Study to Evaluate Boston Scientific Vercise™ Cartesia™ 16-contact Directional Lead (X/HX) with Deep Brain Stimulation (DBS) Systems for the treatment of Parkinson's Disease (PD)

Cartesia eXTend 3D Study

A4092

CLINICAL INVESTIGATION PLAN

Clinicaltrials.gov NCT#04577651

[Eudamed Number/Single Identification Number (SIN): CIV-GB-20-07-034074]

Sponsored By

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2. Protocol Synopsis

Study to Evaluate Boston Scientific Vercise™ Cartesia™ 16-contact Directional Lead (X/HX) with Deep Brain Stimulation (DBS) Systems for the treatment of Parkinson's Disease (PD) Cartesia eXTend 3D Study	
Study Objective(s)	To document patient outcomes including effectiveness for Boston Scientific Corporation's Vercise™ Cartesia™ 16-contact Directional Lead (X/HX) with Deep Brain Stimulation (DBS) Systems for the treatment of Parkinson's Disease (PD).
Planned Indication(s) for Use	The Vercise Deep Brain Stimulation System is indicated for use in unilateral or bilateral stimulation of the subthalamic nucleus (STN) or internal globus pallidus (GPi) for treatment of levodopa-responsive Parkinson's disease which is not adequately controlled with medication.
Test Device and sizes, if applicable	Boston Scientific's Vercise™ Cartesia™ X/HX 16-contact Directional Leads, 16-contact Lead Extensions and 16-contact Push Button OR Cable. All other components of the DBS System are commercially approved.
Study Design	Prospective, multi-center, open-label confirmatory study with an adaptive design.
[redacted]	[redacted]
Planned Number of Investigational Sites / Countries	Up to 15 global sites.
Primary Effectiveness Endpoint	Mean change in MDS-UPDRS III scores from Baseline in *meds off* condition to 12 weeks post device-activation in *stim on/meds off* condition.

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Secondary Effectiveness Endpoint	[redacted]
[redacted]	[redacted]

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	• [redacted] [redacted] [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Study Visit Schedule	• Screening Period (up to 45 days post informed consent) • Baseline Visit • Implant procedures (up to 45 days post baseline visit) • Device Activation (Day 0) • Week 10 Visit post-activation (+ 7 days) • Week 12 Visit post-activation (+ 7 days) • Week 26 Visit post-activation (± 21 days) • Years 1, 2, 3, 4 and 5 Visit post-activation (± 45 days) Year 5 Visit will be the End of Study Visit.
[redacted]	[redacted]

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Inclusion Criteria	[redacted] IC2. Candidate for DBS implant in the treatment of Parkinson's disease IC3. Must be on stable anti-parkinsonian medications for 28 days prior to Informed Consent IC4. Persistent disabling Parkinson's disease symptoms such as dyskinesias, motor fluctuations, or disabling "off" periods despite optimal medical therapy [redacted] IC8. Be willing and able to comply with all visits and study related procedures (e.g., using the remote control, charging system, etc.). [redacted]
Exclusion Criteria	EC1. Any intracranial abnormality or medical condition that would contraindicate DBS surgery EC2. Have any significant psychiatric or cognitive condition likely to compromise the subject's ability to comply with requirements of the study protocol (e.g. bipolar, schizophrenia, mood disorder with psychotic features, cluster B personality disorders) [redacted] EC4. Any current drug or alcohol abuse, as determined by the investigator EC5. Any history of recurrent or unprovoked seizures

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	[redacted]
Staged Procedures	Subjects may undergo staged surgical procedures prior to device activation, as determined by local standards of care
Statistical Methods	
Primary Statistical Hypothesis	H_0: $\mu_B - \mu_{12} \leq 5$ H_1: $\mu_B - \mu_{12} > 5$ where μ_B and μ_{12} are the mean MDS-UPDRS III scores in *meds off* condition at Baseline and 12 weeks, respectively. The minimal clinically important difference (MCID) using MDS-UPDRS III scores (meds off) condition is assumed to be 5 based on Schrag et al. [24]
[redacted]	[redacted]

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[redacted]	[redacted]
[redacted]	[redacted] Flemming α-spending function and Pocock β-spending function [1-3].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. Introduction

4.1. *Background*

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 5.2 million people worldwide [4]. The prevalence of PD is estimated at 0.3% of the overall population in industrialized countries and advances to 1% by age 60 and 4% in the highest age group [5]. The hallmark signs of PD include movement disorders such as bradykinesia, resting tremors, and muscle rigidity[6].

The motor symptoms of PD are associated with a dopamine deficiency resulting from the degradation of dopaminergic neurons in the substantia nigra pars compacta (SNc). At present there is no cure for PD; treatment is focused on medical management of motor symptoms. Medical therapy has been primarily focused on restoring dopamine levels through the administration of levodopa, dopamine agonists, or monoamine oxidase B inhibitors. Current standards for patient care recommend levodopa as first line of therapy for the symptomatic control during the early, uncomplicated stages of PD [7, 8]. Unfortunately, chronic treatment with levodopa frequently leads to significant side effects, especially dyskinesias and motor fluctuations [9].

Previously, for subjects who had reduced response to medical therapy, pallidotomy (destruction of the globus pallidus) and thalamotomy (destruction of the thalamus) were the only available treatment options. In the 1990s, high-frequency deep brain stimulation (DBS) was demonstrated to be effective in reducing the motor complications of subjects with PD [10]. Since that time, numerous case studies and trials have substantiated these early findings. In addition, six recent large, multicenter, randomized trials have demonstrated the effectiveness of the therapy [11-17].

Timmermann et al. published the results of Boston Scientific sponsored VANTAGE Study: a non-randomized, prospective, multicenter open-label study where 40 idiopathic PD patients at 6 European centers received bilateral STN DBS with Vercise™ DBS System [18]. The study successfully achieved its primary endpoint ($p < 0.0001$) and reported a mean difference of 23.8 ± 10.6 points in MDS-UPDRS III scores in the stim ON/meds OFF condition at 6 months after implantation compared with Baseline.

Results from a large prospective, multi-center double blinded study with a sham control (INTREPID) using the Vercise™ DBS System reported a mean 6 hour improvement in ON time without troublesome dyskinesias (n = 160 randomized) at 1 year (PD diary) and

sustained improvement in motor function and quality of life measures thereafter up to 3 years [19].

Several systematic reviews and results from multi-center, randomized controlled trials provide solid evidence in support of the effectiveness and safety of DBS as a therapy for PD [17-19]. In addition, the review of published outcome studies has also shown that DBS is associated with favorable health economic and quality of life outcomes [20].

Recent advances in technology including directional stimulation has the potential to further improve patient outcomes. Several pilot studies have corroborated the use of directionality and its impact on therapeutic window and adverse effects [21-23].

This confirmatory study will document patient outcomes including effectiveness for Boston Scientific Corporation's Vercise™ Cartesia™ 16-contact Directional Lead (X/HX) with Deep Brain Stimulation (DBS) Systems for the treatment of Parkinson's Disease (PD). Additionally, safety parameters will also be collected.

5. Device Description

Boston Scientific DBS Systems are comprised of leads for stimulation and extensions that allow the leads to be extended to reach the Implantable Pulse Generator (IPG). The various components are shown in **Error! Not a valid bookmark self-reference.**.

The Boston Scientific Vercise™ Cartesia™ X/HX 16-contact Directional Leads (30 cm or 45 cm) used with a commercially approved Vercise™ Genus 32-contact IPG will provide directional stimulation. These leads extend the span of contacts when compared with commercially available directional leads. However, the length of the distal contact array span is no greater than that of the existing standard DBS 8-contact Leads with non-directional arrays.

Once the leads are placed, they are typically secured using standard lead fixation technique. A commercially available SureTek™ Burr Hole Cover may be used. Since the leads are often placed under the scalp for some time before being connected to lead extensions or IPG, lead boots may be used to cover the proximal ends of the leads during this period. External commercially available devices, including a Clinician Programmer, Remote Control and Charging System, are provided for patient/physician use. Boston Scientific's GUIDE XT software may be used as a planning tool for programming as applicable.

The leads, lead extensions, and OR cable will be considered test devices in the study. All other components of the DBS system are commercially approved.

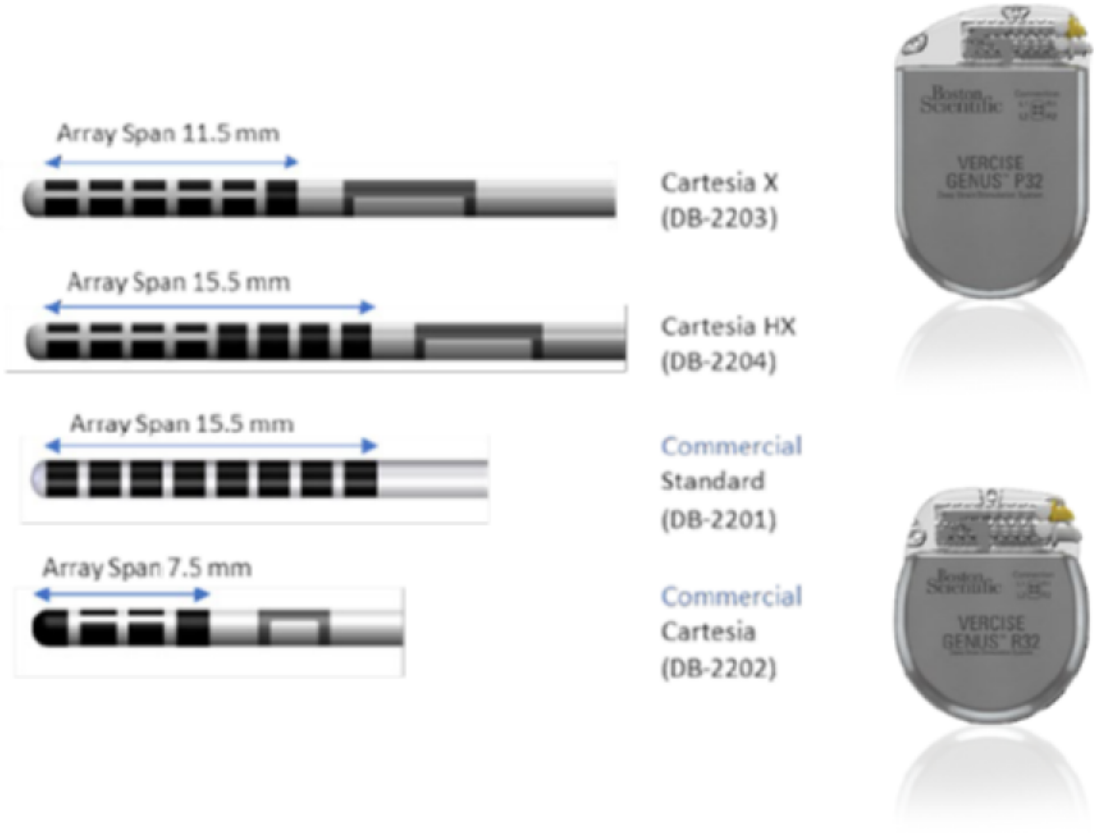

Figure 1: Cartesia X/HX 16-contact Directional Lead with Genus DBS System

6. Study Objectives and Endpoints

The primary objective of this confirmatory study is to document patient outcomes including effectiveness for Boston Scientific Corporation's Vercise™ Cartesia™ 16-contact Directional Lead(s) (X/HX) with Deep Brain Stimulation (DBS) systems for the treatment of Parkinson's Disease (PD). Additionally, safety parameters will also be collected.

6.1. *Primary Endpoint*

Mean change in MDS-UPDRS III scores from Baseline in *meds off* condition to 12 weeks post device-activation in *stim on/meds off* condition.

[redacted]

7. Study Design

The study is a prospective, multi-center, open label confirmatory study. The Cartesia eXTend 3D study meets all the requirements of a confirmatory study per ISO 14155 Annex I.

Subjects will receive the Vercise™ Cartesia™ (X/HX) 16-contact Directional Lead with the Vercise™ Genus™ DBS System and will be followed per study schedule as shown in Figure 2 2 below.

[redacted]

[redacted]

8. Subject Selection

[redacted]

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 Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	[redacted] IC2. Candidate for DBS implant in the treatment of Parkinson's disease IC3. Must be on stable anti-parkinsonian medications for 28 days prior to Informed Consent IC4. Persistent disabling Parkinson's disease symptoms such as dyskinesias, motor fluctuations, or disabling "off" periods despite optimal medical therapy [redacted] IC8. Be willing and able to comply with all visits and study related procedures (e.g., using the remote control, charging system, etc.) [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

Exclusion Criteria	EC1. Any intracranial abnormality or medical condition that would contraindicate DBS surgery EC2. Have any significant psychiatric or cognitive condition likely to compromise the subject's ability to comply with requirements of the study protocol (e.g. bipolar, schizophrenia, mood disorder with psychotic features, cluster B personality disorders) [redacted] EC4. Any current drug or alcohol abuse, as determined by the investigator EC5. Any history of recurrent or unprovoked seizures [redacted]

9. Subject Accountability

9.1. *Point of Enrollment*

A subject will be considered enrolled in this study at the time of the study-specific informed consent form (ICF) execution. No study-related procedures or assessments can take place until the ICF is signed.

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

investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include but are not limited to:

- Loss of treatment efficacy
- Adverse events,
- physician discretion,
- subject choice to withdraw consent,
- subject's failure to meet the study's eligibility criteria after enrollment but prior to system implant,
- failure to receive the BSC DBS system,
- lost to follow-up,
- pregnancy*,
- death,
- explant of the entire DBS system**

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment.

All applicable case report forms (CRFs) up to the point of subject withdrawal and an "End of Study" form must be completed. Any subject deemed "lost to follow-up" should have a minimum of three documented attempts to contact him/her prior to completion of the "End of Study" form.

Additional study data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws consent, for whatever reason. Data collected up to the point of subject withdrawal may be used. Subjects withdrawn after completing the implant procedure will not be replaced and will be included in the site's overall total for activated subjects.

*Women who become pregnant during the study, will be withdrawn and their device de-activated.

**If the entire DBS system of a study subject was explanted, it is recommended to follow the subject for 30 days after the explant of the system.

9.3. *Lost to Follow-Up*

A subject is considered as lost to follow-up if they failed to return for scheduled visits upon several attempts of contact.

Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent

methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9.4. *Subject Status and Classification*

A subject will be considered enrolled in this study at the time of the study-specific informed consent form (ICF) execution.

9.5. *Enrollment Controls*

[redacted]

The study will implement a formal *Enrollment Communication Plan*. The plan will outline the specific activities, as well as the nature and timing of communications to investigators in order to minimize the risk of enrollment beyond the protocol-specified enrollment caps determined by the statistical analysis plan.

9.6. *End-of-Study Definition*

The study is considered complete when the last subject's last study visit has occurred.

9.7. *End of Study Action Plan*

[redacted]

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in Table 10.1 1.

10.2. *Study Candidate Screening*

Enrolled subjects will be screened for participation in the study based on study Inclusion/Exclusion criteria as listed in Section 8. Subjects who have provided informed consent and who have been determined to not meet all eligibility requirements will be withdrawn.

10.3. *Informed Consent*

Written informed consent must be obtained from all potential study candidates. A subject is considered enrolled only after the subject signs and dates the ICF.

- Subjects will be asked to sign the ICF before any study-specific tests or procedures are performed;
- The context of the study must be fully explained, and the subjects must be given the time and opportunity to ask questions and have those questions answered to their satisfaction;
- Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, certain screening procedures might demonstrate that the subject is not eligible to continue participation;
- The ICF is study specific and must be approved by the Ethics Committee (EC) and the sponsor.
- Written informed consent must be recorded appropriately by means of the subject's dated signature.

Participants are required to be on stable anti-parkinsonian medications for 28 days prior to informed consent.

10.4. *Screening Period/Baseline Visit (up to 45 days post informed consent)*

During the screening period, subjects will undergo screening procedures as listed in Section 8 to determine their eligibility in the study. Subjects may have multiple visits to the neurologist and/or neurosurgeon for this purpose.

Subjects are required to be on stable anti-parkinsonian medications for 28 days prior to informed consent. Those subjects who meet all inclusion criteria and none of the exclusion criteria may continue participation in the study.

The Baseline Visit may occur anytime within the screening period and will serve as the final determination of eligibility in the study. It is recommended that *meds off/meds on* assessments be completed at the Baseline Visit.

All baseline OFF-ON assessments have to be completed on the same day.

[redacted]

- [redacted]

[redacted]

10.6. *Device Activation – Day 0*

The Vercise™ DBS System will be activated following completion of the system implant and this visit will be considered Day 0 for the study.

Subjects will be asked about any adverse events since their last study visit. Any changes to subjects' anti-parkinsonian medications will be documented.

The device stimulation parameters will be chosen based on subject and physician preference. Subjects will be instructed on the use of the remote control and charging system. Any precautions/restrictions will be discussed.

Initial programming will be completed, and information related to efficacy, side-effect thresholds and programming parameters may be collected. It is recommended that the initial programming be done in the *meds off* condition. If GUIDE XT is used for planning purposes, additional information may be collected.

Subjects may return to the clinic for optimization of stimulation parameters as needed.

10.7. *Week 10 Visit post-activation (+ 7 days)*

Subjects will return to the clinic for optimization of stimulation parameters and any adverse events since their last study visit will be collected.

Prior to Week 12 Visit:

Subjects must discontinue taking their anti-parkinsonian medications for at least 12 hours (or overnight) prior to the visit. Additionally, long acting anti-parkinsonian medications may be withdrawn for 24 hours prior to visit.

10.8. *Week 12 Visit post-activation (+ 7 days)*

At Week 12 Visit post-activation, subjects will return to the clinic in the *stim on/meds off* condition.

Any adverse events since the last study visit will be collected. Any changes to subjects' anti-parkinsonian medications will be documented. Only upon completion of study related assessments, subjects' device may be programmed or further optimized as needed.

[redacted]

10.9. *Week 26 Visit post-activation (± 21 days)*

At Week 26 Visit post-activation, subjects will return to the clinic in the *stim on/meds off* condition.

Any adverse events since the last study visit will be collected. Any changes to subjects' anti-parkinsonian medications will be documented. Only upon completion of study related assessments, subjects' device may be programmed or further optimized as needed.

[redacted]

10.10. *Years 1, 2, 3, 4 and 5 Visit post-activation (± 45 days)*

Subjects will return to the clinic in the *stim on/meds off* condition at these annual visits.

Any adverse events since the last study visit will be collected. Any changes to subjects' anti-parkinsonian medications will be documented. Only upon completion of study related assessments, subjects' device may be programmed or further optimized as needed.

[redacted]

10.11. *Replacements/Revisions*

It is possible that leads may be placed incorrectly, migrate, fail or get infected. This may require repositioning, replacement or explant. It is also possible that the IPG may fail and require replacement or explant, or need repositioning due to migration, discomfort, etc. The

decision to reposition or replace any device component will be made by the investigator along with the subject. Site staff should notify BSC before the procedure. Subjects not agreeing to a recommended lead revision will be withdrawn from the study but will be included in the intent-to-treat and safety analyses. Subjects agreeing to lead revision will continue on study and will be followed according to the study schedule. Effectiveness data from these subjects will be included in the intent-to-treat analysis. Any replacements, revisions or explants performed during the course of the study should be recorded in the electronic database. Subjects who are not willing to an IPG revision will only be withdrawn, per investigator discretion, if the performance of the device has been compromised e.g. unable to charge due to migration.

10.12. *Study Completion*

Subjects will be followed up to 5 years post-activation visit. Year 5 Visit will be considered their end of study and End of Study Action Plan will be followed as described in Section 9.7.

10.13. *Source Documents*

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

- All source documentation (Table 9.1-2) will be retained at the investigational site. The type of the source documentation will be specific to each study visit and whether the visit was conducted at the neurologist's or a neurosurgeon's office. When neurologist and neurosurgeons are not at the same institution, each office will be responsible for keeping source documentation related to only those study visits conducted at their institution.

Table 10.1-1: Source Documentation Requirements

Requirement	Disposition
Informed Consent Form	**Retain at investigational site**
Consent Process Documentation	**Retain at investigational site**
Inclusion & Exclusion Criteria Documentation	**Retain at investigational site**
Medical Records	**Retain at investigational site**
Patient and Clinician Questionnaires	**Retain at Investigational site**
Clinician Programmer's (CP) files	**Retain at Investigational site and submit copy to Boston Scientific**
Guide XT files (if applicable)	**Retain at Investigational site and submit copy to Boston Scientific**
Imaging (CT, MRI)	**Retain at investigational site and submit copy to Boston Scientific**
Technical Source Form	**Retain at investigational site**

11. Statistical Considerations

11.1. *Primary Endpoint*

The primary endpoint for this confirmatory study is the mean change in MDS-UPDRS III scores from Baseline in *meds off* condition to 12 weeks post device-activation in *stim on/meds off* condition

11.1.1. Hypotheses

The primary statsitical hypothesis in this study is that the mean change in MDS-UPDRS III scores from Baseline in *meds off* condition to 12 weeks post device-activation in *stim on/meds off* condition is greater than 5 (MCID). More specifically,

H_0: $\mu_B - \mu_{12} \leq 5$

H_1: $\mu_B - \mu_{12} > 5$

Where μ_B and μ_{12} is the mean MDS-UPDRS III scores in *meds off* condition at Baseline and at 12 weeks post device-activation respectively.

[redacted]

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

The following sets will be analyzed.

- **Intent-to-Treat (ITT) Population**: All subjects in which implantation of the device is attempted (successful or not), will be included in the ITT population. This will be the primary analysis set.
- **Per Protocol (PP) Population**: All subjects who receive the study device, with no major protocol deviations.
- **Safety Population**: All subjects who sign the IRB-approved written Informed Consent form

Subjects who have been withdrawn due to an explant or loss of treatment inefficacy will be analyzed as treatment withdrawals, while all other withdrawals will be considered as study withdrawals.

11.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient load. 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 are not implanted, will be indicated in the eCRF (electronic Case Report Forms). Boston Scientific will report to the ethic committee any evidence of fraud, including deliberate tampering with the selection of subjects.

[redacted]

[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.

[redacted]

[redacted]

- [redacted]

[redacted]

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 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.

[redacted]

[redacted]

14. 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, the reviewing EC 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 eCRF. Sites may also be required to report deviations to the EC/regulatory authority, per local guidelines and national/government regulations.

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

The sponsor will not approve protocol waivers.

- [redacted]

16. Compliance

16.1. *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 ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, European Medical Device Regulation, ICH-GCP, 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 EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

16.2. *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, ISO 14155, ICH-GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, 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 Investigator Brochure Signature Page and 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 course of the clinical investigation.
- 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 EC 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 EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the investigational devices, ensuring that the investigational devices are used only by authorized/designated users and in accordance with this protocol and instructions for use.
- 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 EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC 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.
- 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, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with

identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- 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.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

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.

16.2.1. 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, are competent to perform the tasks they have been delegated and 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.

16.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written EC and/or competent authority (CA) 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 and shipment of investigational product/equipment. 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 EC before the changes are implemented to the study. All changes to the ICF will be EC 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 EC approval and renewals will be obtained throughout the duration of the study as required by applicable

local/country laws or regulations or EC requirements. Copies of the study reports and the EC continuance of approval must be provided to the sponsor.

16.4. *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, regulatory application(s), 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.

[redacted]

[redacted]

17. 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. For more details on monitoring, please refer to the Cartesia eXTend 3D Monitoring plan (92572890).

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events*

Subjects participating in this study have the same risks for DBS as those who have DBS for treatment of PD outside of the study. Because the handling characteristics of the Vercise™ Cartesia™ 16-contact Directional Leads are similar to those of commercially-available leads, it is expected that the type and rate of lead-related adverse events will be similar for both kinds of leads

The following anticipated adverse events (AE) have been identified for this study:

- Allergic or immune system response;
- CSF leak;
- Death, including suicide;
- Embolism, including air embolism and pulmonary embolism
- Failure or malfunction of any of the device components or the battery, including but not limited to lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits and lead insulation breaches, whether or not this requires explant and/or re-implantation;
- Hemorrhagic or ischemic stroke, immediate or delayed, which could result in temporary or permanent neurologic deficits such as muscle weakness, paralysis or aphasia;
- Implant site complications such as pain, poor healing, wound reopening;
- Infection;
- Injury to tissues adjacent to implant or within surgical field, such as blood vessels, peripheral nerves, brain (including pneumocephalus), or pleura (including pneumothorax);
- Interference from external electromagnetic sources;
- Lead, extension (including extension header) and IPG erosion or migration;
- Loss of adequate stimulation;
- Mentation impairment such as attention or cognitive deficits, memory disturbances, or confusion;
- Psychiatric disturbances such as anxiety, depression, apathy, mania, insomnia, suicide, or suicidal ideation or attempts;

- Motor problems such as paresis, weakness, incoordination, restlessness, muscle spasms, postural and gait disorders, tremor, dystonia, or dyskinesias, and falls or injuries resulting from these problems;
- During an MRI examination, there are potential interactions with the implanted DBS lead, Extension, and Stimulator, and risk of patient harm. Make sure to follow the ImageReady™ MRI Guidelines for Boston Scientific DBS Systems, available on the website www.bostonscientific.com/manuals;
- Musculoskeletal stiffness;
- Neuroleptic malignant syndrome or acute akinesia can occur very rarely;
- New onset or worsening depression, which may be temporary or permanent, and suicidal ideations, suicide attempts, and suicide;
- Overstimulation or undesirable sensations, such as paresthesia, transient or persistent;
- Neurosurgery risks, including unsuccessful implant, exposure to blood borne pathogens;
- Pain, headache or discomfort, transient or persistent, including symptoms due to neurostimulation;
- Poor initial lead location, which may lead to ineffective therapy, side effects, or a surgical revision;
- Radiation exposure due to imaging (CT, fluoroscopy x-ray);
- Seizures;
- Sensory changes (e.g. changes in hearing, taste, or other senses);
- Seroma, edema or hematoma;
- Skin irritation or burns at IPG site;
- Speech or swallowing problems such as dysarthria or dysphagia, as well as complications of dysphagia such as aspiration pneumonia;
- Status dystonicus;
- Systemic symptoms-autonomic (tachycardia, sweating, fever, dizziness), changes in renal function, urinary retention, sexual effects, gastrointestinal (nausea, bowel retention, bloating);
- Thrombosis;
- Visual disturbances or periorbital symptoms, such as diplopia, eyelid movement difficulty, oculomotor difficulties or other visual field effects;
- Weight changes

18.2. *Anticipated Adverse Device Effects*

From the Anticipated Adverse Events listed above, the following anticipated adverse device effects (ADE) have been identified for use of DBS in treatment of PD. These include potential effects due to presence of the device, whether it is "on" or "off," effects due to use of stimulation, and effects caused by the device during a study surgical procedure. Note that some of these stimulation-related symptoms may be resolved or reduced by current steering, changing stimulation parameters, or by surgical repositioning of the lead:

- Allergic or immune system response;
- CSF leak;
- Death, including suicide;
- Failure or malfunction of any of the device components or the battery, including but not limited to lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits and lead insulation breaches, whether or not this requires explant and/or re-implantation;
- Hemorrhagic or ischemic stroke, immediate or delayed, which could result in temporary or permanent neurologic deficits such as muscle weakness, paralysis or aphasia;
- Implant site complications such as pain, poor healing, wound reopening;
- Infection;
- Injury to tissues adjacent to implant or within surgical field, such as blood vessels, peripheral nerves, brain (including pneumocephalus), or pleura (including pneumothorax);
- Interference from external electromagnetic sources;
- Lead, extension (including extension header) and IPG erosion or migration;
- Loss of adequate stimulation;
- Mentation impairment such as attention or cognitive deficits, memory disturbances, or confusion;
- Psychiatric disturbances such as anxiety, depression, apathy, mania, insomnia, suicide, or suicidal ideation or attempts;
- Motor problems such as paresis, weakness, incoordination, restlessness, muscle spasms, postural and gait disorders, tremor, dystonia, or dyskinesias, and falls or injuries resulting from these problems;
- During an MRI examination, there are potential interactions with the implanted DBS lead, Extension, and Stimulator, and risk of patient harm. Make sure to follow the ImageReady™ MRI Guidelines for Boston Scientific DBS Systems, available on the website www.bostonscientific.com/manuals.

- Musculoskeletal stiffness;
- Neuroleptic malignant syndrome or acute akinesia can occur very rarely;
- New onset or worsening depression, which may be temporary or permanent, and suicidal ideations, suicide attempts, and suicide;
- Overstimulation or undesirable sensations, such as paresthesia, transient or persistent;
- Neurosurgery risks, including unsuccessful implant, exposure to blood borne pathogens;
- Pain, headache or discomfort, transient or persistent, including symptoms due to neurostimulation;
- Poor initial lead location, which may lead to ineffective therapy, side effects, or a surgical revision;
- Radiation exposure due to imaging (CT, fluoroscopy x-ray);
- Seizures;
- Sensory changes (e.g. changes in hearing, taste, or other senses);
- Seroma, edema or hematoma;
- Skin irritation or burns at IPG site;
- Speech or swallowing problems such as dysarthria or dysphagia, as well as complications of dysphagia such as aspiration pneumonia;
- Status dystonicus;
- Systemic symptoms-autonomic (tachycardia, sweating, fever, dizziness), changes in renal function, urinary retention, sexual effects, gastrointestinal (nausea, bowel retention, bloating);
- Thrombosis;
- Visual disturbances or periorbital symptoms, such as diplopia, eyelid movement difficulty, oculomotor difficulties or other visual field effects;
- Weight changes

Please refer to the study-specific Directions for Use for anticipated adverse (device) effects and risks associated with the commercial device components only (e.g. IPG, charger). The Directions for Use also describes warnings and precautions for use of the system.

18.3. *Risks Associated with the Study Device(s)*

There are no additional known risks associated with the investigational device in comparison to commercially-available devices.

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

The following risks maybe associated with subjects' participation in the clinical study:

- Subjects may find it difficult, uncomfortable, or tiresome to complete study visits and/or questionnaires, including discomfort during 'meds off' or 'meds on' conditions for testing;
- Subjects with postural instability or gait disturbances either due to Parkinson's disease or as a side effect of DBS may be at a risk of falling while walking, rising from a chair, or sitting down in a chair as required for certain study assessments.

18.5. *Possible Interactions with Concomitant Medical Treatments*

While concomitant use of anti-Parkinson medications is being adjusted to fit the subject's changed requirements with use of DBS, subjects may experience symptoms of excess or inadequate dopaminergic states (beyond those occurring due to Parkinson's disease). These may include increased dyskinesias, apathy, or other risks already listed in the sections above.

18.6. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital 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.

18.7. *Anticipated Benefits*

High frequency stimulation of deep brain structures has been used since the 1980s for the treatment of motor symptoms associated with PD. Many studies have measured the risks and benefits associated with this type of treatment, and considerable reduction in PD symptoms has been observed. It is possible that some individual patients may experience no direct benefit from participation in this study. However, based on the success of the Boston Scientific Vercise™ DBS Systems, it is anticipated that most patients will experience improvement in PD symptoms. The programming options with the Vercise™ Cartesia™ 16-contact Directional Leads to potentially improve therapy and/or reduce stimulation-related side effects are anticipated to be perceived as benefits.

18.8. *Risk to Benefit Rationale*

The purpose of this study is to document patient outcomes including effectiveness for the BSC Vercise™ DBS Systems including the Vercise™ Cartesia™ 16-contact Directional Leads for the treatment of PD. Based on the clinical data for the approved Vercise™ DBS

Systems, the risk-to-benefit ratio for use of the Vercise™ DBS Systems with the Vercise™ Cartesia™ 16-contact Directional Leads is within reason for foreseeable risks. However, studies do not always predict all side effects that may be experienced. Observation and follow-up of all patients is required as outlined in the protocol.

The components used in this study are similar to others in the Vercise™ DBS Systems and other commercial DBS devices that have an extensive history of use in the treatment of PD. Based on clinical experience with the therapy, the anticipated risks associated with the use of the study device are predicted to be acceptable compared to the expected benefits in the reduction of PD symptoms. The treatment is reversible in that the device may be turned off or explanted at any time for any reason.

All efforts will be made to minimize the aforementioned potential risks using the following approaches:

- Selection of Investigators (neurologists and neurosurgeons) who are experienced and skilled in the treatment of patients with Parkinson's Disease as per BSC's site selection and qualification procedures;
- Clearly defined inclusion and exclusion criteria that ensure only appropriate patients are enrolled;
- Ensuring that treatment and follow-up of patients is consistent with current medical practice;
- Safety review processes by Boston Scientific;
- Monitoring visits to investigational sites.

19. Safety Reporting

19.1. *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:

- Non-related Adverse Events that occur within 1-year post activation
- All Procedure Related Adverse Events
- All Device Hardware and/or Stimulation Related Adverse Events
- All Serious Adverse Events (regardless of relationship)
- All Device Deficiencies
- Unanticipated Serious Adverse Device Effects (USADE)

- New findings/updates in relation to already reported 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 required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether prior to, during or subsequent to the study 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 19.2-1 for AE definitions).

Refer to Section 18 for the known risks associated with the study device(s).

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the safety definitions from 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/-1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 19.2-1: 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 investigational medical device and whether or not anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the

Table 19.2-1: Safety Definitions

Term	Definition
	implantation, the installation, the operation, or any malfunction of the investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or from unintentional misuse of the investigational 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, user or other persons 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 and 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.
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.

Table 19.2-1: Safety Definitions

Term	Definition
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 labeling. **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.

19.3. *Relationship to Study Device(s) (Investigational Device(s))*

The Investigator must assess the relationship of the reportable AE to the study device hardware, device stimulation and/or study procedure. See criteria in Table 19.3-1:

Table 19.3-1: Criteria for Assessing Relationship of Study Device (Investigational Device(s)) 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 has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device; - 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 that cannot 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 investigational device used for diagnosis, when applicable; 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 investigational 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 where 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 investigational device or 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.

Table 19.3-1: Criteria for Assessing Relationship of Study Device (Investigational Device(s)) or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the investigational 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 investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to; -the investigational 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 investigational 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.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19.4-1.

The investigator must report all non-related Adverse Events up to Year 1 Post Activation.

The investigator must report all Adverse Device Effects, Serious Adverse Events (regardless of relationship to device (hardware or stimulation) and/or procedure), Unanticipated Serious Adverse Device Effects, and Device Deficiencies for each subject from the time of Informed Consent through the end of study participation.

These events may be reported via phone, fax or email if the electronic data capture (EDC) system is unavailable. The paper AE Notification Form or Device Deficiency Notification Form should be used to report AEs and/or device deficiencies during this time.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, /MDCG 2020-10/1)
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. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Immediately, when documentation is available
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 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.	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 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.	• Immediately, when documentation is available • At request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete device deficiency eCRF with all available new and updated information.	• Immediately but not later than 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.	• At request of sponsor

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, /MDCG 2020-10/1)
Adverse Event including 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 10 business days) after becoming aware of the information • All non related, non- serious adverse events reporting are required through 1 year post activation • All related adverse events (ADEs) are required through end of the study. • At sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

NOTES:

- Sensations or side effects that occur during programming should not be reported as AEs. However, persistent unpleasant sensations or side effects that occur after the completion of programming will be reported.
- Ineffective therapy (e.g. lack of efficacy, lack or decrease of therapeutic response) will not be collected as an adverse event, since failure to achieve therapeutic response is an issue of efficacy, not safety. No AE of "Ineffective Therapy" should be reported when using the expanded parameter range for purposes of improving ineffective therapy. However, AEs due to sudden loss of efficacy (e.g. loss of stimulation leading to a fall or injury) will be collected.
- The subject's Parkinson's disease symptoms will not be collected as AEs, unless they have worsened beyond baseline and beyond the expected disease progression over time. This worsening event could occur in the context of a device malfunction or with a properly-functioning device as determined by investigator).
- Device migration will not be collected as an adverse event. However, an AE that results from the device/lead migration should be reported as an AE. Device migration should be reported as a device deficiency in the electronic database.

In the case of death linked to device hardware or stimulation and/or procedure, autopsy and explantation of device is recommended. Every effort should be made to return the device to BSC. A copy of the death records including autopsy report should be sent to BSC per the Investigator Reporting Requirements (Table 19.4-1). The stimulator should be explanted in the case of cremation and returned to BSC. Cremation may cause the stimulator battery to explode.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (21 CFR Part 812, /MDCG 2020-10/1)

For Germany, please also refer to the 'Serious Adverse Event Reporting according to MPKPV §3 (4) No. 7 & § 2 (1, 5) and §3 (4), (5), (7) & §5 (2) MPSV statement'.

19.5. *Boston Scientific Device Deficiencies*

Device deficiencies for Boston Scientific devices will be documented and reported to BSC. If possible, the investigational device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. Device deficiencies should also be documented in the subject's source records.

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

19.6. *Reporting to Regulatory Authorities / ECs / Investigators*

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

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

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational 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 or its delegate (e.g. CRO), and approved by the site's EC, or central EC, 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 EC. 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 EC 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 or legal representative 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. If a legal representative sign, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. 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. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), 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 the course of 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 EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

21. Committees

21.1. *Safety Monitoring Process*

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

22. Suspension or Termination

22.1 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 ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination. The investigators will be responsible for communicating any information necessary to the subjects. BSC will support the physicians by providing recommendations for ensuring the safety of the subjects.

22.1.1 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 EC or regulatory authorities to suspend or terminate the clinical investigation.
- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- 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 of the device.

22.2 Termination of Study Participation by the Investigator or Withdrawal of EC 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 IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3. 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 EC 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 EC terminates participation in the study, participating investigators, associated ECs, 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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 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 for a period beyond 6 months after site initiation, 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 study 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 EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Study Registration and Results

23.1. *Study Registration*

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

23.2. *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.

23.3. *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 will 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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25. Abbreviations and Definitions

25.1. *Abbreviations*

Abbreviations are shown in Table 25.1-1.

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CCG	Case Report Form Completion Guidelines
CRF	Case Report Form
DBS	Deep Brain Stimulation
DFU	Directions for Use
EDC	Electronic Data Capture
HCP	Health Care Professional
ICF	Informed Consent Form
IPG	Implantable Pulse Generator
ISO	International Organization for Standardization
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Effect

25.2. *Definitions*

Terms are defined in Table 25.2-1.

Table 25.2-1: Definitions

Term	Definition
Activation	The process of turning on the implantable pulse generator (IPG) for the first time after implant and the programming of stimulation parameters.
CE mark	The CE mark, or formerly EC mark, is a mandatory conformity marking for certain products sold within the European Economic Area (EEA) since 1985.

Table 25.2-1: Definitions

Term	Definition
Enrollment	A subject will be considered enrolled in the study at the time of the study-specific informed consent form (ICF) execution.
End of Study Action Plan	Defines the actions to be taken when the subject reaches the end of their study participation.
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Note 1 to entry: This includes source data initially recorded in an electronic format.
Source Document	Original or certified copy of printed, optical or electronic document containing source data.