery before they will approve a spinal cord stimulator trial. Some patients must endure suboptimal pain control for months to years before targeted, aggressive treatments are considered. Functional capacity and psychological comorbidities such as depression and anxiety may continue to worsen until an effective intervention is used.

BurstDR™ spinal cord stimulation uses a waveform that mimics natural neural patterns and can deliver pain relief with reduced paresthesia or completely without paresthesia. It has been found to alter both

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sensory and emotional pathways in the brain, and achieved statistically superior pain relief compared to tonic SCS (21, 22). This prospective investigation is designed to evaluate the efficacy of BurstDR™ SCS compared with conventional medical management for improving pain and back-related physical function in patients suffering with chronic, refractory axial low back pain with a neuropathic component who have not had lumbar spine surgery and for whom surgery is not an option.

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Clinical Investigation Plan

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary Objective(s)

The objective of this study is to evaluate the efficacy of BurstDR™ spinal cord stimulation, compared with conventional medical management, in improving pain and back pain-related physical function in patients suffering with chronic, refractory axial low back pain, who have not had lumbar spine surgery and for whom surgery is not an option.

2.2 Device(s) Used in the Clinical Investigation

2.2.1 Name of the Device(s) Under Investigation

BurstDR™ capable implantable pulse generators, along with relevant leads and accessories, will be used in this study. A detailed list of devices and system components can be referenced in CL1011119.

2.2.2 Indication for Use

BurstDR™ capable devices are indicated as an aid in the management of chronic, intractable pain of the back, trunk and limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome and intractable low back pain.

2.2.3 Description of the Device(s) Under Investigation

Please refer to the country- and device-specific IFU for additional information regarding the devices used in this clinical investigation.

2.2.4 Description of the Non-Device Cohort

SCS will be compared with conventional medical management (CMM) for CLBP. CMM consists of an array of therapies including, but not limited to structured physical therapy, medications, injections, and complementary and alternative medicine (e.g. acupuncture, massage therapy).

2.2.5 Device Handling

The Sponsor requires all products to be stored according to the appropriate labeling and IFU as per standard practice at each center.

3.0 CLINICAL INVESTIGATION DESIGN

This is a prospective, multi-center, randomized, controlled clinical study with an optional crossover component. It is designed to evaluate the efficacy of BurstDR™ SCS in the treatment of chronic axial low back pain, compared to conventional medical management (CMM).

Subjects will be followed in-clinic for required study visits at [redacted] months and via phone call or optional clinic visit at [redacted] -months. Due to the individualized nature of study therapies, patient reported outcomes will be continually assesses and additional patient outreach conducted in order to

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determine if therapy adjustment(s) are warranted to optimize pain control. The primary endpoint will be assessed at the 6-month follow-up visit. Upon completion of the 6-month follow-up visit, subjects who are dissatisfied with therapy and receiving inadequate improvement with their treatment assignment will be allowed to cross-over to the other treatment arm, if desired.

Up to [redacted] subjects will be randomized in the study [redacted].

Subject enrollment is expected to be completed within [redacted]; subjects will be followed for [redacted] years. The total duration of the study is expected to be approximately [redacted] years, including enrollment, data collection from all subjects, and study close out.

The Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

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3.1 Clinical Investigation Procedures and Follow-up Schedule

Subjects who satisfy eligibility criteria become registered in the clinical investigation. Subjects will have follow-up visits at [redacted], and [redacted] months. A detailed description of procedures/assessments performed at each follow-up visit is provided in Section 6.7.

The Flow Chart and the Follow-up requirements of this clinical investigation are described below.

Figure 3.1-1: Clinical Investigation Flow Chart

[redacted]

3.2 Measures Taken to Avoid and Minimize Bias

An independent Clinical Events Committee (CEC) will adjudicate all serious and non-serious device and procedure related adverse events, and all death events.

An independent board-certified spine surgeon will act as a medical monitor and evaluate each enrolled subject for suitability.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- An oversight committee (e.g., Steering Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)

Should the Sponsor discontinue the clinical investigation, sites will follow subjects per routine practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials to the Sponsor and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate, and return subjects to their standard medical treatment.

A Principal Investigator, IRB/EC, or regulatory authority may also suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

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4.0 ENDPOINTS

4.1 Primary Effectiveness Endpoint and Rationale

The primary effectiveness endpoint is the difference in responders between groups at 6 months. A subject is considered a responder for the primary endpoint if the following criterion is met:

- Improvement in pain, defined as a ≥ 50% decrease on NRS

4.2 Secondary Endpoints

Selected secondary endpoints (e.g., change on ODI from baseline, % change in NRS from baseline) will be compared between the two treatment groups. Details are described in the Statistical Analysis Plan (SAP).

4.3 Descriptive Endpoint(s) or Additional Data

Descriptive endpoints include:

- Proportion of patients who elect to cross-over after the primary endpoint
- Change from baseline at each time point on the following:
  - ODI
  - PROMIS-29 questionnaire
  - Pain Catastrophizing Scale (PCS)
  - Pain-condition related medication usage
  - Exercise frequency
- Healthcare resource utilization
- Device programming and usage
- Patient satisfaction with therapy
- Patient Global Impression of Change (PGIC)
- Serious device-related adverse events

Responder analysis:

- Proportion of subjects with ≥ 30% decrease on NRS
- Proportion of subjects with ≥ 13% improvement, at least one category improvement or score ≤ 20% on ODI

- Proportion of subjects within 1 SD of population norm or reach MCID on PROMIS-29 domains
- Proportion of subjects that are either clinically catastrophizing on PCS at baseline (PCS score ≥ 30) and report a score of < 30 at follow up or report a 40% decrease in score at follow-up compared to baseline.

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5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll subjects with chronic axial low back pain without underlying pathology that can be effectively treated with surgery and who have not had prior lumbar spine surgery. Patients must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Recruitment/Screening and Informed Consent

5.2.1 Subject Recruitment and Screening

Potential patients presenting at clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in Section 5.2.2). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin.

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP and will be recorded in a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure.

Patients meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they wish to participate in the clinical investigation.

Subject data will be collected following enrollment into the study.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect patient's legal rights. Financial incentives will not be given to patients. Patients may be compensated for time and travel directly related to the participation in the clinical investigation. The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's IRB/EC. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any clinical investigation-specific procedures.

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The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1 Special Circumstances for Informed Consent

This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response. This clinical investigation excludes individuals under the age of 18 or age of legal consent from the clinical investigation population. The clinical investigation excludes Individuals unable to read or write. The clinical investigation excludes pregnant or breastfeeding women. All other aspects of the Informed Consent process will follow Section 5.2.2.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the clinical investigation. If ANY general exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled (recruitment failure).

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.2 Inclusion Criteria

1. Patient must be willing and able to provide written informed consent prior to any clinical investigation-related procedure.
2. Age ≥ 18 years
3. Patient has chronic (at least 6 months), refractory axial low back pain with a neuropathic component and is not a candidate for spine surgery
4. Patient has back pain for ≥ 6 months inadequately responsive to supervised conservative care
5. Patient has not had spine surgery for back or leg pain
6. Patient is a candidate for spinal cord stimulation
7. Low back pain ≥ 6 on Numerical Rating Scale
8. Oswestry Disability Index score of ≥ 30%
9. Willing and able to comply with the instructions for use, operate the study device, and comply with this Clinical Investigation Plan

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5.3.3 Exclusion Criteria

1. Pathology seen on imaging tests obtained within the past 12 months that is clearly identified and is likely the cause of the CLBP, that can be addressed with surgery.
2. Primary complaint of leg pain, or leg pain is greater than back pain
3. Back pain is due to any of the following:
    - spinal instability defined as > 2 mm translation on radiographic imaging
    - visceral causes (e.g., endometriosis or fibroids)
    - vascular causes (e.g., aortic aneurysm)
    - spinal infection (e.g., osteomyelitis)
    - inflammation or damage to the spinal cord (e.g. arachnoiditis or syringomyelia)
    - tumor or spinal metastases
4. Has widespread pain (e.g. fibromyalgia) or pain in other area(s), not intended to be treated in this study (e.g. neck pain, shoulder pain)
5. Patient has seronegative spondyloarthropathy (e.g. rheumatoid, lupus, psoriatic)
6. Neurological deficit (e.g. foot drop)
7. Prior lumbar spine surgery or sacroiliac joint fusion
8. Patient has used a morphine equivalent daily dose of more than 50 MME in the last 30 days
9. Patient is bed bound
10. Patients with regular intake of systemic steroids (except inhaled steroids used to treat asthma)
11. Imaging (MRI, CT, X-ray) findings within the last 12 months that contraindicates lead placement
12. Known allergic reaction to implanted materials
13. Severe scoliotic deformity (>11 degrees in thoracic or lumbar spine)
14. Patient has a history of, or existing intrathecal drug pump
15. Patient has previous experience with neuromodulation devices, including a failed trial
16. BMI > 40
17. Patient is enrolled, or intends to participate, in another clinical drug and/or device study or registry that may interfere with the results of this study, as determined by Abbott personnel
18. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results.
19. Failed psychological evaluation
20. Suspicion or evidence of untreated mental illness, substance abuse, or drug-seeking behavior
21. Patient demonstrated 2 or more Waddell's signs of nonorganic behavior
22. Patient is in current litigation for back pain/injury, or is currently receiving worker's compensation
23. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period.
    - Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to enrollment/baseline visit per site standard test.

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent, has been confirmed to meet all inclusion criteria and none of the exclusion criteria, and eligibility has been confirmed by the medical monitor.

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Any subject enrolled into the clinical investigation who is later found not to meet all eligibility criteria, will be evaluated by the study team. If the deviation is found to violate the scientific integrity of the study or unduly influence the study aims, the subject will be withdrawn from the study. Otherwise, the subject will continue in the study and be included in the analysis population.

5.4.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

A portion of the subjects enrolled in the clinical investigation display characteristics consistent with the Medicare population based on age. The clinical investigation results will be analyzed by age (< 65 years and ≥ 65 years) and compared to ensure that the outcomes are similar between the Medicare and non-Medicare populations.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will regularly review enrollment data to investigate whether there is under-representation of these demographic subgroups
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical investigation population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups

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- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5.5 Subject Deregistration

There will be no subject deregistration in this clinical investigation. If a subject was randomized and registered in the clinical investigation, the subject will be included in the analysis populations defined in Section 8.1.

5.6 Subject Withdrawal and Discontinuation

Each subject meeting all general and screening eligibility criteria shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to Section 3.3
- Subject's neurostimulation system has been explanted
- Subject becomes pregnant
- Subject fails to comply with the protocol requirements

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow-up is required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the study device, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the subject will undergo the following assessments:

- Review of adverse events
- Administration of patient reported outcomes

<u>Lost-to-Follow-up</u>

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

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- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

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5.7 Number of Subjects

Approximately [redacted] subjects will be enrolled in the study. No site may contribute more than [redacted] % of the total sample. Assuming 25[redacted] attrition from randomization to 6 months in both groups, we expect approximately [redacted] evaluable subjects sufficient for the primary endpoint analysis ([redacted] %).

5.8 Total Expected Duration of the Clinical Investigation

This protocol assumes the following durations for key steps: approximately [redacted] for the payor approval process, approximately [redacted] days for the trial period, approximately [redacted] months to schedule permanent implant procedure, and [redacted] months of follow-up. Based on these assumptions, each subject is expected to be enrolled in the study for approximately [redacted] months.

This protocol assumes the following durations for key steps: [redacted] months for full enrollment, [redacted] months from the time the last subject receives a permanent implant to final follow-up, and [redacted] months for study closure. Based on these assumptions, the clinical investigation is expected to take [redacted] months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Enrollment

During Enrollment, the following procedures will be performed:

- Verification of written informed consent
- Inclusion/Exclusion eligibility
- Verification of eligibility by an independent medical monitor

6.2 Baseline

6.2.1 Baseline Clinical Assessments

The baseline visit should occur no later than [redacted] days after the enrollment visit. Baseline data will be collected regarding the subject's demographics, health status, and previous treatments for low back pain. The following data will be recorded at baseline:

- Subject demographics including occupational status
- Medical history (pain history and other interventions for pain management)
- Pain condition-related medication use

6.2.2 Baseline Physical Function and Quality of Life Assessments

Baseline data will be collected regarding physical function and quality of life. The following data will be recorded at baseline:

- Numerical Rating Scale (NRS) for low back pain, and leg pain as applicable
- PROMIS-29

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- painDetect questionnaire
- Pain Catastrophizing scale (PCS)
- Oswestry Disability Index (ODI)
- Exercise frequency

6.3 Randomization

After enrollment has been completed, subjects will be randomized (3:2 ratio) to either the SCS arm or the CMM arm. Randomization will be stratified by site.

6.4 Conventional Medical Management (CMM arm)

During the follow-up period, subjects in the CMM arm will receive supervised medical care, including medication optimization and supervised non-interventional therapy. Medication optimization should include use of non-steroidal anti-inflammatories and muscle relaxants, as appropriate. Supervised non-interventional therapy may include, but is not limited to, physical therapy, chiropractic care, back school, cognitive behavioral therapy, and acupuncture. Interventional therapy such as injections and radiofrequency ablation, is also allowed. Patient reported outcomes should be assessed after each patient interaction and therapy adjustment(s) (i.e. medication change) made as needed in order to optimize pain control.

6.5 Spinal Cord Stimulation (interventional arm)

A successful trial, defined as 50% decrease in pain recorded on Numerical Rating Scale is required for a subject to receive a permanent implant.

6.5.1 Procedures Involved in the Use of the Device Under Investigation

Descriptions of procedures associated with each device can be found in their respective IFU.

6.5.2 Trial Period

Subjects randomized to receive spinal cord stimulation will first undergo a trial of the therapy. The trial period implementation should start no more than [redacted] days after the Baseline visit and should last at least 4 days. Only percutaneous leads may be used for the trial procedure. “On the table” trials and the use of paddle leads for the trial procedure are not allowed.

The following data will be recorded at trial implementation:

- Trial system details
- Device programming
- Device- and/or procedure related adverse events (if applicable)
- All serious adverse events (if applicable)
- Withdrawal (if applicable)

6.5.3 End of Trial Period

The End of Trial Period data collection will occur after the trial period. At this visit, the following data will be recorded:

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- NRS for back pain, and leg pain as applicable
- Patient reported pain relief
- Device- and/or procedure related adverse events (if applicable)
- All serious adverse events (if applicable)
- Withdrawal (if applicable)

6.5.4 Permanent System (if applicable)

Subjects reporting at least 50% improvement in back pain NRS and wish to proceed with the study will receive a permanent implant. The procedure will be performed according to the IFU. Permanent implant should be performed no later than 45 days after the end of the trial period.

6.5.5 Procedures Involved in the Use of the Device Under Investigation

Descriptions of procedures associated with each device can be found in their respective IFU.

6.5.6 Permanent System Implementation

The spinal cord stimulator will be activated and programmed by trained personnel either during post-operative recovery or at an office visit in accordance with standard operating procedures. The subject's spinal cord stimulator will be programmed according to the most recent Abbott programming guidance. After programming, the subject will receive a patient programmer and will be instructed on how to use the system to relieve their pain. Subjects will be able to adjust the stimulation to ensure the best results.

The following data will be recorded during permanent implementation:

- Spinal cord stimulator system details
- Surgical procedure details
- Device programming (if applicable)
- Device- and/or procedure related adverse events (if applicable)
- All serious adverse events (if applicable)
- Withdrawal (if applicable)

6.6 Follow-up Assessments

6.6.1 Follow-up for All Subjects (Site/Office/Telemedicine Visit or Telephone Call)

Required follow-up visits will occur at [redacted] month (±14 days), and at [redacted] (±30 days), and [redacted] -months (± [redacted] days) after randomization or permanent implantation. Patient reported outcomes should be assessed after each follow-up visit and therapy adjustment(s)_(i.e. reprogramming) made as needed in order to optimize pain control. Ongoing technical reprogramming assistance will be provided by the sponsor.

The following data will be collected at each visit:

- Occupational status
- Pain condition-related medication use
- Patient-reported pain relief (PRPR)
- NRS for back pain, and leg pain as applicable
- PROMIS-29

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- Pain Catastrophizing scale (PCS)
- Oswestry Disability Index (ODI)
- Patient Global Impression of Change (PGIC)
- Exercise frequency
- Patient satisfaction with therapy
- Device- and/or procedure related adverse events (if applicable)
- System revision (if applicable)
- Protocol deviation (if applicable)
- Device programming (if applicable)
- All serious adverse events (if applicable)
- Withdrawal (if applicable)

If a study participant is unable or unwilling to attend an in-person visit, the visit may be conducted remotely using telemedicine as provided by the study center. Questionnaires may be administered during the remote visit. The Coordinator or designee must document the subject's responses on the worksheet, note that the responses were collected via phone, save that document as source data, and enter the information in the EDC system. Alternately, questionnaires may be mailed to the participant in a return postage provided envelope. If this method is chosen, the Coordinator or designee should schedule a call with the subject to clearly explain the questionnaires and answer any questions the subject may have.

6.6.2 Patient Reported Outcome (PRO) Measures

The Investigator, Coordinator or site designee will administer the patient-reported outcome questionnaires via paper for later transcription to EDC, or electronically. If the subject reported outcome questionnaire is provided to the subject electronically, the source data will be available in the EDC system for the site's records. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires, if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided. If the subject is unable to attend a follow up visit in person, questionnaires may be sent to the subject and returned to the site. The Coordinator or designee should schedule a call with the subject to clearly explain the questionnaires and answer any questions the subject may have. Alternatively, If the subject is unable to attend a follow up visit in person, the Investigator or designee may also schedule a phone call or telemedicine visit with the subject to review the questionnaires. The Coordinator or designee should document the subject's responses on the worksheet, note that the responses were collected via phone, save that document as source data, and enter the information in the EDC system.

- Patient Global Impression of Change (PGIC)
- Patient-reported pain relief (PRPR)
- Numerical Rating Scale (NRS)
- PainDetect (PD-Q)
- Oswestry Disability Index (ODI)
- PROMIS-29
- Pain Catastrophizing Scale (PCS)

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6.6.2.1 Patient Global Impression of Change (PGIC)

The PGIC is a categorical rating scale used to evaluate the subject's impression of change in his/her condition since the beginning of the study treatment. The subject will be requested to rate their overall change in activity limitations, symptoms, emotions and overall quality of life related to his/her condition on a seven-point categorical scale via an interview technique. The categories are as follows: 1- no change, 2- almost the same, 3 - a little better, 4 - somewhat better, 5-moderately better, 6 - better, and 7- a great deal better. Although this tool does not specify the area of change (e.g., pain, function, quality of life, etc.), it allows for an overall integrated assessment from the prospective of the subject. PGIC values of 6 or 7 are reported to correlate best with actual change (23, 24).

6.6.2.2 Patient-reported pain relief (PRPR)

The PRPR asks a subject to state the percentage pain relief they receive from their treatment. The scale ranges from 0% = no relief to 100% = complete pain relief.

6.6.2.3 Numerical Rating Scale (NRS)

The pain NRS consists of 1 question that will be asked by interviewing the subjects. Patients will be asked to rate, from 0 (no pain) to 10 (worst imaginable pain), their average pain over the past 24 hours specific to the area(s) of chronic pain being treated. A higher score indicates greater pain intensity

6.6.2.4 PainDETECT Questionnaire (PD-Q)

The painDETECT (PD-Q) is a validated self-reported questionnaire that discriminates between neuropathic and nociceptive pain components in patients with chronic pain. The PD-Q is comprised of three sections: gradation of pain (7 questions), pain course pattern (1 question), and radiating pain (1 question). Each question addresses the quality of neuropathic pain symptoms and is scored individually. Gradation of pain questions are scored from 0-5. The pain course pattern question score ranges from -1 to +1, and the radiating pain question score ranges from +2/0. The overall PD-Q score ranges from 38 to -1. The higher the score, the higher the likelihood of a neuropathic pain component. A score ≤ 12 suggests that a neuropathic pain component is unlikely. Scores ≥ 19 suggest that a neuropathic pain component is likely. Scores between 12 and 19 suggest that the presence of a neuropathic pain component is unclear and requires further examination to ensure a proper diagnosis. The sensitivity of this tool was validated by Freynhagen et al. at 84% (25).

6.6.2.5 Oswestry Disability Index (ODI)

The ODI is an index derived from the Oswestry Low Back Pain Questionnaire used by clinicians and researchers to quantify disability for low back pain (26). The self-completed questionnaire contains ten topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic category is followed by 6 statements describing different potential scenarios in the subject's life relating to the topic. The subject checks the statement which most closely resembles their situation. Each question is scored on a scale of 0–5 with the first statement being zero and indicating the least amount of disability and the last statement is scored 5 indicating most severe disability. The scores for all questions answered are summed, divided by the total possible score based on the number of questions answered and converted to a percentage. Zero is equated with no disability and 100 is the maximum disability possible. Five different levels of disability are defined within that range; minimal (0%-20%), moderate (21%-40%), severe (41%-60%),

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crippling (61%-80%), and bed bound or exaggerated symptoms (81-100%). A decrease of 13% or more on the 0%-100% scale demonstrates a meaningful, clinical improvement in disability (27).

6.6.2.6 Patient-Reported Outcome Measure Information System (PROMIS) 29

The PROMIS-29 is a 29-item profile instrument developed in partnership with the National Institutes of Health (NIH) to estimate overall quality of life by assessing 7 health domains known to impact activities of daily living: depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and social function. The final item is an 11-point pain intensity numerical rating scale (NRS). Subjects should read each item and check the one box that most closely represents their response. Each item is scored on a scale from 1-5 with total scores for each domain ranging from 4-20. Greater scores represent more of whatever concept is being measured (e.g., depression or physical function). Scoring tables have been provided in the measure manual. Raw domain scores are converted to t-scores with a mean of 50 and a standard deviation of 10.

6.6.2.7 Pain Catastrophizing Scale (PCS)

The PCS is a validated, 13-item scale that evaluates 3 domains of pain-related negative thoughts (rumination, magnification, and helplessness). Subjects rate how often they have the given thought from 0 “not at all” to 4 “all the time”. The total score is a sum of all responses, ranging from 0-52. Each domain has a sub-scale score calculated as a sum of the constituent responses with ranges of 0-16 for rumination, 0-12 for magnification, and 0-24 for helplessness. Outcomes have been evaluated to set scores expected in normal, non-chronic pain populations and changes in scores that are clinically meaningful to patients. A score of 13.87 is representative of a normal, healthy population (28). A total score of 30 or above indicates a patient is clinically catastrophizing. A 38-44% reduction in score represents a noticeable improvement to the patient (29).

6.6.3 Follow-up Phone Call Visits

Follow-up phone call visits will occur at [redacted] and [redacted] -months (± 30 days) after randomization or permanent implantation, whichever is more applicable. The following data will be collected at each visit:

- Patient Global Impression of Change
- Verbal pain rating scale for pain intensity (0-10 numerical rating scale administered verbally)
- Device- and/or procedure related adverse events (if applicable)
- All serious adverse events (if applicable)
- Programming details (if applicable)

6.6.4 Crossover

Crossover prior to the study primary endpoint is not allowed. To ensure valid analysis of all endpoints, investigators and coordinators must make concerted efforts to prevent crossover from CMM to SCS prior to completing the 6-month visit. If a subject is unwilling to complete the assigned treatment, they should be withdrawn. Upon completion of the 6-month primary endpoint visit, a subject is allowed to crossover to the other arm. The permanent implant must occur prior to the [redacted] follow up visit.

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Subjects crossing over to the SCS arm will follow the trial and permanent SCS procedures as part of standard of care. Upon receiving a permanent implant, subjects will continue to participate in the study according to Section 6.6. The follow-up timeline will not be reset; the subject will continue with the follow-up schedule. Subjects are not allowed to crossover more than once.

6.6.5 Unscheduled Visits

An unscheduled visit is defined as a visit that occurs between any of the required follow-up visits, such as a visit to document a potential or actual adverse event and standard re-programming or therapy adjustment visits. Any data collected related to the clinical study endpoints should be documented by completing the appropriate CRF as applicable.

Following an unscheduled visit, the subject should be seen for the next scheduled study visit within window.

6.6.6 Schedule of Events

[redacted]

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7.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:

Note 1: This definition includes events related to the medical device under investigation or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death
b) Led to a serious deterioration in 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. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
    5. chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered to be an SAE.

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7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility and patient condition (pre-existing condition).

7.2.1 1.1.1 Serious Health Threat

Serious Health Threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons
Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

7.3 Adverse Events

7.3.1 Adverse Event Reporting

General AE Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites will collect all adverse event data including deaths per protocol throughout the period defined above and will report these events to the Sponsor on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

SAE Reporting

The investigator must report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	Sites must report SAEs to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

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Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Reportable events to the sponsor are considered:

- All adverse events related to the SCS device and/or SCS procedure regardless of seriousness criteria.
- All serious adverse events including deaths

  Refer to the specific device manuals for adverse events associated with the use of SCS systems.

Device deficiencies (DD) are not collected on a DD form in this study. Sites should report all device deficiencies/malfunctions to the Sponsor's Customer Service Department.
Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

If device deficiency does not involve an AE, the investigator must notify the Abbott Post Market Surveillance Department by submitting the device deficiency information via email to [redacted] or by phone [redacted] as soon as possible after becoming aware of the complaint.

7.3.2 Procedure for recording and reporting subject death

Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the AE case report form and submit to Sponsor. The death events must be reported as per the SAE reporting requirements provided in the "Adverse Events Reporting" section 7.3.1.

- All efforts to obtain the details about the circumstances surrounding the subject death should be made by the Investigator.

  The subject's death, is an outcome of an AE and an early conclusion of the subject's participation in the clinical investigation. Therefore, the Investigator is required to complete the Withdrawal form.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. A separate Statistical Analysis Plan (SAP) will provide additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses, and analysis of descriptive endpoints, if applicable.

8.1 Analysis Populations

The following analysis populations are defined for the study:

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1. [redacted].

8.2 Statistical Analyses

This section describes the analysis for the primary effectiveness endpoint, secondary endpoints, and descriptive endpoints. Further details are provided in the Statistical Analysis Plan.

8.2.1 Primary Endpoint(s) Analyses

The null and alternative hypotheses for the primary effectiveness endpoint are as follows:

$$H_0: P_{SCS} = P_{CMM}$$

$$H_1: P_{SCS} \neq P_{CMM}$$

P_{SCS} and P_{CMM} denote the response rate at 6 months for SCS and CMM groups, respectively.

The response rates between the two groups will be compared using [redacted] at the significance level of [redacted].

8.2.2 Secondary Endpoint(s) Analyses

Selected secondary endpoints (e.g., composite responder rate based on NRS or ODI improvements, change on ODI from baseline, % change in NRS from baseline) will be compared between the two treatment groups. Appropriate statistical methods will be used according to the types of the data. Continuous variables may be analyzed using the [redacted]. Binary variables may be analyzed using tests such [redacted]. Further details are described in the Statistical Analysis Plan (SAP).

8.2.3 Descriptive Endpoint(s) Analyses

Descriptive summary statistics will be presented for the descriptive endpoints within each treatment group. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using [redacted]. Time-to-event variables will be analyzed using the [redacted]. The 95% confidence intervals for each type of data will be provided as appropriate.

Difference between groups will be summarized using descriptive statistics including [redacted].

8.3 Sample Size/Power Calculation

The study was designed to enroll approximately [redacted]. The following assumptions are used in the power calculation for the primary endpoint:

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[redacted]
Based on the assumptions above, there is at least [redacted] power to evaluate the primary endpoint.

The sample size calculation was performed using [redacted].

8.4 Timing of Analysis

Primary endpoint analysis will be performed after subjects [redacted].

8.5 Subgroup Analysis

Subgroup analyses by age, diagnosis or other clinical important variables will be considered and described in the Statistical Analysis Plan.

8.6 Multiplicity

For the additional tests on the secondary endpoints, multiplicity adjustment will be described in the Statistical Analysis Plan.

8.7 Procedures for Accounting for Missing Data

Primary endpoint analysis will be based on available data. Sensitivity analysis may be considered to assess the impact of missing outcome data. Details will be described in the Statistical Analysis Plan.

8.8 Planned Interim Analysis

An interim analysis will be performed for sample size re-estimation, [redacted] is sufficient for meeting the study endpoints. This analysis is detailed in the Adaptive Design Plan.

8.9 Success Criteria

The study will be considered as successful if the primary effectiveness endpoint is met, i.e., the SCS is superior to CMM with regards to the response rate.

8.10 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

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9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/Institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

Abbott will finance the clinical investigation and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational site.

10.3 CIP Amendments

The Sponsor will provide approved CIP amendments to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Sites must document in writing acknowledgement/approval of the CIP amendment by the IRB/EC prior to implementation of the CIP amendment. Sites must also provide copies of this documentation to the Sponsor.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion, clinical investigation personnel responsibilities, and site compliance expectations. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training

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log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 Monitoring

Sponsor and/or designee will monitor the clinical investigation throughout its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The Investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Investigator Agreement or the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of CIP for evaluation of investigator compliance to the CIP and regulatory requirements and handle according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the Investigator and/or delegate
- Telephoning the Investigator and/or delegate

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- Corresponding with the Investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP, or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the Investigator's participation in the clinical investigation.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

If an Investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Sponsor Auditing

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.
2. Individuals engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

10.9 Committees

10.9.1 Steering Committee

The Steering Committee is assigned by the Sponsor and may consist of Investigators. The Sponsor will also be represented on the committee. Meeting minutes from this committee will be filed with the Sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, and to review operational issues that may arise and warrant a CIP amendment or other corrective action.

10.9.2 Publications Committee

A Publication Committee may be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor, and a statistician. The Publication Committee will determine policy and strategies regarding individual

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presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

10.9.3 Clinical Events Committee (CEC)

The CEC is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate pre-specified events reported by Investigators and identified by Safety personnel for the clinical study as defined in the CEC charter and according to definitions provided in this CIP.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

[redacted].

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the end of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device

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implant or procedures, monitoring and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the Sponsor may update the DMP throughout the duration of the clinical investigation. The Sponsor will track and document control all revisions.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. To comply with these regulatory requirements/GCP, sites should include the following information in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number, and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. This serves as source documentation.
- Patient reported outcome measures may be completed by the patient electronically on PRO-Q application. The electronic CRF output will serve as source documentation.
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, consult reports, office notes, x-ray results, lab results and other source documents as applicable per the reported AE. The documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs should be included.

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11.4 Case Report Form Completion

Site research personnel trained on the CIP and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The Investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Sites will collect data on all subjects enrolled into the clinical investigation.
[redacted]

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain IRB/EC approval for the CIP and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the Sponsor.

Sites will submit any amendments to the CIP as well as associated ICF changes to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to Investigators or the Sponsor has provided formal documentation of clinical investigation closure.

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In addition, specify that the Sponsor will submit the clinical investigation report within one year of the end of the investigation, or specify another timeline as applicable per the design of the clinical investigation.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. The Sponsor must review and approve any proposals for publications or presentations by the investigators in a timely manner in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will be responsible for determining whether to register the clinical investigation on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event the Sponsor determines that the clinical investigation should be registered, the Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation.

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15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

Published literature on current treatment options for patients with chronic, intractable, low back pain report mild, if any, improvements in pain and physical function. [redacted]. A recent review of opioid therapy in subacute and chronic low back pain concluded even though opioids reduce pain intensity, non-opioid treatments in these studies show a statistically significant greater reduction. Furthermore, improvements in pain relief are outweighed by harms associated with opioids (30). Deterioration in functional outcomes has also been associated with opioid therapy in low back pain populations (31).

In contrast, small case series report significant improvements in pain and function using various spinal cord stimulation systems in this population (19, 32). On average, pain is reduced by over 70% and disability is reduced to a minimal level (average ODI < 20%). These small studies provide support for investigating the effect of SCS in this population. In addition, the unique mechanism of action of BurstDR provides the ability to evaluate improvement in psychometric measures.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

The use of a neurostimulation system involves risks. In addition to the risks commonly associated with surgery, below are listed the anticipated potential adverse effects with the use of a neurostimulation system:

[redacted]

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Management Report / Risk Analysis Report

The clinical risks associated with Abbott's spinal cord stimulation systems are well known. Any potential residual risks are considered outweighed by the benefits, and the overall residual risk was determined to be acceptable. Clinical evidence demonstrates acceptable safety and performance of the device under this post-market study.

15.4 Risks Associated with Participation in this Clinical Investigation

The risks involved with this study are comparable to those associated with the implant of any other commercially available neurostimulation system. Risks specific to Abbott neurostimulation systems are outlined in the associated IFU, and these disclosed risks are not modified by participation in this study.

15.5 Steps Taken to Control or Mitigate Risks

The Sponsor will employ measures throughout the course of this study to minimize these risks such as clearly defined inclusion and exclusion criteria and independent medical monitor review to ensure that only appropriate subjects are enrolled, proper consenting process, selection of investigational sites that have a sufficient level of clinical expertise, investigator selection, and appropriate training for all involved in the study activities. In-depth recommendations, special precautions and instructions regarding [patient selection, device handling, device placement and system removal] are included in IFU documents of all devices included in this study. All device-related adverse events and device deficiencies will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

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15.6 Risk to Benefit Rationale

The risks associated with Abbott's neurostimulation systems are anticipated to be comparable to those associated with the use of other commercially available neurostimulation systems. The patients participating in this study are indicated for using a neurostimulation system as part of their standard medical management and are subject to the risks associated with these devices.

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Clinical Investigation Plan

APPENDIX I: ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CLBP	Chronic Low Back Pain
CMM	Conventional Medical Management
CRF	Case Report Form
CT	Computed Tomography
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
MCID	Minimal Clinically Important Difference
MHRA	Medicines and Healthcare Products Regulatory Agency
MME	Morphine Milligram Equivalents
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
ODI	Oswestry Disability index
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PRO	Patient Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
SD	Standard Deviation
UADE	Unanticipated Adverse Device Effect
US	United States

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Clinical Investigation Plan

APPENDIX II: DEFINITIONS

APPENDIX III: SITE CONTACT INFORMATION

Contact information for each participating clinical site is available under a separate cover by contacting the Sponsor at:

APPENDIX IV: LITERATURE REVIEW

APPENDIX VI: LABELS

[redacted]

APPENDIX VII: CASE REPORT FORMS

Final (draft) CRFs will be provided under a separate cover.

APPENDIX VIII: INFORMED CONSENT FORM

A template informed consent form will be provided under a separate cover.

APPENDIX IX: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

APPENDIX XI: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

[redacted]

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Clinical Investigation Plan

APPENDIX XII: CIP SUMMARY

Clinical Investigation Name and Number	CRD_988 DISTINCT
Title	Dorsal spInal cord STImulatioN vs mediCal management for the Treatment of low back pain
Objective(s)	The objective of this study is to evaluate the efficacy of BurstDR™ spinal cord stimulation, compared with conventional medical management, in improving pain and back pain-related physical function in patients suffering with chronic, refractory axial low back pain, who have not had lumbar spine surgery and for whom surgery is not an option.
Device Under Investigation	BurstDR™ capable products
Number of Subjects Required for Inclusion in Clinical Investigation	The study will enroll up to 270 patients at up to 30 US sites.
Clinical Investigation Design	This is a prospective, randomized, controlled, clinical trial
Primary Endpoint(s)	The primary effectiveness endpoint is the difference in responders between groups at 6 months. A subject is considered a responder for the primary endpoint if the following criteria are met: • Improvement in pain, defined as a ≥ 50% decrease on NRS
Subject Follow-up	• [redacted]
Inclusion Criteria	1. Patient must be willing and able to provide written informed consent prior to any clinical investigation-related procedure. 2. Age ≥ 18 years 3. Patient has chronic (at least 6 months), refractory axial low back pain with a neuropathic component and is not a candidate for spine surgery 4. Patient has back pain for ≥ 6 months inadequately responsive to supervised conservative care 5. Patient has not had spine surgery for back or leg pain 6. Patient is a candidate for spinal cord stimulation 7. Low back pain ≥ 6 on Numerical Rating Scale 8. Oswestry Disability Index score of ≥ 30% Willing and able to comply with the instructions for use, operate the study device, and comply with this Clinical Investigation Plan

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Clinical Investigation Plan

Exclusion Criteria	1. Pathology seen on imaging tests obtained within the past 12 months that is clearly identified and is likely the cause of the CLBP, that can be addressed with surgery. 2. Primary complaint of leg pain, or leg pain is greater than back pain 3. Back pain is due to any of the following: • spinal instability defined as > 2 mm translation on radiographic imaging • visceral causes (e.g., endometriosis or fibroids) • vascular causes (e.g., aortic aneurysm) • spinal infection (e.g., osteomyelitis) • inflammation or damage to the spinal cord (e.g. arachnoiditis or syringomyelia) • tumor or spinal metastases 4. Has widespread pain (e.g. fibromyalgia) or pain in other area(s), not intended to be treated in this study (e.g. neck pain, shoulder pain) 5. Patient has seronegative spondyloarthropathy (e.g. rheumatoid, lupus, psoriatic) 6. Neurological deficit (e.g. foot drop) 7. Prior lumbar spine surgery or sacroiliac joint fusion 8. Patient has used a morphine equivalent daily dose of more than 50 MME in the last 30 days 9. Patient is bed bound 10. Patients with regular intake of systemic steroids (except inhaled steroids used to treat asthma) 11. Imaging (MRI, CT, X-ray) findings within the last 12 months that contraindicates lead placement 12. Known allergic reaction to implanted materials 13. Severe scoliotic deformity (>11 degrees in thoracic or lumbar spine) 14. Patient has a history of, or existing intrathecal drug pump 15. Patient has previous experience with neuromodulation devices, including a failed trial 16. BMI > 40 17. Patient is enrolled, or intends to participate, in another clinical drug and/or device study or registry that may interfere with the results of this study, as determined by Abbott personnel 18. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results. 19. Failed psychological evaluation 20. Suspicion or evidence of untreated mental illness, substance abuse, or drug-seeking behavior 21. Patient demonstrated 2 or more Waddell's signs of nonorganic behavior

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Clinical Investigation Plan

	22. Patient is in current litigation for back pain/injury, or is currently receiving worker's compensation 23. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. • Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to enrollment/baseline visit per site standard test.

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Clinical Investigation Plan

APPENDIX XIII: EXCEPTIONS FROM ISO 14155 COMPLIANCE

Minimal exceptions to ISO 14155:2020 compliance are expected, though these exceptions do not affect the safety and protection of the clinical investigation subjects and do not compromise data quality and security.

- This clinical investigation provides market approved devices, which will be used within their intended purpose, thus clinical investigation labelling will not be applied, a separate investigator Brochure will not be created, and clinical device accountability will not be set up.
- The study will not be submitted for review to the Competent Authority, only standard vigilance reporting will be observed. Local and/or regional requirements might be still applicable and will be tracked in a study specific Safety Plan.
- Financial disclosures will not be collected from the Investigators.

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