Radiofrequency (RF) Ablation Prospective Outcomes Study

RAPID

Clinical Investigation Plan

(A4087)

Sponsored By

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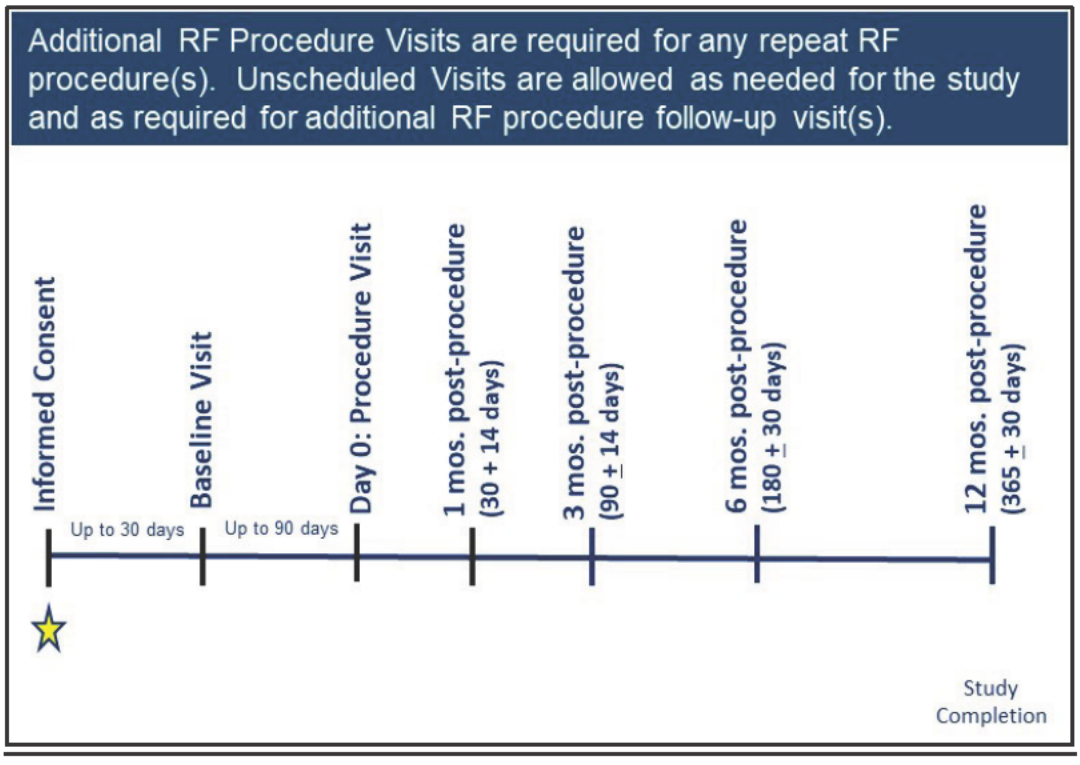
2. Protocol Synopsis

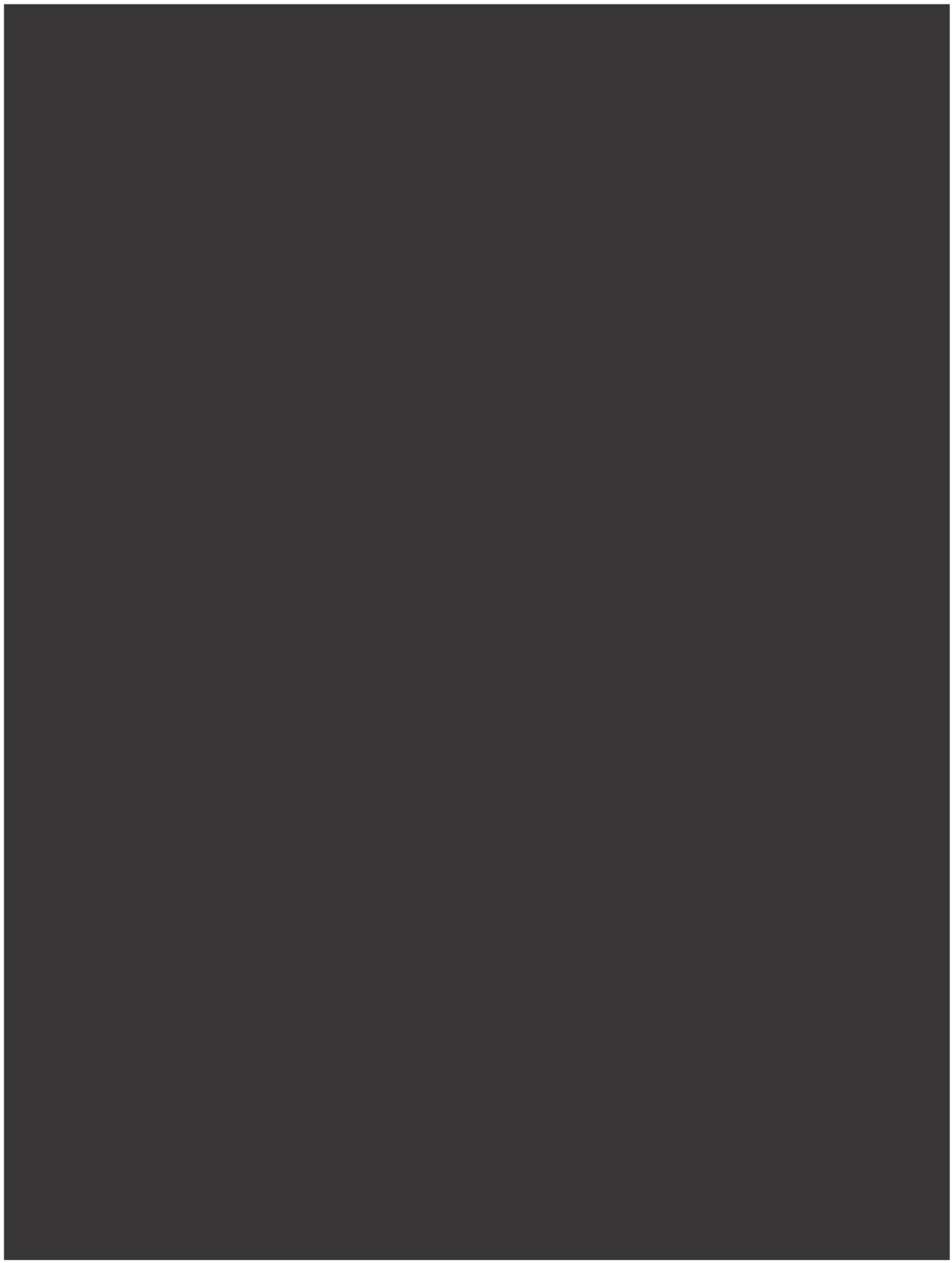
RAPID: RF Ablation Prospective Outcomes Study	
Study Objective	To compile real-world outcomes of Boston Scientific commercially approved radiofrequency (RF) ablation systems in the treatment of patients diagnosed with pain.
Indication(s) for Use	All commercially approved Boston Scientific radiofrequency ablation systems will be used as indicated per local directions for use. Refer to the applicable Directions for Use for detailed indication(s) for use.
Commercial Device/System	All commercially approved Boston Scientific RF Systems
Study Design	Prospective, multi-center, global outcomes study
[redacted]	[redacted]
[redacted]	[redacted]
Clinical Endpoints	The following endpoints will be evaluated. Assessments required for deriving each endpoint are denoted in parentheses. • Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (*VRS*) at 1-, 3-, 6- and 12-months post-procedure • Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (PPR) at 1-, 3-, 6- and 12-months post-procedure • Change in targeted pain[1] intensity from Baseline Visit through 1-, 3-, 6- and 12-months post-procedure (*VRS*) • Percent Pain Relief in targeted pain[1] through 1-, 3-, 6- and 12-months post-procedure (*PPR*) • Patient global impression of change at 1-, 3-, 6- and 12-months post-procedure (*PGI-C*)

RAPID: RF Ablation Prospective Outcomes Study	
	• Change in disability from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (*ODIv2.1a*) • Change in opioid pain medications from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (Concomitant Medications) [1]*Targeted pain – Pain intended to be treated using RF*
Health Economic Endpoints	• Economic value post-procedure (*RUI, EQ-5D-5L*, *Concomitant Medications*, *Procedure Information)*
Safety Parameters	• Rate of occurrence of all device-related and procedure-related non-serious adverse events (AEs) • Rate of occurrence of all serious adverse events (SAEs) and unanticipated adverse events
Follow-up Schedule	• Baseline Visit • Procedure Visit (Day 0) • 1-Month Post-Procedure Visit (30 + 14 days) • 3-Month Post-Procedure Visit (90 ± 14 days) • 6-Month Post-Procedure Visit (180 ± 30 days) • 12-Month Post-Procedure Visit (365 ± 30 days) • Additional RF Procedure for any additional RF procedure(s) • Unscheduled visits as needed for the study and as required for additional RF procedure(s)
[redacted]	[redacted]
[redacted]	[redacted]
Key Inclusion Criteria	IC1. Study candidate is scheduled to be treated with a commercially approved Boston Scientific RF system for pain per local Directions for Use (DFU) IC2. Signed a valid, IRB/EC/REB-approved informed consent form

RAPID: RF Ablation Prospective Outcomes Study	
	[redacted]
Key Exclusion Criteria	EC1. Meets any contraindications per locally applicable Directions for Use (DFU) EC2. Currently diagnosed with cognitive impairment, or exhibits any characteristic, that would limit study candidate's ability to assess pain relief or to complete study assessments
Statistical Methods	
Primary Statistical Hypothesis	Descriptive statistics will be utilized to report the clinical endpoints and their changes from baseline at 1-, 3-, 6- and 12-months post-procedure.

Study Schematic





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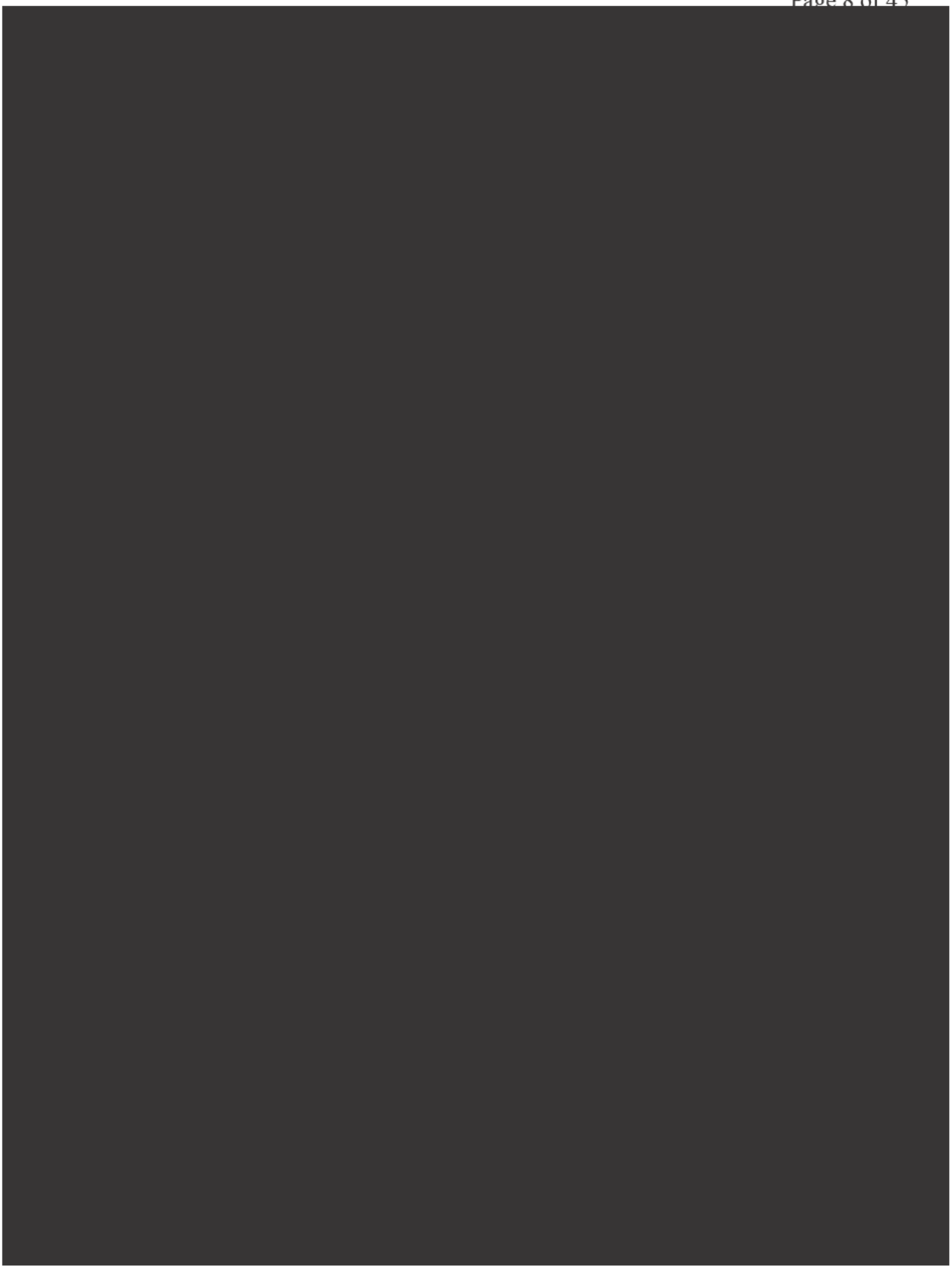

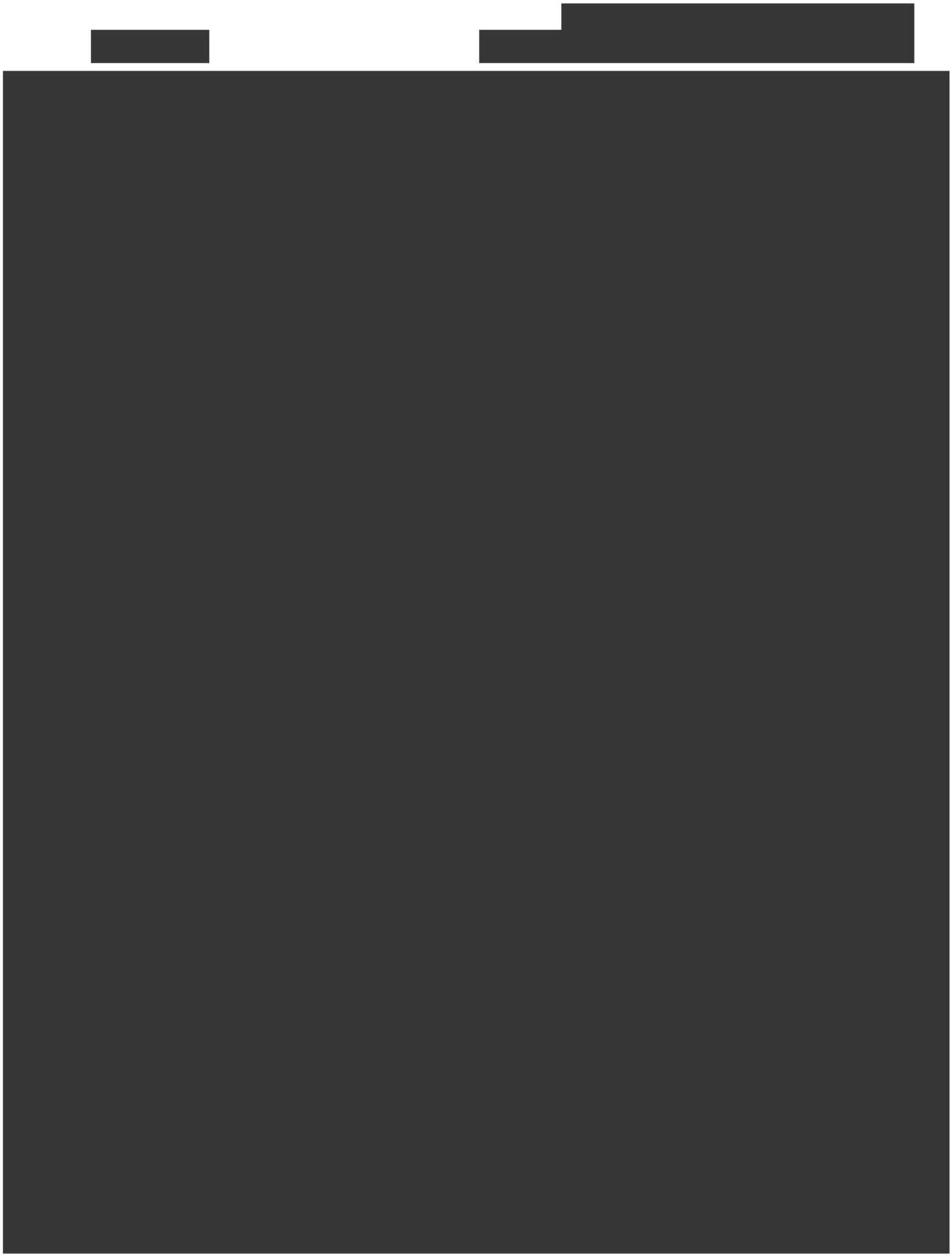

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4. Introduction

4.1. *Chronic Intractable Pain*

Chronic intractable pain is often defined as pain persisting for at least 6 months which has not responded to conservative treatment(s). The pain may be due to current or past nerve injury and causes significant disability, reduced work productivity, reduced quality of life, and significant cost burden.

The complexity of chronic pain and the diverse population it affects have resulted in varying results between the various treatment approaches including medications, physical therapy, stimulation etc. Early treatments for chronic pain typically include over the counter and prescription medications. Later treatment typically includes physical therapy before any interventional pain procedures, such as radiofrequency ablation (RF), are attempted.

4.2. *Thermal Radiofrequency Ablation*

Radiofrequency (RF) ablation is a minimally invasive procedure that uses heat to reduce or stop the transmission of neurological signals. During the procedure, an insulated needle is used to create a small lesion within a nerve to disrupt the neurological signal. The needle has high-frequency electrical current passing through it, which creates an electric field at the tip of the needle. The electric field produces thermal energy via molecular movement, resulting in enough heat produced at the needle tip to apply the lesion (Shealy, 1975).

Radiofrequency ablation (RFA) was first introduced in 1931 with the treatment of trigeminal neuralgia (Krischner, 1931). In the mid-1950's, RF was used in thalamotomy procedures in the brain (Alajouanine & Houdart, 1957) and has since expanded into a multitude of useful applications. These include treatment of chronic low back pain, sciatica, and rhizotomy of problematic nerve roots in the spinal cord in the 1970's (Uematsu, Udrarhelyi, Benson, & Seibens, 1974; Shealy, 1975), and catheter ablation of the heart in the 1980's (Scheinman, Morady, Hess, & Gonzalez, 1982).

RF ablation has been shown to be effective for chronic intractable pain originating from a variety of locations, including, but not limited to cervical zygapophyseal (Lord et al., 1996), lumbar zygapophysial (van Kleef et al., 1999), sacroiliac (Cohen et al., 2008), hip (articular branches of the femoral and obturator nerves), and knee (genicular nerve) (Choi et al., 2011) joints.

While there are randomized controlled studies evaluating RF for chronic pain that reported negative or equivocally positive results, most have shown improvement in outcomes for patients with chronic pain treated with RF compared to baseline, although some control groups also improved correspondingly (Chen, et al., 2015; Cho, Cho, Kwak, & Chang, 2017; Cohen, et al., 2015; Juch, et al., 2017; Luo, et al., 2017; Makharita & Amr, 2015; Pi, Lin, He, Cai, & Xu, 2015; Saxena AK, 2016; Van Tilburg, Stronks, Groeneweg, & Huygen, 2016; Wu YT, 2017) (Walega, McCormick, Manning, & Avram, 2019; Davis, et al., 2018; Mehta,

Poply, Husband, Anwar, & Langford, 2018; Fischgrund, et al., 2019; Hunter, Davis, Loudermilk, Kapural, & DePalma, 2019; McCormick, et al., 2019)

The largest controlled study to report negative results was Juch, et al., which evaluated the effectiveness of adding RF denervation to a standardized exercise program to treat chronic low back pain in multicenter, nonblinded, randomized trials (Mint study). Participants were eligible if they had chronic low back pain, a positive diagnostic block at the facet joints (facet joint trial, 251 participants), sacroiliac joints (sacroiliac joint trial, 228 participants), or a combination of facet joints, sacroiliac joints, or intervertebral disks (combination trial, 202 participants), and did not benefit from conservative care. All participants underwent a 3 month exercise program with the intervention group also receiving up to 3 RF denervation procedures. The primary outcome was NRS score at a follow up time of 3 months, with a minimal clinically important difference specified as 2 NRS points or more. Final follow-up was at 12 months. Among 681 randomized participants (mean baseline pain intensity=7.1), 599 (88%) completed the 3-month follow-up and 521 (77%) completed the 12-month follow-up. At 3 months, the mean difference in pain intensity between the intervention and control groups was −0.18 (95%CI, −0.76 to 0.40) in the facet joint trial; −0.71 (95%CI, −1.35 to −0.06) in the sacroiliac joint trial; and −0.99 (95%CI, −1.73 to −0.25) in the combination trial. The authors concluded that RF denervation near the facet joint, sacroiliac joint, or intervertebral disk was no different than a standardized exercise program for treating chronic low back pain (Juch, et al., 2017). These conclusions are untenable for numerous reasons; significant methodological flaws exist in the study including design and analysis, patient selection and inclusion/exclusion criteria, outcome measurement, and diagnostic block and RF techniques to name a few (Provezano, Buvanendran, de Leon-Casasola, Narouze, & Cohen, 2018; McCormick, et al., 2018; Vorobeychik, Stojanovic, & McCormick, 2017). Meaningful conclusions are difficult to draw from this study given the many flaws and drawing conclusions such as the authors did may prevent appropriately selected patients from receiving RF treatment performed with appropriate technique.

RF ablation performed with proper technique is an effective option in well-selected patients with chronic pain.

4.3. *Study Rationale*

The purpose of this outcomes study is to gather evidence of Boston Scientific commercially approved radiofrequency (RF) ablation systems in the treatment of patients diagnosed with pain.

5. (Commercial) Device Description (Part of Standard of Care)

This outcomes study includes all commercially approved Boston Scientific radiofrequency ablation systems, per local Directions for Use. Refer to the Directions for Use for detailed device description.

6. Study Objectives and Endpoints

6.1. *Primary Objective*

To compile real-world outcomes of Boston Scientific commercially approved radiofrequency (RF) ablation systems in the treatment of patients diagnosed with pain.

6.2. *Secondary Objective*

To evaluate the economic value and technical performance of Boston Scientific commercially approved radiofrequency systems for pain in routine clinical practice, when used according to the applicable Directions for Use.

6.3. *Clinical Endpoints*

The following endpoints will be evaluated. Assessments required for deriving each endpoint are denoted in parentheses.

- Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (*VRS*) at 1-, 3-, 6- and 12-months post-procedure
- Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (PPR) at 1-, 3-, 6- and 12-months post-procedure
- Change in targeted pain[1] intensity from Baseline Visit through 1-, 3-, 6- and 12-months post-procedure (*VRS*)
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- Patient global impression of change at 1-, 3-, 6- and 12-months post-procedure (*PGI-C*)
- Change in disability from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (*ODIv2.1a*)
- Change in opioid pain medications from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (Concomitant Medications)

[1]*Targeted pain – Pain intended to be treated using RF*

Additional endpoints will be evaluated post-hoc for data collected in assessments not listed in the predefined clinical endpoints.

6.4. *Health Economics Endpoints*

The following health economics endpoints will be evaluated. Assessments required for deriving each endpoint are denoted in parentheses.

- Economic value at 1-, 3-, 6- and 12-months post-procedure (*RUI, EQ-5D-5L, Concomitant Medications, Procedure Information)*

6.5. *Safety Parameters*

The following safety endpoints will be evaluated.

- Rate of occurrence of all device-related and procedure-related non-serious adverse events (AEs)
- Rate of occurrence of all serious adverse events (SAEs) and unanticipated adverse events

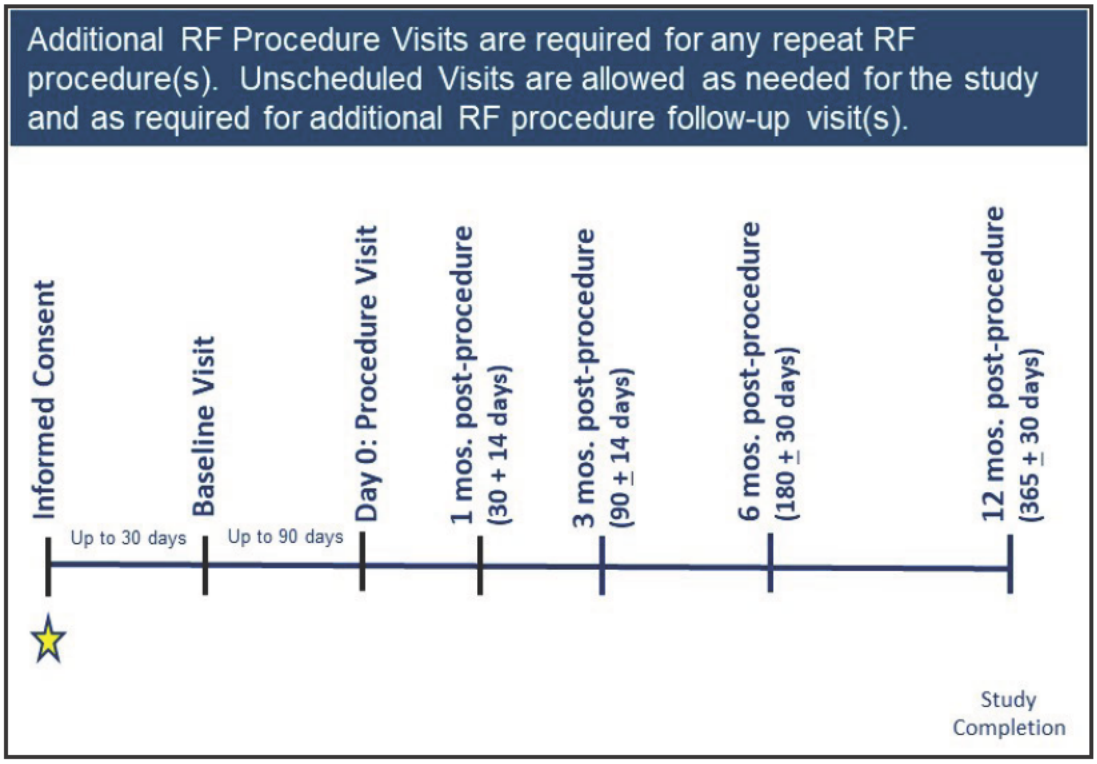
7. Study Design

The study is a prospective, multi-center, global outcomes study of BSC radiofrequency ablation systems for pain. All participants will follow the study schedule as shown in study schematic Figure 7.1-1.

7.1. *Scale and Duration*

[redacted]

Figure 7.1-1: RAPID Design Schematic



7.2. *Treatment Assignment*

Consecutive eligible patients receiving radiofrequency ablation with the Boston Scientific RF system per standard of care who provide written informed consent to participation and have met all of the inclusion and none of the exclusion criteria will be enrolled in the study and assigned a unique subject identifier in the Electronic Data Capture (EDC) system.

[redacted]

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects are established patients in a medical practice (e.g. pain management, neurologist, surgical, physical medicine and rehabilitation) who will receive radiofrequency ablation therapy to treat pain utilizing a commercially approved BSC radiofrequency ablation system per local DFU according to standard of care.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Table 8.3-1) is met.

Table 8.2-1: Inclusion Criteria

Clinical Inclusion Criteria	IC1. Study candidate is scheduled to be treated with a commercially approved Boston Scientific RF system for pain per local Directions for Use (DFU) IC2. Signed a valid, IRB/EC/REB-approved informed consent form [redacted]

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Clinical Exclusion Criteria	EC1. Meets any contraindications per locally applicable Directions for Use (DFU) EC2. Currently diagnosed with cognitive impairment, or exhibits any characteristic, that would limit study candidate's ability to assess pain relief or to complete study assessments

9. Subject Accountability

9.1. *Point of Enrollment*

A subject will be considered enrolled in the study when the Informed Consent Form (ICF) is signed. All treated subjects will be included in the intent to treat analyses and all treated subjects with no major protocol deviations will be included in the study analyses.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal or discontinuation, the Investigator will make all reasonable efforts to determine the reason for the subject's withdrawal. Subjects may be discontinued from the study for the various reasons, such as:

- Withdrawal of consent
- A safety concern defined by the Principal Investigator and/or Boston Scientific Neuromodulation (e.g., adverse event)

- Study non-compliance
- Inadequate use of device that may impact study outcomes
- Subject did not meet inclusion criteria or met an exclusion criterion after signing informed consent
- Subjects who decline an additional RFA procedure recommended by the study physician
- Lost to follow-up
- Death of the subject

A subject is considered lost-to-follow-up after a minimum of 3 unsuccessful contact attempts have been made to reach the subject (including those who relocate but cannot be transferred to another participating site). Staff at the participating site should make a good faith effort to contact the subject with three documented communication attempts, at least one of which must be in writing, sent via a traceable method.

Data collected up to the point of subject withdrawal or lost to follow-up may be used for study analysis in accordance with applicable regulations.

Withdrawn subjects will be followed per standard of care

[redacted]

9.4. *End-of-Study Definition*

A clinical trial is considered completed when the last participant's last study visit has occurred. A participant is considered to have completed the study if they have completed all study visits including the 12-Month Visit. Upon end of study, subjects will be followed per standard of care.

10. Study Methods

10.1. *Data Collection*

The data collection schedules are shown in Tables 10.1-1.

[redacted]

[redacted]

[redacted]

10.2. *Study Candidate Screening*

All interested subjects will undergo screening during which their eligibility for the Registry will be determined.

10.2.1. Informed Consent

Written Informed Consent must be obtained from all potential study candidates before any study-specific tests or procedures are performed.

- The context of the study must be fully explained to the patient and patients must be given an opportunity to ask questions and have those questions answered to their satisfaction.
- Study personnel should explain to each potential participant that even if he or she agrees to participate in the study and signs an informed consent form, further testing might demonstrate that he or she is not eligible for the study.
- Written informed consent must be recorded appropriately by means of the subject's dated signature.

- The consent process must be documented in the subject's medical chart.

10.2.2. *Screening Period*

Subjects' eligibility for the study will be assessed based on study Inclusion and Exclusion criteria listed in Sections 8.2 and 8.3, respectively. Any subjects that do not meet the criteria defined in the local Directions for Use (DFU) will be withdrawn.

10.3. *Baseline Visit (up to 30 days following Informed Consent)*

At the Baseline Visit, subjects will return to the clinic to complete assessments. Any reportable adverse events or changes in opioid pain medications since the last study visit will be collected. [redacted]

- [redacted]

Subjects that meet all criteria will be scheduled for the radiofrequency (RF) ablation procedure. If a subject is not a good candidate and/or fails to meet all the criteria defined in the local DFU, they will be withdrawn from the study.

10.4. *Procedure Visit (Day 0, up to 90 days following Baseline Visit)*

Subjects will have up to 90 days following the Baseline Visit to receive the planned treatment with the Boston Scientific Radiofrequency Ablation System per standard of care. Any reportable adverse events or changes in opioid pain medications will be collected.

[redacted]

- [redacted]

Following completion of this visit, subjects may undergo additional radiofrequency ablation procedure(s) as needed, until the 12 month visit window opens, to treat pain targeted during the initial study procedure or new pain not treated as part of the study, with a Boston Scientific Neuromodulation radiofrequency ablation system according to the locally approved Directions for Use, and [redacted]

10.5. *1-Month Visit (30 + 14 days)*

During the 1-Month Visit, subjects will return to the clinic for study evaluations. Any reportable adverse events or changes in opioid pain medications since the last study visit will be collected. [redacted]

10.6. *3- (90 ± 14 days) and 6-Month (180 ± 30 days) Visits*

During the 3- and 6-Month Visits, subjects will return to the clinic for study evaluations. The same assessments performed at the 1-Month Follow-up Visit will be conducted, as outlined in Table 10.1-1.

10.7. *12-Month Visit (365 ± 60 days, End of Study)*

During the 12-Month Visit, subjects will return to the clinic for study evaluations. Any reportable adverse events or changes in opioid pain medications since the last study visit will be collected. The same assessments performed at the 1-Month Follow-up Visit will be collected, as outlined in Table 10.1-1.

A subject's participation in the study ends after completion of the 12-Month Visit.

10.8. *Additional RF Procedure (s)*

Subjects may have additional radiofrequency (RF) ablation procedures per standard of care, with commercially approved Boston Scientific Neuromodulation RF ablation systems. Radiofrequency ablation may be repeated to retreat pain targeted during the initial study procedure or may be performed to treat new pain not initially treated as part of the study. Subjects may have as many additional RF procedures as needed, until the 12 month visit window opens, to treat pain during participation in the study. Subjects who decline an additional RF procedure recommended by the study physician will be withdrawn from the study.

Once the need for an additional RF procedure is determined, the procedure should be scheduled as soon as possible. After each Additional RF Procedure, a Study Visit is required between 1 to 3 months (30 – 90 + 14 days) for evaluation and assessment as described in **Table 10.1-1**.

If this time period falls within the visit window of the next Study Visit, these Study Visit assessments will be used. If this is not the case, an additional (Unscheduled) visit is required.

For an Additional RF Procedure, subjects will return to the clinic to first complete pre-procedure assessments and then have the additional RF procedure. Any reportable adverse events or changes in opioid pain medications since the last study visit will also be collected.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Subjects will receive additional RF treatment with a Boston Scientific Neuromodulation Radiofrequency Ablation System per standard of care and according to the local Directions for Use (DFU).

[redacted]

- [redacted]

10.9. *Unscheduled Visits*

Subjects may have as many unscheduled visits as required for device or procedure related visits (e.g. assessing if additional intervention may be warranted) or for evaluation of possible adverse events. [redacted]

An unscheduled visit is also required to perform follow-up for an additional RF procedure, if there is no Study Visit scheduled 1 to 3 months (30 – 90 + 14 days) after the additional procedure.

10.10. *Study Completion*

All treated subjects will be followed through completion of the 12-Month Visit or study withdrawal as defined in section 9.2.

10.11. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.12-1.

Table 10.11-1: Source Documentation Requirements

Requirement	Disposition
Hospital records and/or clinical and office charts including the evidence of but not limited to inclusion/exclusion criteria, informed consent, exams, procedures and devices used, evaluations, health economic assessments, laboratory results, medications, assessment of adverse events.	Retained at investigational site
Assessments and questionnaires	Retained at investigational site and/or electronic data collection platform/EDC
Imaging films/prints documenting treatment location	Retained at investigational site

11. Statistical Considerations

11.1. *Clinical Endpoints*

A number of clinical endpoints are included (but not limited to) in this study, as described below. Continuous variables will be summarized using descriptive statistics which include number of non-missing observations, mean, median, standard deviation, minimum, maximum. For categorical variables, descriptive statistics include frequencies, and percentages of categories. Estimates of all endpoints will be reported, as well as the 95%

confidence intervals. Hypothesis test of change from baseline for the continuous variables may be performed when it is appropriate.

- Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (*VRS*) at 1-, 3-, 6- and 12-months post-procedure
- Proportion of subjects with a 30% or greater reduction from Baseline in targeted pain[1] intensity (PPR) at 1-, 3-, 6- and 12-months post-procedure
- Change in targeted pain[1] intensity from Baseline Visit through 1-, 3-, 6- and 12-months post-procedure (*VRS*)
- Percent Pain Relief in targeted pain[1] through 1-, 3-, 6- and 12-months post-procedure (*PPR*)
- Patient global impression of change at 1-, 3-, 6- and 12-months post-procedure (*PGI-C*)
- Change in disability from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (*ODIv2.1a*)
- Change in opioid pain medications from Baseline Visit to 1-, 3-, 6- and 12-months post-procedure (Concomitant Medications)

[1]*Targeted pain – Pain intended to be treated using RF*

Additional endpoints will be evaluated post-hoc for data collected in assessments not listed in the predefined clinical endpoints.

11.1.1. Primary Endpoint

11.1.1.1. Hypotheses

No primary endpoint was defined in the study.

11.1.1.2. Sample Size

No sample size calculation was performed.

11.1.1.3. Statistical Methods

No formal statistical hypothesis is planned. Descriptive statistics will be utilized to report the clinical endpoints and their changes from Baseline at 1-, 3-, 6- and 12-months post-procedure.

[redacted] who receive treatment with the study device, with no major protocol deviations.

11.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient population. All patients meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be eligible for participation in the study. The reasons for exclusion, for subjects who sign an informed consent form but do not have an RFA procedure, will be indicated in EDC. Boston Scientific will report to the ethic committee any evidence of fraud, including deliberate tampering with the selection of subjects.

[redacted]

11.2.4. Data Analyses

All statistical analyses will be done using the SAS System software, version 8.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved). Additional details on these analyses can be found in the Statistical Analysis Plan.

11.2.5. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or futility.

11.2.6. Subgroup Analyses

Subgroup analyses will be performed as appropriate, for example, treatment indication, age, gender, et al.

[redacted]

11.2.8. Multivariable Analyses

No formal covariate analyses are planned.

[redacted]

11.2.9. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended protocol approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

[redacted]

12.1.1. Electronic Questionnaires

Questionnaires in electronic form may be collected directly using an electronic data collection platform at the clinical site (e.g. iPad). After completion by the subject or a clinician, data from the electronic questionnaires are transmitted directly into the EDC system.

12.2. *Study Assessments*

12.2.1. Adverse Events

Adverse event evaluation will be conducted to identify adverse events occurring during the study and classify them in regard to seriousness, relationship to the procedure and/or device, action taken and outcome. Safety events will be reported as specified in Table 17.4-1.

All device and procedure related non-serious adverse events, all serious adverse events regardless of relatedness, and unanticipated adverse events will be collected from the time of consent through the end of the study.

12.2.2. Beck Depression Inventory (BDI-II)

BDI-II measures the intensity, severity, and depth of depression. It includes a long form of 21 questions, each evaluating a specific depression symptom (e.g., sadness, pessimism, irritability, loss of energy, concentration difficulty, indecisiveness, changes in sleep pattern, fatigue, etc.).

12.2.3. Concomitant Medications

Opioid medications for pain management will be collected throughout the study in order to obtain a full record of medication-related resource utilization. Information will include medication name, dates of prescription, indication or purpose, dose, frequency, and route of administration.

12.2.4. Demography

Demographic information will include date of birth and gender, if allowed/requested by local regulations.

12.2.5. EQ-5D 5 Level (EQ-5D-5L)

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

EQ-5D-5L is comprised of a descriptive system and a visual analog scale. The descriptive system measures quality of life along five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five levels for each dimension from which subjects are asked to select one. The visual analog scale is used to record the subject's self-rated health on a 20cm vertical line with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'.

12.2.6. Medical History

Medical history will include medical and procedural history relating to pain management, onset of chronic pain, all pain-related diagnoses and medical/psychological conditions, medication use etc.

12.2.7. Oswestry Disability Index Version 2.1a (ODI v2.1a)

ODI v2.1a assesses the degree of subject disability due to pain, measuring the impact of pain on activities of daily living. ODI v2.1a is composed of 10 questions that describe the pain and its impact on daily life on a 0 - 5 scale, with higher values indicating the more severe impact.

12.2.8. Pain Intensity (NRS)

Pain Intensity (NRS) is a questionnaire that numerically assesses the intensity of the subject's pain intensities, including overall pain and pain in targeted area(s).

Pain intensity is expressed on a 0 – 10 numeric rating scale (NRS), where 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine", as reported by the subject.

12.2.9. Pain Intensity (VRS)

Pain Intensity (VRS) is a questionnaire that verbally assesses the intensity of the subject's pain intensities, including overall pain and pain in targeted area(s). This is done based on a clinician interview (e.g. study physician) with the subject.

Pain intensity is expressed on a 0 – 10 verbal rating scale (VRS), where 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine", verbally reported by the subject to study personnel.

12.2.10. Procedure Information

General information will be collected regarding the radiofrequency ablation procedures performed during the study, including initial and any repeat procedures.

12.2.11. Patient Global Impression of Change (PGI-C)

PGI-C is a seven-point scale that requires the subject to assess how much their condition has improved or worsened relative to their baseline. Subjects will rate themselves as: very much improved; much improved; minimally improved; no change; minimally worse; much worse; or very much worse.

12.2.12. Pittsburg Sleep Quality Index (PSQI)

PSQI is a self-rated questionnaire assessing sleep quality and disturbances. This questionnaire include 19 individual items grouped into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of these 7 scores yields a single global score.

12.2.13. Percent Pain Relief (PPR)

PPR is a questionnaire assessing how much of the subject's overall, low back pain and leg pain has been relieved by the RFA treatment. Pain relief is expressed as a percentage from 0 – 100%.

12.2.14. Resource Utilization Inventory (RUI)

Health-related resource utilization data will be collected to support the health economic analyses. Resource utilization categories include office/hospital visits, diagnostic tests, and non-surgical procedures.

12.2.15. Treatment Satisfaction

Treatment satisfaction is an assessment of subjects' satisfaction with treatment received in terms of effectiveness, convenience, and global satisfaction.

12.3. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC/REB, and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the EDC system. Sites may also be required to report deviations to the IRB/EC/REB, and the regulatory authority, per local guidelines and/or national/government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/EC/REB notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with 21 CFR 50 and 56, and 812, European Medical Device Regulations, the spirit of ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin at a site prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol signature page documenting his/her agreement to conduct the study in accordance with the protocol
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the clinical investigation.
- Report protocol deviations to the sponsor, IRB/EC/REB and/or regulatory authorities, as required by the protocol, IRB/EC/REB guidelines, and/or national/regulatory regulations.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary information on the RF system, treatment and follow-up instructions and care.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.

Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation. All investigators will provide their

qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, ensuring individuals are competent to perform the tasks they have been delegated and have adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. *Institutional Review Board / Ethics Committee / Research Ethics Board*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in

the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16. Potential Risks and Benefits

16.1. *Directions for Use*

Please refer to the Directions for Use for an overview of anticipated benefits, adverse (device) effects, and risks associated to the procedure.

16.2. *Risks associated with Participation in the Clinical Study*

The subject might find it difficult, uncomfortable, or tiresome to complete study visits, evaluate the treatment, and/or questionnaires.

16.3. *Possible Interactions with Concomitant Medical Treatments*

No possible interactions have been identified for use of radiofrequency ablation concomitant with any specific medications. However, there may be some risk that is unknown.

16.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.5. *Anticipated Benefits*

Other than the anticipated benefits of the procedure(s) (refer to the Directions for Use for more information) and regular clinical visits, no additional benefits for the individual subject is foreseen.

16.6. *Risk to Benefit Rationale, if applicable*

The risk evaluation for Boston Scientific RF Systems determined that all hazards attributed to the RF Systems and overall remaining residual risks after implementations of the required mitigations have been evaluated. Based on the risk evaluation results, the benefit provided by the RF Systems to treat pain outweighs the remaining residual risk. As the overall residual risk meets BSN's criteria, the RF Systems are acceptable for use in a clinical setting.

Risks and benefits will be similar for Subjects participating in the study and patients being treated according to standard of care. Studies do not always predict all side effects that may be experienced. Observation and follow-up of all Subjects is required as outlined in the protocol. The risk to benefit rationale for study participation is acceptable.

17. Safety Reporting

17.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events (regardless of relationship)
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events
- Device and procedure related non-serious adverse events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after informed consent, whether prior to, during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for AE definitions).

Refer to Directions for Use for the known risks associated with the commercial device(s).

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from ISO 14155, EU 2017/745 and MDCG 2020-10/1 for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or 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 the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device. **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3:** This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) Death, b) Serious deterioration in the health of the subject, users or other person as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, 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 c) Foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Table 17.2-1: Safety Definitions

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat Ref: ISO 14155	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **Note 1** to entry: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2:** This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

NOTES:

1. In the event of subject death during the conduct of the study, efforts should be made to perform an autopsy.
2. Lack of efficacy/decreased therapeutic response should not be reported as AEs. Other clinical sequelae that occur as a result of lack of efficacy/decreased therapeutic response should be reported as AEs.

3. The subject's pain symptoms will not be collected as AEs, unless they are worsened beyond baseline and beyond the expected disease progression over time. This worsening event could occur in the context of a device malfunction (ADE), or with a properly-functioning device (AE or ADE, determined by investigator).
4. Clinically significant worsening of the pattern of intensity or distribution of Baseline symptoms should be reported as an AE.
5. Device deficiencies which are not associated with an adverse clinical outcome should only be reported as device deficiencies. However, if a device deficiency precipitates an AE, the AE should be reported in the Adverse Event eCRF and the device deficiency should be documented in the Device Deficiency eCRF.

17.3. *Relationship to Device(s)*

The Investigator must assess the relationship of the reportable AE to device and/or procedure. See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site, or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1.

Table 0-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*MDCG 2020-10/1*: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event for applicable study*. • Terminating at the end of the study. *Applicable study- post market interventional study non-standard of care
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations.

Table 0-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*MDCG 2020-10/1*: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
		• Reporting required through the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete applicable eCRF form with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through the end of the study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. *Boston Scientific Device Deficiencies*

Device deficiencies will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) as applicable will be provided to study sites. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, a reportable adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF.

17.6. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRB/EC/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC and approved by the site's IRB/EC/REB, or central IRB/EC/REB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,

- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety includes a physician with necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20. Suspension or Termination

20.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRB/EC/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

20.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/EC/REB Approval

Any investigator, or associated IRB/EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRB/EC/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC/REB terminates participation in the study, participating investigators, associated IRB/EC/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled or if the site has multiple or

severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Study Registration and Results

21.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

21.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

22. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in Table 23.1-1.

Table 24.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse device effect
AE	Adverse event
BDI	Beck Depression Inventory
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
DFU	Directions for use
EC	Ethics Committee
eCRF	Electronic case report form
EQ-5D-5L	EuroQol-5D
ICF	Informed consent form
IRB	Institutional review board
ISO	International Organization for Standardization
NRS	Numeric rating scale
ODI	Oswestry Disability Index
PGI-C	Patient Global Impression of Change
PPR	Percent Pain Relief
REB	Research Ethics Board
RF	Radiofrequency
RFA	Radiofrequency Ablation
RUI	Resource Utilization Inventory
SADE	Serious adverse device effect
SAE	Serious adverse event
UADE	Unanticipated adverse device effect
VRS	Verbal rating scale

24.2. *Definitions*

Detailed definitions or descriptions are provided in applicable sections of the protocol.