Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT04873817
ROSTRA
Real-World Outcomes Study on Subjects Treated with Radiofrequency Ablation
Study Document No: ABT-CIP-10495
Version A
Date: 04-JUN-2021

Sponsor

Abbott
The Corporate Village
Da Vincilaan 11 – box F1
1935 Zaventem
Belgium

Abbott
6901 Preston Rd
Plano, TX 75024 USA

Clinical Investigation Plan

[redacted]
CRD_1029
ROSTRA
Real-World Outcomes Study on Subjects Treated with Radiofrequency Ablation

Version Number	[redacted]
Date	04 June 2021
Steering Committee	[redacted]
Planned Number of Sites and Region(s)	Up to [redacted] (EMEA and US)
Clinical Investigation Type	International, prospective, non-randomized, single-arm, multi-center, post-market study
Abbott Medical Expert	[redacted]
Sponsor	Abbott Medical Device entity sponsoring the clinical investigation The Corporate Village Da Vincilaan 11 – box F1 1935 Zaventem Belgium Abbott 6901 Preston Rd Plano, TX 75024 USA
Electronic Data Capture Software	Oracle Clinical
CIP Author of Current Version	[redacted]

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

Clinical Investigation Plan

TABLE OF CONTENTS

Clinical Investigation Plan

LIST OF FIGURES

Clinical Investigation Plan

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 ISO14155:2011) 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.).

Clinical Investigation Plan

1.0 INTRODUCTION

The ROSTRA study is an international, prospective, non-randomized, single-arm, multi-center, and post-market study to collect real-world safety and effectiveness data on Abbott's IonicRF™ Generator and compatible RFA accessories.

All investigators involved in the conduct of this 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

Chronic pain is common and debilitating. It has been linked to restrictions in mobility and daily activities, opioid dependency, anxiety and depression, and poor perceived health or reduced quality of life.[1] Specifically, low back pain is the leading cause of years lived with disability in high to middle income countries.[2] Patients usually undergo a treatment continuum when their pain evolves from acute to chronic; from exercise, manual therapy, and over-to-counter drugs to prescription drugs and non-invasive stimulation techniques, such as transcutaneous electrical nerve stimulation.[3] A high proportion of subjects with chronic pain do not experience long-term benefits from these conservative treatments and seek alternative options, such as nerve blocks, and radiofrequency (RF) ablation (RFA).

Nerve blocks are injections of an anesthetic directly in the region of an affected painful nerve. A nerve block can be used therapeutically to offer short-term pain relief. Prior to RFA procedures, they are often used diagnostically to isolate the anatomical structures that are the source of pain. If the block is successful, an RFA procedure may be recommended. An RFA system is made of a RF generator, a cannula, an electrode (or probe), a grounding pad (for monopolar procedures), and an adaptor cable.

RFA is a minimally invasive procedure that conventionally uses heat generated by radio waves to target specific nerves and temporarily turn off their ability to send pain signals. Common indications are facetogenic, radicular, and sacroiliac joint pain. The Simplicity probe is specifically designed for denervation of the sacroiliac region, including peripheral nerves at S1–S4. It features three independent active areas to create a true strip lesion from a single insertion point.[4] Other indications include knee and hip osteoarthritis, often the result of knee or hip replacements, and trigeminal neuralgia, a chronic pain condition that affects the trigeminal nerve resulting in sudden, severe facial pain.

A range of RFA procedure types can be performed. Conventional thermal RFA causes coagulative necrosis of axons in target nerves by raising the temperature above 65 degrees centigrade. Pulsed RFA is almost identical to conventional RFA, except that the current is typically carried out in 20-ms pulses every 0.5 sec at a temperature that does not exceed 42 °C. The pulsed-dose RF procedure is a technical improvement of the pulsed RF technique in which the delivery mode of the current is adapted.[5] In monopolar mode, RF energy is applied between an electrode and the grounding pad. Monopolar RF is typically performed with multiple independent electrodes. The RF energy is applied between two electrodes in bipolar mode.

1.1.2 Rationale for Conducting this Clinical Investigation

The IonicRF generator obtained CE mark on 31 May 2020. The European Union Medical Device Regulation (EU-MDR) 2017/745 requires that all device manufacturers provide continuous monitoring of

the safety and effectiveness of CE marked devices. The study proposed herein is intended to fulfill the requirements set forth in the EU-MDR.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

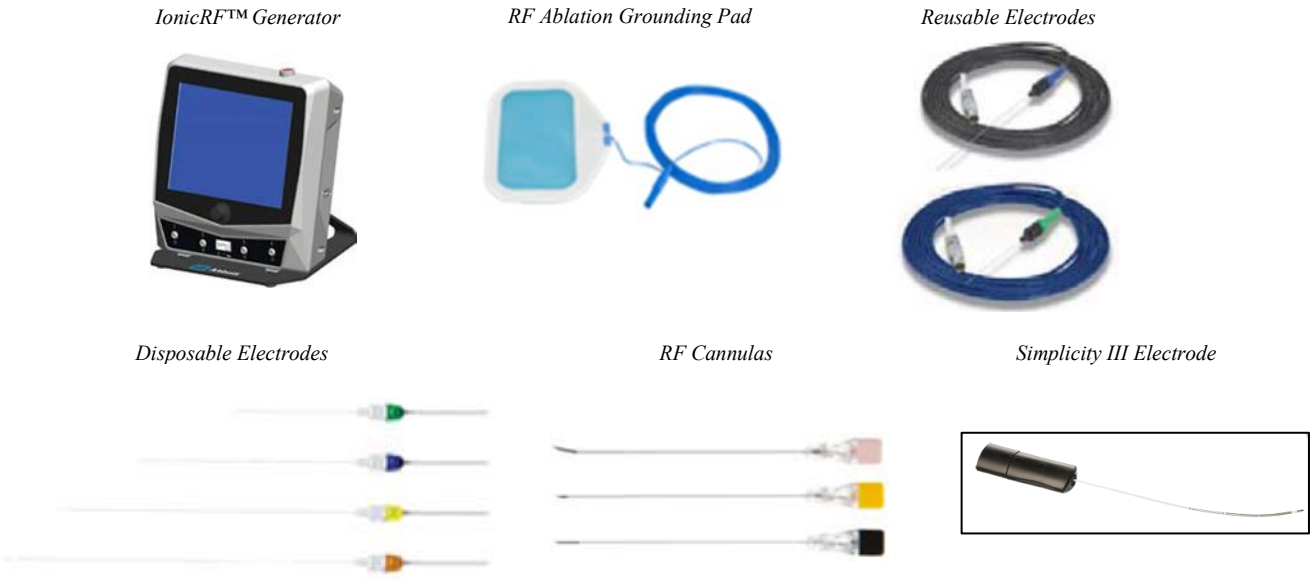
The objective of this study is to collect real-world safety and effectiveness data on Abbott's IonicRF™ Generator and compatible accessories.

2.2 Devices Used in the Clinical Investigation

2.2.1 Name of the Device(s) Under Investigation

IonicRF RF lesion generator, along with any country-specific market-released accessory (i.e. electrode, cannula, grounding pad, and adaptor cable) compatible with the IonicRF Generator.

Figure 1. Components of a RF Pain Management System



2.2.2 Indication for Use

The IonicRF Generator, in combination with approved compatible electrodes and cannulae, is indicated as an aid in the management of pain in the nervous system. Examples include, but are not limited to, facet denervation, rhizotomy, and related functional neurosurgical procedures.

2.2.3 Description of the Device(s) Under Investigation

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

2.2.4 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 an international, prospective, non-randomized, single-arm, multi-center, and post-market study. Subjects will be assessed at baseline and post implant using questionnaires. Specifically, assessments will include pain intensity as assessed by the Numeric Rating Scale (NRS), quality of life as assessed by EuroQol-5 Dimensions (EQ-5D) and PROMIS-29, and procedure satisfaction as assessed by the Patient Global Impression of Change (PGIC) and patient satisfaction level. The Oswestry Disability Index (ODI), Neck Disability index (NDI), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index score will be completed for specific indications only.

Subjects will be followed via clinic visit or remote follow-up at [redacted]. The study will enroll up to [redacted] subjects at up to [redacted] sites in Europe and the United States. No site may enroll more than [redacted] of the total subjects. This study uses a sample size that allows inclusion of multiple indications. Additional centers may be approached for participation in the study as needed.

It is recommended that subjects should limit increases in their prescribed chronic pain medications from Baseline to the assessment of the primary endpoint at [redacted]. Both the types of medication and the prescribed maximum daily dosage of pain medication for their chronic pain condition should not increase significantly (at the discretion of the investigator). If a rescue medication is required, subjects will be allowed additional aspirin or Tylenol (Acetaminophen) at a maximal dose of 2 g within a 24-hour period. (NOTE: Post-operative pain medications prescribed only for acute management of post-procedural pain are allowed.)

[redacted]

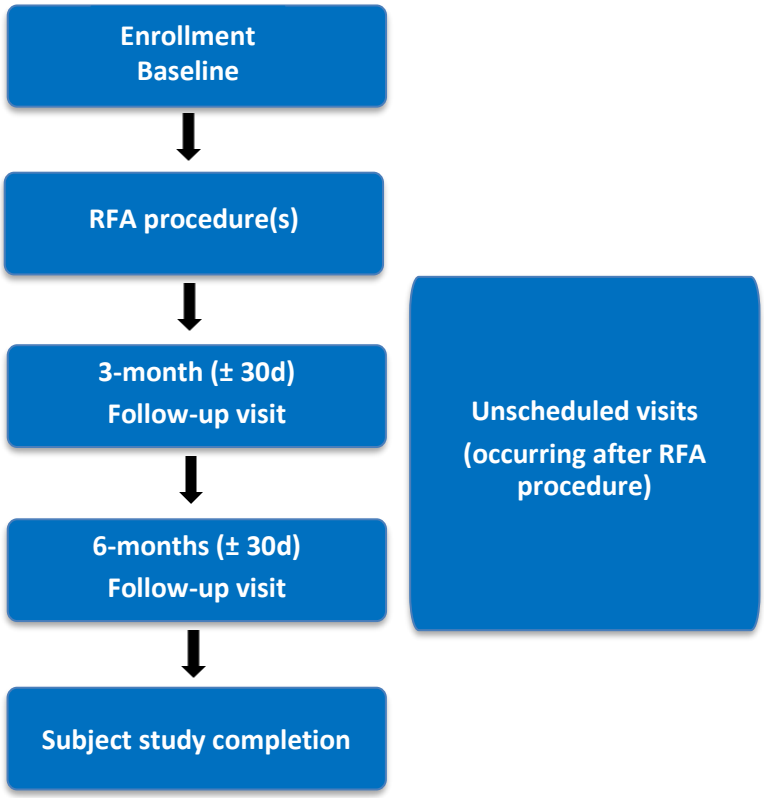
The Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

Clinical Investigation Plan

3.1 Clinical Investigation Procedures and Follow-up Schedule

The flowchart and the follow-up requirements of this clinical investigation are described below.

Figure 2. Clinical Investigation Flowchart



Clinical sites will follow subjects until the last subject completes their 6-month visit.

3.2 Measures Taken to Avoid and Minimize Bias

To avoid bias, investigators are required to screen every patient scheduled for an RFA procedure with the IonicRF generator. Enrollment of consecutive subjects should be attempted.

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 expert may act as a medical monitor and evaluate X-ray or ultrasound images of the RFA procedures to verify correct cannula placement.

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, Clinical Events 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 Sponsor discontinue the clinical investigation, sites will follow subjects per routine hospital practice with device-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 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.

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 Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate.

4.0 ENDPOINTS

4.1 Primary Effectiveness and Safety Endpoint

The primary effectiveness endpoint is the relative change in Numeric Rating Scale (NRS) [redacted] follow-up visit. NRS is the patient's self-rating of average pain intensity for the area being treated over [redacted] from 0 "no pain" to 10 "worst pain imaginable". This will be calculated for each represented indication.

The primary safety endpoint is the incidence of device- and procedure-related serious adverse events.

4.2 Descriptive Endpoints

The following descriptive endpoints will be reported using summary statistics.

1. The following will be characterized at RFA procedure(s):
   - Overall procedure and RF time
   - A summary of Abbott RFA accessory model numbers used in the procedure

2. The following will be characterized at follow-up visits:
   - Patient reported (%) pain relief
   - Patient satisfaction
   - Patient Global Impression of Change (PGIC): to evaluate the subject's impression of change in his/her condition since the beginning of the study treatment
   - Device- and procedure-related adverse events
   - Device deficiencies

3. Change from baseline to each follow-up visit in
   - NRS (raw change); the raw change is defined as (Baseline NRS score– Follow-up NRS score)
   - EQ-5D quality of life survey, consisting of a descriptive system and the EQ VAS. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale
   - PROMIS-29 assesses pain intensity using a single 0-10 numeric rating item and eight health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, cognitive function/abilities, and sleep disturbance) using four items per domain
   - Opioid medication usage
   - Oswestry Disability Index (ODI): 10-item scale that evaluates disability related to low-back pain (only for back pain patients)
   - Neck Disability index (NDI): 10-item scale that evaluates disability related to neck pain (only for neck pain patients)
   - The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index score: measures pain, stiffness, and functional limitations (only for knee and hip pain patients)

4. Relative change in NRS [redacted]

5. Responder analysis [redacted]
   - Proportion of subjects with ≥ 30% decrease on NRS
   - Proportion of subjects with ≥ 50% decrease on NRS

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll subjects of all genders from the general chronic pain population referred to participating pain clinics.

Indications include (approximately 20 subjects each):

- Lumbar facet joint pain
- Cervical facet joint pain
- Sacroiliac joint pain
- Radicular pain
- Trigeminal neuralgia
- Knee pain
- Hip pain
- Other pain

Patients must meet all general eligibility criteria and the eligibility criteria specific to the patient's chronic pain indication and provide written informed consent prior to sites 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 the clinical site will be evaluated for study eligibility by a member of the site's clinical investigation team (physician and/or research coordinator) previously trained to the CIP. Those meeting eligibility criteria will be fully informed about the clinical study using the established Informed Consent process (described in Section 5.2.2). Subjects who do not meet the clinical investigation screening criteria are considered a screen failure and cannot participate in the clinical investigation. The Principal Investigator or the delegated clinical investigation personnel will record the screen failure in the hospital records and on a recruitment/screening log as required.

Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific procedures may begin.

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.

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. 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.
In addition, sites must obtain an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), from the subject or their legally acceptable representative.

5.3 Eligibility Criteria

Assessment for eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria and the inclusion criteria specific to the patient's chronic pain indication to participate in the clinical investigation. If ANY general exclusion criteria or exclusion criteria specific to the patient's chronic pain indication (if applicable) are met, the patient is excluded from the clinical investigation and cannot be enrolled.

If any clinical 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.

5.3.1 All candidate subjects

5.3.1.1 Inclusion Criteria

1. Subject must provide written informed consent prior to any clinical investigation-related procedure
2. Subject is ≥ 18 years of age
3. Subject has chronic pain > 6 months and was unresponsive to conservative management
4. Subject has pain on an NRS scale of ≥ 6
5. Subject is scheduled for an RFA procedure with the IonicRF generator within 30 days of baseline to treat chronic pain at one anatomical region
6. Subject has stable chronic pain medication use for 30 days

7. Subject is willing and able to comply with the prescribed follow-up evaluations

5.3.1.2 Exclusion Criteria

1. Subject is currently participating in another clinical investigation that may confound the results of this study
2. Ongoing systemic or local infection in the area of the procedure
3. Recent use of anticoagulants or subject with coagulopathy
4. Primary complaint of deafferentation pain
5. 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
6. Subject's opioid usage is > 90 morphine equivalents per day

5.3.2 Candidate subjects with facet joint pain (lumbar or cervical)

5.3.2.1 Inclusion criteria

1. Subject has unilateral or bilateral pain on para-spinal palpation and localized pain with extension/lateral bending
2. Subject has facet joint pain confirmed by at least 1 positive medial branch block with 0.5 mL or less of anesthetics (across at least 3 vertebral levels) achieving at least 50% pain relief, with real-time injection of radiographic contrast under fluoroscopic guidance (adapted from the consensus practice guidelines; Cohen et al[6])

5.3.3 Candidate subjects with sacroiliac joint pain

5.3.3.1 Inclusion criteria

1. Subject has sacroiliac joint pain based on medical history and physical exam
2. Subject has sacroiliac joint pain confirmed by an infiltration of local anesthetics in the posterior part of the sacroiliac joint achieving at least 50% pain relief

5.3.4 Candidate subjects with radicular pain

5.3.4.1 Inclusion criteria

1. Subject has radicular pain based on medical history and physical exam
2. Subject has radicular pain confirmed by dermatomal mapping corresponding to at least 1 nerve root level

5.3.5 Candidate subjects with trigeminal neuralgia

5.3.5.1 Inclusion criteria

1. Subject has trigeminal pain based on medical history and physical exam
2. Subject did not have any mass effect or stroke causing trigeminal pain confirmed by MRI
3. Subject is ≥ 60 years of age in case of a neurovascular conflict

5.3.5.2 Exclusion criteria

1. Subject has sensory problems

5.3.6 Candidate subjects with knee or hip pain

5.3.6.1 Inclusion criteria

1. Subject has knee or hip pain based on medical history and physical exam
2. Subject has radiographically confirmed osteoarthritis of the hip or knee, or has chronic pain following joint arthroplasty

5.4 Subject Enrollment

A subject is considered enrolled in the clinical investigation when the following conditions are met:

1. Subject has provided written informed consent
2. Subject has been determined to meet all Inclusion/Exclusion requirements

5.5 Subject Deregistration

Subjects are considered deregistered if the RFA procedure was not performed for any reason (e.g., payor denial), and are excluded from the Full Analysis Set (FAS). [redacted] Deregistered subjects, although excluded from the FAS, must be followed and documented according to the CIP requirements until they are withdrawn. Subjects who are deregistered for the above-mentioned reasons will not count towards the total sample size.

5.6 Subject Withdrawal and Discontinuation

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 (cause must be documented)
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated by the Sponsor (per Section 3.3)
- Subject deregistration (per Section 5.5)
- Subject receives additional chronic pain treatment (neuromodulation implant or other) for the same anatomical region during the follow-up period

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.

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.

Lost-to-Follow-up

If the subject misses two 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 follow-up contact time point, it will be considered a missed visit. The subject may then return for the subsequent visit (if applicable). 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.

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

[redacted] 180 subjects [redacted]

5.8 Total Expected Duration of the Clinical Investigation

[redacted]

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

6.2 Baseline

Baseline assessments should be completed on the same day of enrollment and after the diagnostic block(s) and/or other evaluations to determine if a subject qualifies for an RFA procedure. The diagnostic block should only be used as a diagnostic tool and its therapeutic effect should be completely nullified at the time of the baseline assessment.

6.2.1 Baseline Clinical Assessments

The following data will be recorded at baseline:

- Subject demographics
- Occupational and lifestyle information
- Subject medical history (pain history and other interventions for pain management)
- Subject pain diagnosis and pain location
- NRS score
- EQ-5D-5L
- PROMIS-29
- Opioid medication usage
- ODI (only for subjects with back pain)
- NDI (only for subjects with neck pain)
- WOMAC index score (only for subjects with knee and hip pain)
- Serious adverse events resulting in death (if applicable)

6.3 Radiofrequency ablation procedure(s)

6.3.1 Procedures Involved in the Use of the Device Under Investigation

The RFA procedure(s) will be conducted within 30 days of baseline and according to minimal requirements for different patient populations as outlined in the guidance document “Practice Guidelines for RFA procedures in the ROSTRA study”.

6.3.2 Treatment Procedures

The following information will be collected at (each) RFA procedure:

- Procedure information (e.g., treated vertebral segments, setting, temperature, impedance, voltage)
- Overall procedure and RF time
- X-ray or ultrasound image (documentation of cannula placement)
- A summary of Abbott RFA accessory model numbers used in the procedure
- Device deficiencies (if applicable)
- Serious adverse events resulting in death (if applicable)
- Device- and procedure-related serious adverse events (if applicable)
- Device- and procedure-related adverse events (if applicable)

6.4 Follow-up Assessments

6.4.1 Follow-up for All Subjects

Follow-up visits will occur at 3 and 6 months (± 30 days) after the (last) RFA procedure.

The following data will be collected at each visit:

- Occupational and lifestyle information
- NRS score

- EQ-5D-5L
- PROMIS-29
- Opioid medication usage (only if there is a change in dosage from baseline or previous study visit)
- Patient reported (%) pain relief
- Patient satisfaction
- PGIC
- New area of chronic pain (if applicable)
- ODI (only for subjects with back pain)
- NDI (only for subjects with neck pain)
- WOMAC index score (only for subjects with knee and hip pain)
- Serious adverse events resulting in death (if applicable)
- Procedure-related serious adverse events (if applicable)
- Procedure-related adverse events (if applicable)

6.4.2 Patient Reported Outcome (PRO) Measures

The Investigator, Coordinator or site designee will administer the PRO 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.

Alternatively, 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. A second alternative if the subject is unable to attend a follow up visit in person is that the Investigator or designee may 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 or video call, save that document as source data, and enter the information in the EDC system.

6.4.2.1 Numerical Rating Scale (NRS)

All subjects should answer the NRS question. 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.

6.4.2.2 EuroQol-5 Dimensions (EQ-5D)

All subjects should complete the EQ-5D questionnaire. EQ-5D is a standardized instrument for use as a measure of health outcome applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. A visual analog

scale (VAS) for health is also included in the measure as a patient-reported estimate of overall health status.[7]

6.4.2.3 PROMIS-29

All subjects should complete the PROMIS-29 questionnaire. The PROMIS-29 is an adult scale developed in partnership with the National Institutes of Health (NIH) to estimate overall quality of life by assessing the following domains known to impact activities of daily living: physical function, sleep disturbance, depression, anxiety, fatigue, pain interference, pain intensity, cognitive function, and social role satisfaction. The scale requires subjects to rate the frequency and/or severity of symptoms and experiences related to each of these domains. A total score is calculated and transformed against normative data into a t score indicating global quality of life in relation to population norms. Subscales are defined by each domain described above and can be examined separately to parse separate symptoms or deficiencies in quality of life. The final item is an 11-point pain intensity numerical rating scale (NRS) by which the subject rates their average pain over the past 7 days. Subjects should read each item and check the one box that most closely represents their response.[8]

6.4.2.4 Patient Global Impression of Change (PGIC)

All subjects should answer the PGIC question. 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.[9]

6.4.2.5 Oswestry Disability Index (ODI)

Only subjects with low back disability or buttocks pain should complete the ODI questionnaire. 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. 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, then multiplied by two to obtain the index (range 0 to 100). 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%), 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.[10]

6.4.2.6 Neck Disability Index (NDI)

Only subjects with neck pain disability should complete the NDI questionnaire. The NDI is designed to measure neck-specific disability. The questionnaire has 10 items concerning pain and activities of daily living including personal care, lifting, reading, headaches, concentration, work status, driving, sleeping, and recreation. The measure is designed to be given to the patient to complete and can provide useful information for management and prognosis of those with neck pain. Each item is scored out of five (with no disability response given a score of 0) giving a total score for the questionnaire out of 50. Higher scores represent greater disability. The result can be expressed as a percentage (score out of 100) by doubling the total score.[11]

6.4.2.7 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Only subjects with knee or hip pain should complete the WOMAC questionnaire. WOMAC is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with knee and hip pain, including pain, stiffness, and physical functioning of the joints. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Physical functioning questions cover everyday activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties.[12]

6.5 Unscheduled Visit

An unscheduled visit is defined as a visit that occurs between the RFA procedure and any of the required follow up visits, except for routine medication visits (as applicable). Data regarding opioid usage, NRS, and adverse events should be documented by completing the appropriate question/CRF as applicable. Any additional CRF, not specified above, may be collected if deemed appropriate by the investigator.

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

Clinical Investigation Plan

6.5.1 Schedule of Events

CIP Activity	Enrollment	Baseline	RFA procedure visit(s)	Follow-up visit 3 months (±30 days)	Follow-up visit 6 months (± 30 days)	Unscheduled
Informed Consent	X					
Eligibility	X					
Demographics		X				
Occupational and lifestyle information		X		X	X	
Medical History		X				
Pain diagnosis and pain location		X				
Opioid Medication		X		X	X	X
NRS		X		X	X	X
EQ-5D-5L		X		X	X	
PROMIS-29		X		X	X	
ODI*		X		X	X	
NDI*		X		X	X	
WOMAC index score*		X		X	X	
Device information			X			
Procedure Information and time			X			
X-ray or ultrasound image			X			
Patient reported pain relief				X	X	
PGIC				X	X	
Patient satisfaction				X	X	
New area of chronic pain				(X)	(X)	
Device deficiencies			(X)			
Protocol deviation		(X)	(X)	(X)	(X)	(X)
Serious adverse events resulting in death	(X)	(X)	(X)	(X)	(X)	(X)
Device- and procedure-related SAEs			(X)	(X)	(X)	(X)
Device- and procedure-related AEs			(X)	(X)	(X)	(X)
Withdrawal			(X)	(X)	(X)	(X)

(X) if applicable
*For specific indications only

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.

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.

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 the 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

General AE Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled and approved for the study procedure in the clinical investigation. For deregistered subjects, adverse events will not be collected once the subject is considered deregistered. 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 and device deficiency data, 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 or device deficiency on the appropriate CRF. Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should also not be reported.

Only events that are related to the device and/or procedure and deaths events will be recorded in this study. Events that are not related to the device or procedure will not be recorded.

Reportable events are: Deaths, serious adverse events related to device/procedure (SADE) and non-serious adverse event related to device/procedure (ADE).

Refer to the specific device manuals for the possible adverse events associated with the use of Ionic RF Generator system.

The Sponsor will provide an offline form to allow the investigator to report SADEs 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.

SADE and Death Reporting

The investigator must report all SADEs and Death events to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	Sites must report SADEs and Deaths 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.

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

7.3.2 Device Deficiency/Malfunction Reporting

Sites should report all device deficiencies/malfunctions on the appropriate CRF form.

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

Clinical Sites	Reporting timelines
All Sites	Sites must report device deficiencies/malfunctions 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.

Sites must report device deficiencies/malfunctions to the IRB/EC per the investigative site's local requirements. Sites should return the device to the Sponsor.

Sites will have access to an offline form to allow the investigator to report device deficiencies/malfunctions if sites cannot enter the information in the EDC system. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID and/or randomization number has been assigned, sites should report the device deficiency to the Sponsor via the offline reporting form.

7.3.3 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 safety endpoints will be performed on the Full Analysis Set (FAS), [redacted]. Deregistered subjects will be excluded from the FAS. The effectiveness endpoints will be performed on the As-treated Population (AT), [redacted]

8.2 Statistical Analyses

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

8.2.1 Primary Effectiveness Endpoint Analyses

The primary effectiveness endpoint is [redacted]

The null and alternative hypotheses are as follows:

$$H_0: \mu = 0$$

$$H_1: \mu \neq 0$$

[redacted]

This endpoint will be evaluated [redacted] at the 5% significance level. The endpoint will be analyzed based on AT population described in Section 8.1.

8.2.2 Primary Safety Endpoint Analyses

The device- and procedure-related serious adverse events will be summarized as frequency, proportion and number of events per patient years of follow-up. The analysis will be performed on FAS as described in Section 8.1.

8.2.3 Descriptive Endpoints Analyses

Summary statistics will be presented for the descriptive endpoints. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Time-to-event variables will be analyzed using the Kaplan-Meier method, if applicable. The 95% confidence intervals for each type of data will be provided as appropriate. Difference between groups will be summarized using descriptive statistics including 95% confidence intervals, if applicable.

8.3 Sample Size Calculation

[redacted]

8.4 Timing of Analysis

The primary effectiveness and safety endpoints will be conducted when all enrolled subjects [redacted]. The final analysis will be

conducted, and final report will be written when the enrolled subjects [redacted]

8.5 Subgroup Analysis

Subgroup analyses may be performed on an ad-hoc basis to understand outcomes for specific indications and patient populations.

8.6 Procedures for Accounting for Missing Data

Every effort will be made to collect all required data. All available safety-related data will be used without adjustment to account for missing data. For effectiveness and other measures, all available data will be used. Sensitivity analysis may be performed on patient reported outcome measures using imputation. The details of missing data imputation could be described in SAP.

8.7 Planned Interim Analysis

[redacted]

8.8 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.9 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.

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 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.

10.3 Training

10.3.1 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.

10.4 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 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.

10.5 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
- 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.

10.6 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.

10.7 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.

10.8 Committees

10.8.1 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.

10.8.2 Clinical Events Committee

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 and 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 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 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 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 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 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)
- 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.
- 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 and can serve as the source documentation

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.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. The Sponsor will use an electronic audit trail 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

The Principal Investigator at each investigational site will obtain IRB/EC approval for the CIP and ICF 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:

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

The clinical investigation report will be submitted within one year of the end of the clinical investigation, or if applicable, will be submitted to the appropriate authorities according to current regulatory guidelines.

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. 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.

15.0 RISK ANALYSIS

All devices and accessories used in this study are market-approved; please refer to the device-specific IFU for information on risks. All procedures in this study are considered standard-of-care, therefore there are no anticipated incremental risks to subjects participating in this study.

15.1 Anticipated Clinical Benefits

There are no anticipated clinical benefits to subjects participating in this study, other than the benefits of receiving RFA.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified lesion generator, procedure, and compatible accessories, are described in the IFU documents. The study does not require any additional procedures or assessments other than patient reported outcomes such as NRS, EQ-5D, and other questionnaires. There are no additional risks introduced to patients enrolled in the study.

An RFA procedure involves risks. In addition to the risks commonly associated with any invasive procedure, below are listed the anticipated potential adverse effects with the use of a RF Pain Management System:

- As a consequence of electrosurgery, damage to surrounding tissue through iatrogenic injury can occur.
- Nerve injury, including thermal injury, or puncture of the spinal cord or nerve roots, potentially resulting in radiculopathy, paresis, and paralysis.
- Pain, pulmonary embolism, hemothorax or pneumothorax, infection, unintended puncture wound, including vascular puncture and dural tear, hemorrhage, and hematoma.

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 RF Pain Management systems are well known. Any potential residual risks are outweighed by the benefits, and the overall residual risk was determined to be acceptable. Clinical evidence demonstrates acceptable safety and performance of the device and accessories 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 use of any other commercially available RF Pain Management system.

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 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 warnings and precautions, and device handling are included in IFU documents of the lesion generator and accessories 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.

15.6 Risk to Benefit Rationale

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

Clinical Investigation Plan

APPENDIX I: ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
CE	Conformité Européenne
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF	Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
EQ-5D	EuroQol – 5 Dimensions
FDA	Food and Drug Administration (US)
HIPAA	Health Insurance Portability and Accountability Act
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
M.D.	Medical Doctor
MDR	Medical Devices Regulation
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NDI	Neck Disability Index
NRS	Numerical Rating Scale
ODI	Oswestry Disability index
OUS	Outside of United States
PGIC	Patient Global Impression of Change
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PRO	Patient Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
RF	Radiofrequency
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
US	United States
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Clinical Investigation Plan

APPENDIX II: SITE CONTACT INFORMATION

A list of Clinical Investigational sites will be kept under a separate cover and is available upon request.

Clinical Investigation Plan

APPENDIX III: REFERENCES

1. Dahlhamer J, Lucas J, Zelaya, C et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–1006
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–858
3. van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain: a systematic review of randomized controlled trials of the most common interventions. Spine 1997; 22(18):2128-2156
4. Cosman E, Dolensk, Hoffman RA. Factors That Affect Radiofrequency Heat Lesion Size. Pain Medicine 2014;15:2020–2036
5. Schmidt P, Pino C, and Vorenkamp K. Sacroiliac Joint Radiofrequency Ablation with a Multilesion Probe: A Case Series of 60 Patients. Anesth Analg 2014;119:460–2
6. Cohen S, Bhaskar A, Bhatia A et al. Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group. Reg Anesth Pain Med 2020;45(6):424-467
7. Devlin N, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Appl Health Econ Health Policy 2017;15:127–137
8. HealthMeasures. PROMIS-29+2 Profile v2.1 (PROPr). Available from: https://www.healthmeasures.net/score-and-interpret/calculate-scores/preference-based-scores
9. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27(1):26-35
10. Fairbank J, Couper J, Davies J, O'Brien, J. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66,271-273
11. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991;14(7):409-15
12. Quintana JM, Escobar A, Bilbao A, Arostegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after hip joint replacement. Osteoarthritis Cartilage 2005;13(12):1076-83

[redacted]

16. [redacted]

Clinical Investigation Plan

APPENDIX IV: LABELS

IFU documents will be kept under a separate cover and are available upon request.

Clinical Investigation Plan

APPENDIX V: CASE REPORT FORMS

Case Report Forms will be kept under a separate cover and are available upon request.

Clinical Investigation Plan

APPENDIX VI: INFORMED CONSENT FORM

The study specific sample Informed Consent Form will be kept under a separate cover and is available upon request.

Clinical Investigation Plan

APPENDIX VII: MONITORING PLAN

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

Clinical Investigation Plan

APPENDIX VIII: 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.

Clinical Investigation Plan

APPENDIX IX: CIP SUMMARY

Clinical Investigation Name and Number	ROSTRA (CRD_1029)
Title	Real-World Outcomes Study on Subjects Treated with Radiofrequency Ablation
Objective	The objective of this study is to collect real-world safety and effectiveness data on Abbott's IonicRF™ Generator and compatible RFA accessories. This post-market study is intended to satisfy EU MDR requirements.
Device Under Investigation	IonicRF Radiofrequency Generator, along with any country-specific market-released accessory (i.e. electrode, cannula, grounding pad, and adaptor cable) compatible with the IonicRF Generator.
Number of Subjects Required for Inclusion in Clinical Investigation	The study will enroll up to [redacted] patients at up to [redacted] sites in Europe and the US. Additional centers may be approached for participation in the study as needed.
Clinical Investigation Design	International, prospective, non-randomized, single-arm, multi-center, and post-market study
Primary Endpoints	The primary effectiveness endpoint is the relative change in Numeric Rating Scale (NRS) [redacted] follow-up visit. NRS is the patient's self-rating of average pain intensity for the area being treated over [redacted] from 0 "no pain" to 10 "worst pain imaginable". This will be calculated for each represented indication. The primary safety endpoint is the incidence of device- and procedure-related serious adverse events.
Subject Follow-up	Follow-up visit: Subjects will be followed at 3 and 6 months from the date of (last) RFA procedure
Inclusion Criteria for all candidate subjects	1. Subject must provide written informed consent prior to any clinical investigation-related procedure 2. Subject is ≥ 18 years of age 3. Subject has chronic pain > 6 months and was unresponsive to conservative management 4. Subject has pain on an NRS scale of ≥ 6 5. Subject is scheduled for an RFA procedure with the IonicRF generator within 30 days of baseline to treat chronic pain at one anatomical region 6. Subject has stable chronic pain medication use for 30 days 7. Subject is willing and able to comply with the prescribed follow-up evaluations

Clinical Investigation Plan

Exclusion Criteria for all candidate subjects	1. Subject is currently participating in another clinical investigation that may confound the results of this study 2. Ongoing systemic or local infection in the area of the procedure 3. Recent use of anticoagulants or subject with coagulopathy 4. Primary complaint of deafferentation pain 5. 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 6. Subject's opioid usage is > 90 morphine equivalents per day
Inclusion criteria for candidate subjects with facet joint pain (lumbar, cervical)	1. Subject has unilateral or bilateral pain on para-spinal palpation and localized pain with extension/lateral bending 2. Subject has facet joint pain confirmed by at least 1 positive medial branch block with 0.5 mL or less of anesthetics (across at least 3 vertebral levels) achieving at least 50% pain relief, with real-time injection of radiographic contrast under fluoroscopic guidance
Inclusion criteria for candidate subjects with sacroiliac pain	1. Subject has sacroiliac joint pain based on medical history and physical exam 2. Subject has sacroiliac joint pain confirmed by an infiltration of local anesthetics in the posterior part of the sacroiliac joint achieving at least 50% pain relief
Inclusion criteria for candidate subjects with radicular pain	1. Subject has radicular pain based on medical history and physical exam 2. Subject has radicular pain confirmed by dermatomal mapping corresponding to at least 1 nerve root level
Eligibility criteria for candidate subjects with trigeminal neuralgia	**Inclusion:** 1. Subject has trigeminal pain based on medical history and physical exam 2. Subject did not have any mass effect or stroke causing trigeminal pain confirmed by MRI 3. Subject is ≥ 60 years of age in case of neurovascular conflict **Exclusion:** 1. Subject has sensory problems
Inclusion criteria for candidate subjects with knee or hip pain	1. Subject has knee or hip pain based on medical history and physical exam 2. Subject has radiographically confirmed osteoarthritis of the hip or knee, or has chronic pain following joint arthroplasty