Abbott	Clinical Investigation Plan Cover Page

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PROLONG
PROLONG Prospective, Multi-center, Open-label, Post-market Study
Study Document No: ABT-CIP-10460
Version A
Date: 23 JAN 2019

Sponsor

Abbott
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Plano, TX 75024
USA

Clinical Investigation Plan

CRD_960
PROLONG Study

Version Identifier	A
Date	23 JAN 2019
Planned Number of Sites and Region(s)	Up to 40 sites in the US
Clinical Investigation Type	Prospective, multi-center, open-label, post-market

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56,21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11and 45 CFR part 46). The conduct of the clinical investigation will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

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1.0 INTRODUCTION

Spinal cord stimulation (SCS) has been shown to be effective for relieving intractable chronic pain. However, a portion of patients who initially succeed with SCS will eventually lose their therapeutic benefit. Reliable methods have not been identified for restoring neuromodulation benefit to this underserved population, so additional research is required. This study will prospectively observe subjects who utilize Abbott neurostimulation devices after failing to sustain pain relief with their previous SCS system. The effectiveness of Abbott systems in restoring neuromodulation benefit will be evaluated over the course of a two-year follow-up.

This clinical investigation will be conducted in accordance with this clinical investigation plan (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

Spinal cord stimulation involves the application of electrical stimulation to the large, myelinated fibers of the dorsal column via electrical leads placed in the epidural space. SCS has been used successfully to help manage a variety of pain conditions including diabetic neuropathy,[1] failed back surgery syndrome,[2-4] complex regional pain syndrome,[5,6] phantom limb pain,[7] ischemic limb pain,[8] as well as postherpetic neuralgia and acute herpes zoster pain.[9] A systematic review and meta-analysis of SCS in refractory neuropathic back and leg pain showed that SCS reduces pain, improves quality of life, reduces analgesic use, allows some patients to return to work, and may result in significant cost savings over time with minimal significant adverse events.[10] However, not all patients continue to receive benefit from SCS over time. A recent retrospective review of the MarketScan database found that of the 8727 patients implanted, 805 (9.2%) had the devices explanted. Patients who were explanted incurred 2.65 times more total cost than their counterparts who retained the SCS system.[11] While the MarketScan database does not provide the reason for explant, others have examined the question with smaller cohorts.

Explants occur for a variety of reasons, the most common being loss of therapeutic effect. In a review of 352 patients who had an SCS explant, Pope et al. found that the top three reasons for explant were lack/loss of efficacy (43.9%), complication (20.2%), and a need for MRI (19.4%). Importantly, 71.8% of all explants occurred within the first 30 months.[12] In a similar study by Van Buyten et al., the primary reasons for explant across 955 devices were inadequate pain relief (50.5%), infection (24.7%), and internal pulse generator (IPG) failure (11.8%).[13] The overall explant rate in this study was 19.5% and the majority of explants due to inadequate pain relief occurred within the first two years.[13] Finally, Hayek et al. reviewed 56 explants in 234 patients (23.9%) with the top explant drivers being loss of therapeutic effect (41.0%), infection (17.8%), and IPG discomfort (14.3%).[14] Across these three studies, loss of efficacy comprised 40% - 50% of all SCS explants. In addition to the documented explant rate, it is reasonable to assume that some patients have lost efficacy, but do not want to go through the effort of having their device removed. This population of “virtual explants” is difficult to quantify and, to our knowledge, has not been estimated in the literature.

The underlying reason for therapeutic failure after initial success is unknown. It is possible that neural plasticity may cause the nervous system to habituate to the stimulation, diminishing or eliminating benefit.[15] It is also possible that the loss of benefit is a complex interaction of physical and mental factors such as anxiety and depression, which have been shown to affect other treatments for chronic pain.[16] While the cause is unknown, several attempts have been made to restore neuromodulation efficacy for

failed SCS patients through “stimulation holidays” whereby the stimulator is temporarily turned off for a period of time, or by switching to another form of stimulation.[17]

Stimulation holidays, where the device is shut off for 6 weeks, are believed to allow any neural adaptation to reverse, restoring efficacy when the device is reactivated. However, little evidence supports this method.[15,17] Recent case studies have shown that changing the stimulation waveform or stimulation target are possible solutions for stimulation tolerance. Ten of 16 patients switching from high-frequency to tonic stimulation,[18] and 3 of 3 switching from tonic to BurstDR stimulation reached acceptable levels of pain relief.[19] Additionally, 2 of 2 patients were successful in restoring their pain relief after switching from traditional SCS to dorsal root ganglion (DRG) stimulation.[20]

1.1.2 Rationale for Conducting this Clinical Investigation

This study will examine the utility of Abbott neurostimulation devices for restoring therapeutic benefit from neuromodulation therapy. These devices include programming the BurstDR waveform in an enabled implantable pulse generator (IPG), and dorsal root ganglion stimulation (Proclaim DRG). The BurstDR waveform offers a unique mechanism of action that may explain why it can restore efficacy where tonic stimulation has failed. While all forms of SCS activate the lateral pain pathway, which is responsible for the sensory aspects of pain, only BurstDR has been shown to activate the medial pain pathway which is responsible for the affective components.[21] It is this medial activation that may allow BurstDR to succeed despite psychological factors such as catastrophizing and depression. Additionally, it is possible that BurstDR may be less susceptible to habituation because it more closely mimics natural thalamic firing.[22]

Several different methods of implementing BurstDR may be included in this investigation to account for a range of possible existing systems and patient needs. It can be implemented by reprogramming a BurstDR-capable device, connecting a BurstDR-capable IPG to existing leads with an adapter or compatible header, or through full system replacement.

While traditional SCS applies stimulation to the dorsal horn of the spinal cord, DRG stimulation targets a bundle of sensory nerve cell bodies just outside of the spinal cord known as the dorsal root ganglion. This form of stimulation has been shown to make it easier to achieve pain-paresthesia overlap, provide consistent stimulation irrespective of body position, and produce paresthesia with a lower current than traditional SCS.[23] A recent RCT found that DRG was superior to SCS in providing pain relief for individuals with complex regional pain syndrome (CRPS).[24] Using DRG stimulation as a replacement or supplement to SCS may ensure reliable coverage of the entire painful area and improve pain outcomes.

This is the first prospective investigation designed to evaluate the effectiveness of Abbott neurostimulation devices for restoring pain relief in patients with waning or failed therapy.

2.0 CLINICAL STUDY OVERVIEW

2.1 Clinical Study Objectives

The objectives of this study are to evaluate the effectiveness of Abbott neurostimulation devices in restoring pain relief, improving quality of life, and reducing related medication use for patients with failed SCS.

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2.2 Devices to Be Used in the Clinical Investigation

Any market-released Abbott BurstDR-capable or DRG neurostimulation device may be used in this study along with its relevant accessories. This study allows for the inclusion of future iterations of Abbott's neurostimulation systems and expanded indications as they receive approval from the applicable country regulatory authority.

2.2.1 Indications for Use

Indications for use for each neurostimulation device/system are detailed in the country-specific individual Instructions for Use (IFU) document.

2.2.2 Description of the Study Devices

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

2.2.3 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 study is a prospective, multi-center, open-label, post-market study designed to evaluate the effectiveness of Abbott neurostimulation devices in restoring pain relief for patients who no longer receive adequate therapeutic benefit from SCS. The Investigator will select the most appropriate BurstDR or DRG implementation method according to their standard of care.

A trial of BurstDR or DRG may be performed as deemed appropriate by the Investigator. This includes the option for multiple trials to test both BurstDR and DRG therapy. Similarly, the permanent implementation method will be performed as deemed appropriate by the Investigator.

This clinical investigation will enroll up to 100 patients at up to 40 sites in the US. Subject enrollment is expected to be completed within 12 months; subjects will be followed for 24 months after permanent implementation.

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

3.1 Study Procedures and Follow-up Schedule

3.2 Measures Taken to Avoid and Minimize Bias

An independent Clinical Events Committee (CEC) will adjudicate all serious device/procedure related adverse events.

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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 study devices 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:

- Unanticipated adverse device effect (UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering/Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine clinical practice with device/procedure related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The Investigator shall return all clinical investigation materials (including devices) 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.

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

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 patients to their standard medical treatment.

4.0 ENDPOINTS

- Numerical rating scale (NRS) for pain intensity
- Patient reported pain relief
- Patient satisfaction
- Physician satisfaction
- PROMIS-29
- Pain Catastrophizing Scale (PCS)
- Pain Vigilance and Awareness Questionnaire (PVAQ)
- Pain condition-related medication usage

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5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects with chronic pain who are considered to have failed therapy with their existing SCS system. Subjects 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 Screening and Informed Consent

5.2.1 Subject Screening

Potential patients presenting at the 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. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and on a screening log as required.

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. These patients will also be recorded in the screening log.

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. Special Circumstances for Informed Consent.
Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. Individuals under the age of 18 or age of legal consent are excluded from the study population. Individuals unable to read or write are excluded from the study population. Pregnant or breastfeeding women are excluded from the study population. All other aspects of the Informed Consent process will be in compliance with [Section 5.2.2]

In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject.

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. If some of the clinical and laboratory tests are not included in site standard tests, they must be done after written informed consent is obtained. Patients must meet ALL inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

5.3.1.1 Inclusion Criteria

1. Patient must provide written informed consent prior to any clinical investigation related procedure.
2. Patient has a spinal cord stimulator implanted for chronic, intractable pain.
3. Patient has inadequate pain relief from their current SCS system.
4. Patient has a pain NRS ≥ 6.
5. Physician has determined that the patient's original pain is still addressable with neurostimulation.

5.3.1.2 Exclusion Criteria

1. Patient is enrolled, or intends to participate, in a competing clinical study, as determined by Abbott.
2. Patient is seeking care for a new pain complaint outside of the original indication for SCS.
3. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the Investigator's opinion, could limit the patient's ability to participate in the clinical investigation or to comply with follow-up requirements.
4. Physician has determined that patient's pain relief is inadequate due to a malfunction or damage to the existing system.
5. Patient requires frequent MRI.
6. Patient is involved in active disability litigation related to their pain or seeking worker's compensation.
7. Patient is a member of a vulnerable population (See Section 5.2.2.1).

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent and has been confirmed to meet all eligibility criteria.

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.

5.5 Subject Deregistration

Subjects are considered deregistered if a study device was not introduced to the subject for any reason (e.g., payor denial or inability to place leads), and are excluded from the analysis set.

The Full Analysis Set (FAS) is the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all enrolled subjects. Deregistered subjects will be excluded from the FAS, but must be followed and documented according to the CIP requirements until they withdraw informed consent.

Subjects who are deregistered or discontinued for the above-mentioned reasons will not count towards the total sample size.

5.6 Subject Withdrawal

Each enrolled subject 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 (per Section 3.3)
- Subject's neurostimulation system has been explanted

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be 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 device under investigation, 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.

Lost-to-Follow-up

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:

- 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, a letter (certified if applicable) should be sent 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.

5.7 Number of Subjects

A sample size of 100 subjects is planned for this study. No site may contribute more than 20% of the total sample.

5.8 Expected Duration of Each Subject's Participation

5.9 Total Expected Duration of the Clinical Investigation

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline

After enrollment has been completed, baseline data will be collected regarding the patient's background, health, and existing SCS system.

6.1.1 Baseline Clinical Assessments

The following data will be recorded at baseline:

- Subject demographics
- Relevant medical history related to implantation and failure of the current SCS system
- Occupational status
- Pain condition-related medication usage (e.g., analgesics, opioids, anti-convulsants, anti-depressants)
- Current neurostimulation system details (if available)
- Device programming (if available)
- NRS
- PROMIS-29
- PCS
- PVAQ
- X-ray images (if available)

6.2 Trial Procedure (if applicable)

6.2.1 Procedures Involved in the Use of the Study Devices

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

6.2.2 Trial Period Implementation

The trial period will be executed according to the Investigator's discretion. The trial period may be repeated to allow for use of an additional trial method.

The following data will be recorded at trial implementation:

- Trial system details
- Device programming
- Device-related adverse events (if applicable)
- Serious adverse events (if applicable)
- Device deficiency (if applicable)
- Withdrawal (if applicable)
- Death (if applicable)

6.2.3 End of Trial Period

The End of Trial Period data collection will occur after each trial period. The following data will be recorded at the End of Trial Period visit:

- NRS
- Patient reported pain relief
- Patient satisfaction
- Physician satisfaction
- Device-related adverse events (if applicable)
- Serious adverse events (if applicable)
- Device deficiency (if applicable)
- Withdrawal (if applicable)
- Death (if applicable)

6.3 Permanent System Implementation

Permanent implementation of the chosen neurostimulation system will be performed according to the Investigator's standard operating procedures. The stimulator will be activated and programmed by trained personnel and/or an Abbott representative either during post-operative recovery or at an office visit in accordance with standard operating procedures. The subject's stimulator will be programmed according to the most recent Abbott programming guidance. After programming, the subject will receive a patient controller 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:

- Neurostimulation system details
- Device programming
- Device-related adverse events (if applicable)

- Serious adverse events (if applicable)
- Device deficiency (if applicable)
- Withdrawal (if applicable)
- Death (if applicable)

Neither the physician nor the subject should actively attempt to wean opioid usage for the first 45 days after permanent implementation. After this period, Investigators are encouraged to decrease opioid usage according to current guidelines or practices.

6.4 Follow-up Assessments

6.4.1 Follow-up for All Subjects

Follow-up visits will occur in-office at 3, 6, 12, 18, and 24-months (± 30 days) after permanent system implementation is complete. Any reprogramming must be performed only after all patient questionnaires have been administered.

The following data will be collected at each visit:

- Occupational status
- Pain condition-related medication usage (e.g., analgesics, opioids, anti-convulsants, anti-depressants)
- NRS
- PROMIS-29
- PCS
- PVAQ
- Patient satisfaction
- Physician satisfaction
- Device programming (if applicable)
- Device-related adverse events (if applicable)
- Serious adverse events (if applicable)
- Device deficiency (if applicable)
- Withdrawal (if applicable)
- Death (if applicable)

6.4.2 Unscheduled Visits

An unscheduled visit is defined as a visit that occurs between any of the required follow-up visits where the patients is examined for an adverse event, and not for expected reprogramming. 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.

6.4.3 Schedule of Events

6.5 Patient Reported Outcome (PRO) Measurements

The responsible site designee will administer patient reported outcome questionnaires. It is important that 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. The site designee may read the items to the subject and record the subject's response if requested. Once the questionnaires are completed, the designee will review for completeness to verify that all questions have been answered according to the directions provided. All PROs must be administered before device reprogramming.

- PROMIS-29
- Pain Catastrophizing Scale (PCS)
- Pain Vigilance and Awareness Questionnaire (PVAQ)

6.5.1 PROMIS-29

The PROMIS-29 is a 29-item profile instrument that covers 7 health domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and social function) with 4 questions each. 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). Version 2.1 of the PROMIS-29 will be used for this study and 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. The t-scores were validated on a sample from the general population and all items must be answered to utilize the scoring tables. If forms are incomplete, the Health Measures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice) can be used to generate appropriate t-scores.

6.5.2 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.

6.5.3 Pain Vigilance and Awareness Questionnaire

The PVAQ is a validated, 16-item scale that evaluates attention to pain. Subjects rate how frequently each statement represents their experience over the last 2 weeks from 0 "never" to 5 "always". Item scores are summed to produce the total score, which ranges from 0-80 with a higher score indicating greater attention to pain.

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.

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

Should death related to the procedure or device occur, the Investigator is requested to record death information in the hospital records and immediately document the information on the Adverse Event CRF and submit to Sponsor.

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 early conclusion of the subject's participation in the study. Therefore, the Investigator is required to complete the Withdrawal CRF.

7.1.3 Device Deficiency/Device Malfunction

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.

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A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended when used in accordance with the Instructions for Use or CIP.

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 assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiency data (if applicable), will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

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

An offline form will be made available 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. All information must still be entered in the EDC system as soon as feasible.

SAE Reporting

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

Clinical Site	Reporting timelines
All Sites	SAEs must be reported 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.

The date the site staff became aware the event met the criteria of an SAE must be recorded 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 sponsor are considered:

1. All serious adverse events regardless of relatedness to the device and/or procedure
2. All device/procedure related adverse events

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7.3.2 Device Deficiency/Malfunction Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF form.

The Investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported 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.

The device, if not implanted or not remaining in the subject, should be returned to the Sponsor.

Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

An offline form will be made available to allow the Investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID number has been assigned, the device deficiency should be reported to the Sponsor via the offline reporting form.

7.3.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses, and analysis of descriptive endpoints may be maintained in a separate Statistical Analysis Plan.

8.1 Analysis Populations

The Full Analysis Set (as defined in Section 5.5) will be the analysis population.

8.2 Statistical Analyses

Summary statistics will be provided and significance values will be provided for comparisons and measures of change. Validated questionnaires will be assessed per their respective instructions.

8.3 Sample Size Calculation and Assumptions

8.4 Timing of Analysis

8.5 Subgroup Analysis

8.6 Procedures for Accounting for Missing Data

8.7 Planned Interim Analysis

8.8 Statistical Criteria for Termination

8.9 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents for the purpose of 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, 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

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor 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.

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided 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, and clinical investigation personnel responsibilities. 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 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 over 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.
- 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.
- Source documentation (including original medical records) must be available 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. A monitoring visit sign-in log will be maintained 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 eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of Investigator compliance to the CIP and regulatory requirements and dealt with 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
- 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, 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.

In the event that 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 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.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Committees

10.8.1 Steering Committee

The Steering Committee is assigned by the Sponsor and consists 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, to review operational issues that may

arise and warrant a CIP amendment or other corrective action, and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

10.8.2 Clinical Events Committee (CEC)

The Clinical Events Committee (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 or identified by Safety personnel for the clinical investigation 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.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review, or correct data. Passwords and electronic signatures will be strictly confidential.

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

At the conclusion 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.

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 that 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 transfer into Sponsor’s data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient’s medical condition, treatment, dates of treatment, etc. 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 implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The

privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

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 DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

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. In order to comply with these regulatory requirements/GCP, the following information should be included 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)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of Investigator assessment of device relationship for SAEs
- 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. These serve as the source documentation.
- Patient reported outcome measures may be completed using electronic sources, such as directly into an Investigator's electronic health record. In this event, the direct entry by the subject is considered the source.

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The

Investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

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

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted 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.

No investigative procedures other than those defined in this CIP will be undertaken 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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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. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the Investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review 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 Sponsor determines that the clinical investigation should be registered, 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.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The information collected in this study will be added to the current knowledge and understanding of treatment options for patients with SCS systems that do not currently provide sufficient pain relief.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified devices and procedure are described in the relevant IFU. There may be risks related to the study devices that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.3 Residual Risks Associated with the Study Devices, as Identified in the Risk Analysis Report

The clinical risks associated with neurostimulation 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 each device are outlined in the associated IFU, and these disclosed risks are not modified by participation in this trial.

15.5 Steps Taken to Control or Mitigate Risks

The devices used in this study are approved and in commercially distribution. Risks associated with the use of the device under investigation are minimized through device design, Investigator selection and training, pre-specified patient eligibility requirements, and study monitoring to ensure adherence to the

protocol and the use of a DMC. All adverse events and device deficiencies will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

Any undesirable side effects, under normal conditions of use, are considered acceptable risks when weighed against the performance of the device and benefits to the subject.

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APPENDIX I: ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRPS	Complex Regional Pain Syndrome
DMP	Data Management Plan
DRG	Dorsal Root Ganglion
EC	Ethics Committee
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
PCS	Pain Catastrophizing Scale
PRO	Patient Reported Outcome
PVAQ	Pain Vigilance and Awareness Questionnaire
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
UADE	Unanticipated Adverse Device Effect

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APPENDIX II: SITE CONTACT INFORMATION

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APPENDIX III: CASE REPORT FORMS

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APPENDIX IV: INFORMED CONSENT FORM

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APPENDIX V: MONITORING PLAN

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APPENDIX VI: 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.

Amendment Number	Version	Date	Details	Rationale
Not Applicable	A	23 JAN 2019	First release of CIP	NA

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APPENDIX VII: CIP SUMMARY

Clinical Investigation Name and Number	CRD_960 Prolong
Objectives	The objectives of this study are to evaluate the effectiveness of Abbott neurostimulation devices in restoring pain relief, improving quality of life, and reducing related medication use for patients with failed SCS.
Study Devices	Any market-released Abbott BurstDR-capable or DRG neurostimulation device may be used in this study along with its relevant accessories. This study allows for the inclusion of future iterations of Abbott's neurostimulation systems and expanded indications as they receive approval from the applicable country regulatory authority.
Number of Subjects Required for Inclusion in Clinical Investigation	100 subjects will be registered at up to 40 sites in the US
Clinical Investigation Design	Prospective, multi-center, open-label, post-market
Endpoints	• NRS • Patient reported pain relief • Patient satisfaction • Physician satisfaction • PROMIS-29 • Pain Catastrophizing Scale (PCS) • Pain Vigilance and Awareness Questionnaire (PVAQ) • Pain condition-related medication usage
Subject Follow-up	• Enrollment • Baseline • Start of Trial (if applicable) • End of Trial (if applicable) • Permanent Implementation • 3-month follow-up • 6-month follow-up • 12-month follow-up • 18-month follow-up • 24-month follow-up
Inclusion Criteria	1. Patient must provide written informed consent prior to any clinical investigation related procedure.

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	2. Patient has a spinal cord stimulator implanted for chronic, intractable pain. 3. Patient has inadequate pain relief from their current SCS system. 4. Patient has a pain NRS ≥ 6. 5. Physician has determined that the patient's original pain is still addressable with neurostimulation.
Exclusion Criteria	1. Patient is enrolled, or intends to participate, in a competing clinical study, as determined by Abbott. 2. Patient is seeking care for a new pain complaint outside of the original indication for SCS. 3. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the Investigator's opinion, could limit the patient's ability to participate in the clinical investigation or to comply with follow-up requirements. 4. Physician has determined that patient's pain relief is inadequate due to a malfunction or damage to the existing system. 5. Patient requires frequent MRI. 6. Patient is involved in active disability litigation related to their pain or seeking worker's compensation. 7. Patient is a member of a vulnerable population (See Section 5.2.2.1).

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APPENDIX VIII: REFERENCES

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