Directional Lead: Investigation of Rotational Current Steering, Ease of Use of Clinical Effects Map, and Therapeutic Outcomes of Deep Brain Stimulation

DIRECT-DBS

CLINICAL INVESTIGATION PLAN

[redacted]

Sponsored By

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2. Protocol Synopsis

Directional Lead: Investigation of Rotational Current Steering, Ease of Use of Clinical Effects Map, and Therapeutic Outcomes of Deep Brain Stimulation **DIRECT-DBS STUDY**	
Study Objective(s)	The primary objective is to characterize the programming effects of Boston Scientific Vercise™ PC System using the DBS Directional Lead for bilateral STN DBS for the treatment of Parkinson's disease in acute and chronic settings. [redacted]
Test Device	Boston Scientific Neuromodulation (BSN) Vercise™ PC System with BSN Directional Lead
Control Device	None; each patient will serve as their own control
Study Design	Prospective, multi-center, open label study with double-blinded exploratory and crossover phases
Planned Number of Patients	Up to 12 randomized patients
Planned Number of Investigational Sites / Count11ries	Up to 4 sites in the EU
Primary Endpoint	Collected data will be used to guide product development and to build early experience to define the best practice for programming
[redacted]	[redacted]

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Method of Assigning Patients to Treatment	Eligible patients who consent to participation and have met all of the inclusion and none of the exclusion criteria will undergo implant and intraoperative testing. After 3 months of omnidirectional (Ring Mode) stimulation, the patient will undergo 3 Programming Visits. Patients are then randomized in an equal distribution to best Ring Mode settings or best Unrestricted settings for 4 weeks, followed by crossover to the opposite programming method for 4 additional weeks. After this, patients are followed up to one year post implant where programming can be further optimized
Follow-up Schedule	• Screening (prior to implant) • Implant • 3 Programming Visits (up to 7 days prior to Randomization Visit) • Randomization Visit (90 ± 30 days post first lead placement) • Crossover Visit (28 ± 7 days post Randomization Visit) • Release Visit (56 ± 7 days post Randomization Visit) • 1-Year Follow Up Visit (365 ± 30 days post first lead placement) The overall study will be considered complete when the last patient not lost to follow up completes the 1 Year Follow Up Visit

Directional Lead: Investigation of Rotational Current Steering, Ease of Use of Clinical Effects Map, and Therapeutic Outcomes of Deep Brain Stimulation **DIRECT-DBS STUDY**	
Study Duration	The entire study will take less than 2 years to complete. Each patient will be enrolled for approximately 1 year.
Key Inclusion Criteria	IC1. Candidate for Vercise™ PC DBS with bilateral implant of BSN DBS Directional Leads in STN, and meets: • Diagnosis of bilateral idiopathic PD with the presence of rigidity and at least one (1) of the following: resting tremor or bradykinesia. • UPDRS III score of >25 in the meds OFF condition • Medication must improve PD symptoms by ≥30%, as measured by UPDRS subset III score [redacted] IC4. [redacted]
Key Exclusion Criteria	EC1. Any significant psychiatric problems, including unrelated clinically significant depression as determined by the investigator EC2. Any current drug or alcohol abuse as determined by the investigator EC3. Any history of recurrent or unprovoked seizures EC4. Any significant medical condition that is likely to interfere with study procedures or likely to confound evaluation of study endpoints, including any terminal illness with survival <12 months
Statistical Methods	
Primary Statistical Hypothesis	NONE
Statistical Test Method	Descriptive statistics will be employed in post-hoc analysis

Directional Lead: Investigation of Rotational Current Steering, Ease of Use of Clinical Effects Map, and Therapeutic Outcomes of Deep Brain Stimulation DIRECT-DBS STUDY	
Sample Size Parameters	Sample size not determined in prospective manner

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3.1. *Table of Figures*

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4. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 2.0 million Europeans (1). 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 groups (2). The hallmark signs of PD include movement disorders such as bradykinesia, resting tremors, and muscle rigidity (3).

The motor symptoms of PD are associated with a dopamine deficiency resulting from the degradation of dopaminergic neurons in the substantia nigra pars compacta. 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 therapy for the symptomatic control during the early, uncomplicated stages of PD (4, 5). Unfortunately, chronic treatment with levodopa frequently leads to significant side effects, especially dyskinesias and motor fluctuations (6).

Previously, for patients who had reduced response to medical therapy, pallidotomy (destruction of the globus pallidus) and thalamotomy (destruction of the thalamus) were the only available surgical treatment options. In the 1990s, high-frequency deep brain stimulation (DBS) was demonstrated to be effective in reducing the motor complications of patients with PD (7). Since that time numerous case studies and trials have substantiated these early findings. In addition, three recent large, multicenter, randomized trials have demonstrated the efficacy of the therapy (8-10). Currently, DBS of the subthalamic nuclei (STN) is recommended as a therapeutic option for appropriate PD patients (5, 11).

This study will compare various program settings for the bilateral stimulation of the STN using the BSC implantable Vercise™ PC DBS System for the treatment of levodopa-responsive, moderate to severe idiopathic PD. The Vercise™ PC System is capable of delivering stimulation similar to other commercially available DBS systems. [redacted]

5. Device Description

The Boston Scientific Vercise™ DBS System received CE mark approval in September 2012 for treatment of Parkinson's disease, in September 2013 for treatment of intractable primary and secondary dystonia and in July 2014 for Essential Tremor. The directional lead, Vercise™ PC system and programming system received CE mark in September 2015

The implantable portion of the Vercise™ PC System includes leads for bilateral stimulation and extensions that allow the leads to be extended to reach the Implantable Pulse Generator (IPG) near the clavicle. The electrode array is placed into the brain, typically targeting the subthalamic nucleus (STN) or Globus Pallidus (GPi). The directional leads can provide stimulation in a ring mode (equally around the lead) or in a directional mode (away from the center of the lead). Once the leads are placed, they are typically secured using physician's standard lead fixation technique. A 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 will be provided to cover the proximal ends of the leads during this period.

Surgical tools for the Vercise™ PC System include a tunneler. A lead stop (which may be attached to the lead to allow the lead to be located at the appropriate depth in the tissue during its initial placement) will also be provided.

External devices including a Clinician Programmer, programming wand and Remote Control will also be provided for patient/physician use. During implant, the positioning of the lead(s) may be checked using macrostimulation provided by a Vercise™ PC External Trial Stimulator (ETS).

A copy of the device labeling and DFU will be provided in local language(s) as required per national regulations.

5.1. *Medical Equipment Description*

Kinesia ONE

Commercial, tablet-based system created by Great Lakes NeuroTech (GLNT) which assesses tremor, bradykinesia, hypokinesia, and dysrhythmia in an automated fashion via a patient-worn, finger mounted motion sensor.

Kinesia 360

Commercial tablet-based motor diary system created by Great Lakes NeuroTech (GLNT) which assesses tremor, dyskinesia and mobility during the day in an automated fashion via patient-worn sensors and a mobile app to continuously measure Parkinson's disease.

The Kinesia ONE system is used in the hospital environment while the Kinesia 360 system is used by the patient at home.

6. Study Objectives

The primary objective of this exploratory study is to characterize the programming effects of Boston Scientific Vercise™ PC System using the DBS Directional Lead for bilateral STN DBS for the treatment of Parkinson's disease in an acute and chronic setting.

[redacted]

8. Study Design

Prospective, multi-center, open label, study with double-blinded exploratory and crossover phases.

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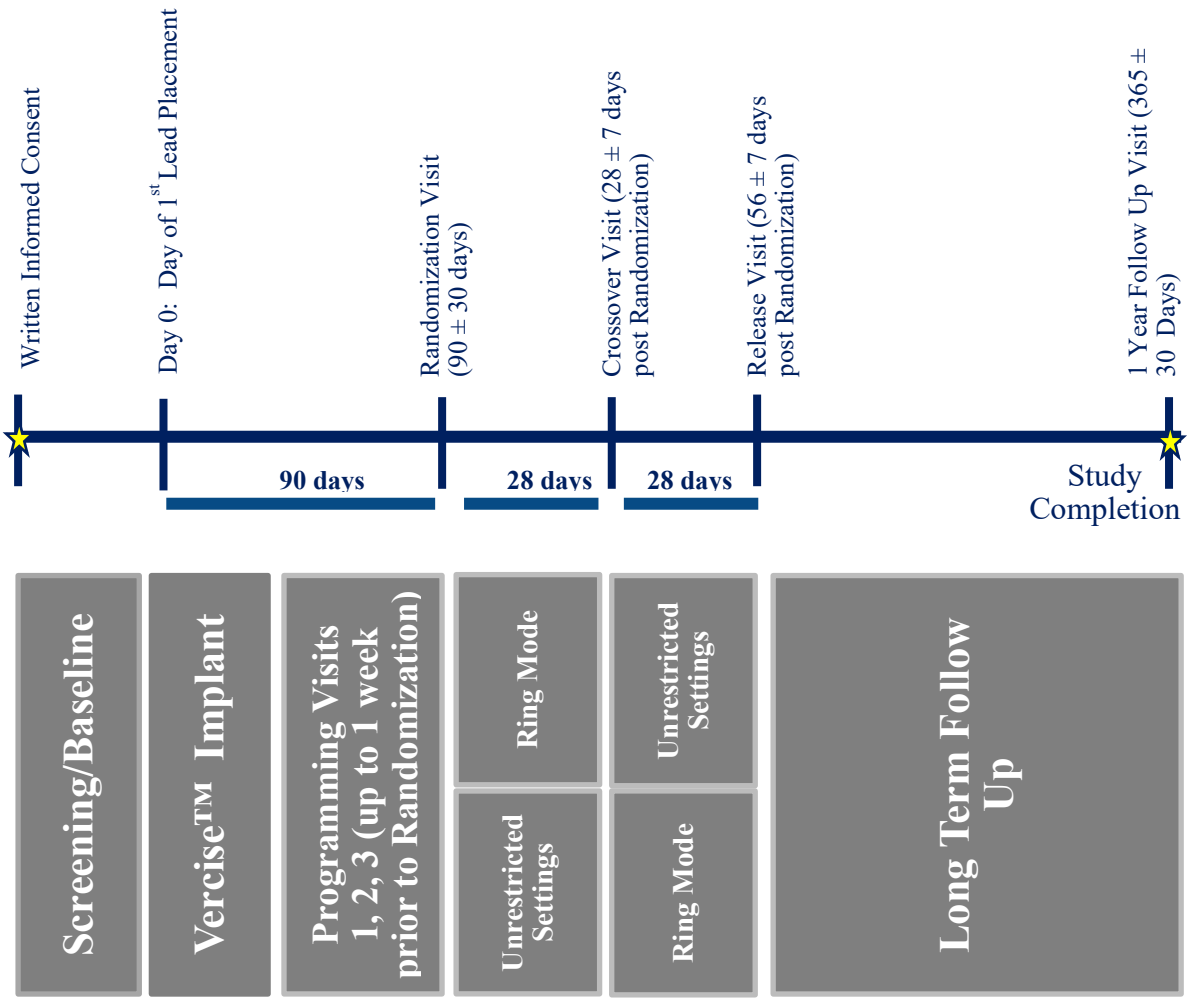

Figure 8.1-1: DIRECT-DBS Study Design

8.2. *Treatment Assignment*

Eligible patients who consent to participation and have met all of the inclusion and none of the exclusion criteria will undergo implant and intraoperative testing. After 3 months of omnidirectional (Ring Mode) stimulation, the patient will undergo 3 Programming Visits. Patients are then randomized in an equal distribution to best Ring Mode settings or best Unrestricted settings for 4 weeks, followed by crossover to the opposite programming method for 4 additional weeks. After this, patient is followed up to one year post implant where programming can be further optimized.

8.2.1. Treatment and Control

Each patient will serve as their own control during Crossover Phase. Symptom comparisons will be made across time and across different stimulation settings.

8.3. *Justification for the Study Design*

The study design is a prospective, multi-center, open label, study with double-blinded exploratory phase and un-blinded crossover phase with a blinded evaluator, characterizing the programming effects of Boston Scientific Vercise™ PC System using the DBS Directional Lead for bilateral STN DBS for the treatment of Parkinson's disease in an acute and chronic setting.

A multi-center design will minimize the impact on treatment outcome that may potentially result from differences in patient selection, regional differences in the patient demographic, and differences in investigator technique and patient management.

The study will include multiple instances of randomization, where the patient will receive stimulation parameters from a preset list in a random order. Randomization will minimize bias due to order of presentation of stimulation settings. A double blind (patient and neurologist assessor) will minimize bias that might impact subjective outcome measures. The programmer will remain un-blinded to provide appropriate care for each patient's programming variables.

The crossover phase requires that the patient is programmed with each of Ring Mode and Unrestricted programming settings for an equal amount of time, in a random order. In this way, patients can each serve as their own control. In order to minimize bias that might impact subjective outcome measures, the physician responsible for evaluating these arms will be blinded.

9. Patient Selection

9.1. *Study Population and Eligibility*

Up to 12 randomized patients may be included in the study.

Patients will generally be recruited from physician's practice and will be eligible to receive Deep Brain Stimulation to treat their Parkinson disease using the commercially-approved BSC Vercise™ PC System per local DFU.

9.2. *Inclusion Criteria*

Patients who meet all of the following criteria (see **Error! Reference source not found.**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	IC1. Candidate for Vercise™ PC DBS with bilateral implant of BSN DBS Directional Leads in STN, and meets: • Diagnosis of bilateral idiopathic PD with the presence of rigidity and at least one (1) of the following: resting tremor or bradykinesia. • UPDRS III score of >25 in the meds OFF condition • Medication must improve PD symptoms by ≥30%, as measured by UPDRS subset III score. [redacted]

9.3. *Exclusion Criteria*

Patients who meet any one of the following criteria (**Error! Reference source not found.**) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	EC1. Any significant psychiatric problems, including unrelated clinically significant depression as determined by the investigator. EC2. Any current drug or alcohol abuse as determined by the investigator. EC3. Any history of recurrent or unprovoked seizures. EC4. Any significant medical condition that is likely to interfere with study procedures or likely to confound evaluation of study endpoints, including any terminal illness with survival <12 months.

10. Patient Accountability

10.1. *Point of Enrollment*

A patient will be considered enrolled in this study after he/she signs and dates the informed consent form (ICF). No study-related procedures or assessments can take place until the informed consent form is signed.

10.2. *Withdrawal*

All patients enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a patient 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 patient's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal could include but are not limited to

- physician discretion,
- patient choice to withdraw consent; in case of patients under the age of 18 years old, parent/guardian choice to withdraw consent will be considered a valid reason for withdrawal.
- patient's failure to meet inclusion or not meet exclusion criteria after enrollment but prior to system implant,
- failure to receive a BSC DBS system,
- lost to follow-up, or
- death.

While study withdrawal is discouraged, patients 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 patient withdrawal and an "End of Study" form must be completed. Any patient 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 data may no longer be collected after the point at which a patient has been withdrawn from the study or withdraws consent, for whatever reason. All open adverse events should be closed or documented as unresolved. Data collected up to the point of patient withdrawal may be used and analyzed.

Patients withdrawn after completing the implant procedure will be replaced and will not be included in the site's overall total for randomized patients.

10.3. *Enrollment Controls*

Enrollment will remain open until one of the following events occurs:

- The maximum of 12 patients are randomized
- The study is terminated at any time, at the Sponsor's discretion.

Enrollment controls will be implemented per the Enrollment Communication Plan developed for this study.

11. Study Methods

11.1. *Data Collection*

The data collection schedule is shown in Table 11.1-1.

Table 11.1-1: Data Collection Schedule

Procedure/Assessment	Screening /Baseline	Implant Visit (Day 0)	Program. Visit 1 (up to 7 days prior to Randomization Visit)	Program. Visit 2 (up to 6 days prior to Randomization Visit)	Program. Visit 3 (up to 5 days prior to Randomization Visit)	Randomization Visit (90±30 days)	Crossover Visit (28±7 days post Randomization Visit)	Release Visit (56±7 days post Randomization Visit)	1 Year Follow Up (365±30 days)	Unscheduled Visits
Informed consent form, including signatures and dates	X									
Side effect thresholds (amplitude and effect)		X	X	X						
Full rigidity control threshold (amplitude)			X	X						
Clinical Effects Scores			O	O	O	O	O	O	O	O
Electrode impedances		X	X	X	X	X	X	X	X	X
Brain Imaging (If done per Standard of Care)	X	X	*	*	*	*	*	*	*	*
MER		O								
Surgical Plan		O								
Induced Field Potentials		O	O	O	O	O	O	O	O	O
Clinician Programmer Reports		X	X	X	X	X	X	X	X	X
Clinician Programmer Database		X	X	X	X	X	X	X	X	X
UPDRS III	X		X	X	X	X	X	X	X	O
PDQ-39	X					X	X	X	X	O
Motor assessments			X	X	X	X	X	X	X	O
Motor assessments							X	X		

Procedure/Assessment	Screening /Baseline	Implant Visit (Day 0)	Program. Visit 1 (up to 7 days prior to Randomization Visit)	Program. Visit 2 (up to 6 days prior to Randomization Visit)	Program. Visit 3 (up to 5 days prior to Randomization Visit)	Randomization Visit (90±30 days)	Crossover Visit (28±7 days post Randomization Visit)	Release Visit (56±7 days post Randomization Visit)	1 Year Follow Up (365±30 days)	Unscheduled Visits
Motor diary							X	X		
Directional Lead Implant questionnaire		O								
Directional Lead Programming questionnaire					O					
Adverse events assessment		*	*	*	*	*	*	*	*	*

X = required; O = optional but recommended; * = required if new

11.2. *Study Candidate Screening*

All interested patients will undergo screening during which their eligibility for the study will be determined.

11.3. *Informed Consent*

Written Informed Consent must be obtained for all patients who are potential study candidates. Patients will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed, including any adjustments of medications that are made specifically for study eligibility purposes. The context of the study must be fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction. The Informed Consent form is study specific and must be approved by the study Independent Ethics Committee (IEC). Study personnel should explain that even if a patient agrees to participate in the study and signs an ICF, certain diagnostic or screening procedures might demonstrate that the patient is not eligible to continue participation.

11.4. *Screening/Baseline Visit*

Screening and baseline visit can be done during the same hospitalization, provided patient gave consent before any study specific testing. UPDRS III and PDQ-39 will be collected as well as Kinesia ONE testing. Brain imaging, as done per center's standard of care for surgical and targeting planning, will be collected.

11.5. *Implant Visit (Day 0)*

The Vercise™ PC and directional lead surgical implant will be done according to center's standard of care and applicable DFUs. If the surgical implant is done in several day stages, the date of the first lead placement shall be considered as day 0 for the study timeline.

Upon intraoperative data collection, the surgical procedure is completed per center's standard of care and the study visits will resume after approximately 3 months.

In the interim, the patient follow up and device programming occurs according to center's standard of care, with the exception that programming is limited to Ring Mode fractionalizations. Data will be collected from any unscheduled programming visits which occur.

11.6. *Programming Visits 1, 2 and 3*

The Programming Visits, not to occur on simultaneous days, take place in the 7 days prior to the Randomization Visit (90 ± 30 days post first lead implantation).

At the beginning of each test visit, the patient must be in a practically defined Meds OFF and Stim OFF state. All testing shall be done unilaterally. At the end of each visit, patient may resume their meds and DBS therapy per physician discretion.

The data collected includes, but is not limited to: efficacy and stimulation induced side effect amplitude thresholds, impedances, UPDRS III and Kinesia ONE system scores. The details of the measurement procedures are described in the Manual of Operations.

11.6.1. Programming Visit 1

Personnel needed: blinded evaluator and non-blinded operator

Goal: obtain the best Position of stimulation along one lead, in Ring Mode

11.6.2. Programming Visit 2

Personnel needed: blinded evaluator and non-blinded operator

Goal: obtain the best setting of directional stimulation on one lead using Position found during Day 1.

11.6.3. Programming Visit 3

Personnel needed: non-blinded evaluator and non-blinded operator

Goal: obtain the best clinical outcome possible (under Programming Visit conditions)

11.7. *Randomization Visit (90 ± 30 days post first lead placement)*

A UPDRS III assessment is performed, as well as the full battery of Kinesia ONE tests. The patient is also assessed using the PDQ-39 questionnaire. Assessments are performed with stim ON, meds ON, at the time of best ON. The patient is programmed according to randomization and educated again on the use of the Kinesia 360 system to be used at home.

11.8. *Crossover Visit (28 ± 7 days post Randomization visit)*

A UPDRS III assessment is performed by a blinded evaluator, as well as the full battery of Kinesia ONE tests. The patient is also assessed using the PDQ-39 questionnaire. Assessments are performed with stim ON, meds ON, at the time of best ON. The patient is

programmed according to randomization and, if needed, educated again on the use of the Kinesia 360 system to be used at home.

11.9. *Release Visit (56 ± 7 days post Randomization visit)*

A UPDRS III assessment is performed by a blinded evaluator, as well as the full battery of Kinesia ONE tests. The patient is also assessed using the PDQ-39 questionnaire. Assessments are performed with stim ON, meds ON, at the time of best ON. The patient is programmed according to standard of care.

11.10. *1 Year Follow Up Visit (365 ± 30 days post first lead placement)*

A UPDRS III assessment is performed, as well as the full battery of Kinesia ONE tests. The patient is also assessed using the PDQ-39 questionnaire. Assessments are performed with stim ON, meds ON, at the time of best ON.

11.11. *Study Completion*

Each patient's participation in the study will be considered complete upon completion of the 1 Year Follow Up Visit.

11.12. *Source Documents*

Error! Reference source not found. summarizes all source data requirements for this protocol. 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 investigational site team with a statement that it is a true reproduction of the original source document.

Table 11.12-1: Source Documentation Requirements

Requirement	Disposition
Hospital records or clinical and office charts including the evidence of but not limited to inclusion/exclusion criteria, informed consent, procedures, and assessment of adverse events	Retain at center
Clinician programmer printouts for programming information about trialed settings, clinical responses, and impedance measurements.	Retain at center
Brain imaging performed per standard of care	Retain at center
Clinical evaluations (e.g. UPDRS III, Kinesia)	Retained on a cloud-based server (paper copy retained at the center)

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint

Due to the exploratory nature of the study no prospectively defined, formal statistical methods will be employed.

12.1.2. Hypotheses

No formal hypotheses has been defined.

12.1.3. Sample Size

The sample size has not been determined in prospective manner.

12.1.4. Statistical Methods

Descriptive statistics will be employed in post-hoc analysis

[redacted]

12.2. *General Statistical Methods*

[redacted]

12.3. *Data Analyses*

All data analysis will be performed using standard methods and tools, with appropriate validation when needed.

[redacted]

13. Data Management

13.1. *Data Collection, Processing, and Review*

13.1.1. Electronic Transmission

The questionnaires/forms collected on paper will be transmitted from the site via fax or email and stored on the secure server.

13.1.2. Kinesia System

Exploratory data related to PD symptoms may be collected using the Kinesia quantitative assessment system from Great Lakes NeuroTechnologies. The Kinesia system is a patient-worn motion sensor for the quantitative assessment of tremor and bradykinesia. Real-time

motion sensor data and clinical response questionnaires may be captured and transferred to a secure server for review, storage and analysis.

13.1.3. Brain Imaging Data

Brain imaging data taken per standard of care will be transmitted electronically for storage via burned CD or flash drive and stored on a secure server.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study patients in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. 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.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the patient or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., Ethics Committee (EC)/ Competent Authority (CA)) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a patient in an emergency. An investigator shall notify the sponsor and the reviewing EC of any deviation from the investigational plan to protect the life or physical well-being of a patient 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 paper CRF. Sites may

also be required to report deviations to the EC, per local guidelines and government regulations.

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

16. Device/Equipment Accountability

The study will use only the commercially available Boston Scientific Vercise™ PC System with the DBS Directional Lead. No investigational equipment will be used as test equipment. No device tracking/accountability is required.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and pertinent 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. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

17.2. *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, 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 patient.

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 patient 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 Serious Adverse Events (SAEs) and device deficiencies that could have led to a Serious Adverse Device Event (SADE) and potential/Unexpected Serious Adverse Device Event (USADE) or Unexpected Adverse Device Event (UADE).
- 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 the national 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 device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions 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 patient during and after a patient's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the patient of the nature and possible cause of any adverse events experienced.
- As applicable, provide the patient with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the patient.
- Inform the patient of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the patient 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 patient is enrolled in this clinical study.
- Ensure that, if appropriate, patients 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 patient's approval or when required by national regulations, the patient's personal physician about the patient's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a patient's premature withdrawal from clinical investigation while fully respecting the patient'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.

17.2.1. 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 and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of patients into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to patient recruitment or which will be provided to the patient.

Annual EC approval and renewals will be obtained throughout the duration of the study as required by local/country or EC requirements. Copies of the Investigator's reports and the EC continuance of approval must be provided to the sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning patients or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. 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. All data used in the analysis and reporting of this study will be without identifiable reference to specific patient name.

Boston Scientific will keep patients' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use patients' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to patients; patient names will not be placed on any mailing lists or sold to anyone for marketing purposes.

[redacted]

[redacted]

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for patients in the study will be obtained.

18. 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 study may also be patient 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.

19. Potential Risks and Benefits

Based on clinical experience with the commercially available DBS therapy for PD, there are anticipated risks that may be associated with the use of the Vercise™ PC System. These include risks in the surgical implant procedure, from the presence of the device within the

body, related to stimulation (e.g. neuropsychiatric, neurocognitive, motor, etc.), and symptoms that are difficult to distinguish from PD progression and/or medication side effects.

19.1. *Anticipated Adverse Events*

All potential Anticipated Adverse Events as specified in the Vercise™ PC system's Directions for Use (DFU) are applicable to study subjects.

19.2. *Anticipated Adverse Device Effects*

All potential Anticipated Adverse Device Effects as specified in the Vercise™ PC system's Directions for Use (DFU) are applicable to study subjects.

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

All potential risks associated with the Study Devices as specified in the Vercise™ PC system's Directions for Use (DFU) are applicable to study subjects.

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

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

- Subjects may find it difficult, uncomfortable, or tiresome to complete study visits, study-diaries and questionnaires.
- Subjects may experience various symptoms related to the temporary withdrawal of Parkinson medications and withdrawal of neurostimulation, which is a condition required of specific study visits. Symptoms may include, but are not limited to, worsening of Parkinson's disease signs, apathy, anxiety, disturbance in cognition, or changes in sleep. In addition, the discontinuation of Parkinson medications is associated with a remote risk of developing a life-threatening condition known as neuroleptic malignant syndrome.
- As various deep brain stimulation settings are tested, subjects may experience side effects including, but not limited to, a sensation of tingling, muscle spasm, change in speech, mood, vision, cognition, disturbance of balance, coordination, tremor, dizziness.
- Subjects with postural instability or gait disturbances either due to their Parkinson's disease or as a side effect of DBS may be at a risk of falling while completing motor tasks as required for certain study assessments.

19.5. *Possible Interactions with Concomitant Medical Treatments*

While concomitant use of Parkinson medications is being adjusted to fit a subject's changed requirements with use of DBS, subjects may experience symptoms of excess or inadequate dopaminergic states. As a result, subjects may experience symptoms including, but not limited to dyskinesias, rigidity, tremor, apathy or other known symptoms associated with changes in Parkinson medication dosage.

19.6. *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 patient selection criteria, close monitoring of the patient's physiologic status during research procedures and/or follow-ups, and by promptly supplying BSC with all pertinent information required by this protocol.

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

- Selection of Investigators who are experienced and skilled in the treatment of patients with Parkinson's Disease as per BSC's site selection and qualification procedures;
- Physician judgment may be used to eliminate, halt, reduce, or avoid testing that may pose a greater risk to a patient.
- Clearly defined inclusion and exclusion criteria that ensure only appropriate patients are enrolled;
- Ensuring that follow-up of patients is consistent with current medical practice;
- Safety review processes;
- Frequent monitoring visits to investigational sites.

19.7. *Anticipated Benefits*

While it is uncertain if a patient will experience significant benefit from study participation, it is possible that a more effective DBS programming setting than with conventional programming approaches or cylindrical electrodes can be identified.

19.8. *Risk to Benefit Rationale*

The purpose of this study is to compile characteristics of real-world outcomes for Boston Scientific Corporation's commercially approved Vercise™ PC System for DBS, when used according to the applicable Directions for Use. The mechanism of action of the Vercise™ PC System is the same as other commercially available DBS systems. Based on the clinical data for BSC's approved Vercise™ DBS system, Medtronic's approved Activa DBS System, and St Jude's approved Infinity DBS system, the risk-to-benefit ratio for BSC Vercise™ DBS System 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.

20. Safety Reporting

20.1. *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
- All Device Related Adverse Events
- All Study Procedure Related Adverse Events
- Unanticipated Serious Adverse Device Effects
- 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 AE required by the protocol, experienced by the study patient after informed consent and once considered enrolled in the study (as defined in study patient classification section), whether during or subsequent to the procedure, must be recorded in the CRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of 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 **Error! Reference source not found.** for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

20.2. *Definitions and Classification*

Adverse event definitions are provided in **Error! Reference source not found.**. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015).

Table 20.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons, whether or not related to the investigational medical device.

Table 20.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3 (2015)	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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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 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 intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization , or o in medical or surgical intervention to prevent life-threatening illness o injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **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 analysis report.
Device Deficiency	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include

Table 20.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155-2011 *Ref: MEDDEV 2.7/3 (2015)*	malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Underlying diseases 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 a specific SAE (see **Error! Reference source not found.Error! Reference source not found.** for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

NOTES:

- For the purposes of this study, hospitalization is defined as any in-patient admission.
- Hospitalizations occurring for the purpose of performing a planned procedure as per routine/standard of care such as programming sessions or standard evaluation, staged implant procedures or rehabilitation are NOT to be reported as a SAE.
- Any complications or adverse events that occur during an elective/planned hospitalization, should be reported if they meet the protocol specified definitions. However, the original elective/planned hospitalization(s) should not be reported as an SAE.
- Sensations or side effects that occur during programming should not be reported as AEs. However, persistent unpleasant sensations or side effects caused 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 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.

20.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device (hardware and stimulation) or procedure. See criteria in Table 20.3-1:

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device 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 investigational 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 investigational device used for diagnosis, when applicable; harms to the patient 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.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device 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	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship	The serious event is associated with the investigational device 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 o the investigational device or procedures are applied to; o 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 patient 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.

Adverse events must be assessed according to their relationship to one of the following categories:

- Device Hardware-Related AEs: AEs that can reasonably be attributed to the mere physical presence of the device or to deficiency of the device (i.e., an allergic response to device materials).
- Stimulation-Related AEs: AEs that can reasonably be attributed to the effects of stimulation. A relationship to stimulation may be determined by demonstrating a predictable response to the alternating between stimulation-on and stimulation-off settings. However, a relationship to stimulation may also be reported without demonstrating a predictable response to the alternating between the stimulation-on and stimulation-off settings if in the opinion of the Investigator the AE is potentially related to stimulation.
- Study Surgical Procedure Related AEs: AEs that can reasonably be attributed to a study protocol required surgical procedure.

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.4-1. All protocol required safety reporting may be reported to Boston Scientific via phone, fax or email.

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

Table 20.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Serious Adverse Device Effect	Complete AE CRF 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
Serious Adverse Event	Complete AE CRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. . • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	• When documentation is available
Serious Adverse Device Effects	Complete AE CRF page with all available new and updated information.	• Within 2 business 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 (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious	Complete device deficiency form with all available new and updated information.	• Within 2 business days of first becoming aware of the event. Reporting required through the end of the study

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
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.		
Adverse Device Effects	Complete AE CRF 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 • Reporting required for procedure, hardware and stimulation related adverse events.

Abbreviations: AE=adverse event; CRF=case report form;
*Please note that post-market studies are clinical studies where the medical devices used in the study bear the regulatory approval and are used for the same approved indications

20.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the patient's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the appropriate CRF.

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.

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

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

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

20.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of site notification. The site's EC must be notified of any deaths in accordance with that site's EC policies and procedures. Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether the death was related to the pulse generator, lead/catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Device status and/or activity at the time of death
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.
- Investigator or sub-investigator signature and date

Also submit the following documentation:
If the patient expired in the hospital:

- A copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the patient expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to Boston Scientific)
- Death certificate (if available)

Whenever possible, the IPG should be interrogated. Investigational leads and related Boston Scientific system components (e.g., IPGs) should be removed intact and returned promptly to Boston Scientific for analysis.

21. Informed Consent

Patient participation in this clinical study is voluntary. Informed Consent is required from each patient 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 body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central IRB, 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 patient 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 patient's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of patients to participate,
- not waive or appear to waive patient's legal rights,
- use native language that is non-technical and understandable to the patient or his/her legal representative,
- provide ample time for the patient to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing patients throughout the clinical study.

The ICF shall always be signed and personally dated by the patient 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 signs, the patient 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 patient consent will be reported by BSC to the applicable regulatory body 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. EC), as appropriate.

If new information becomes available that can significantly affect a patient's future health and medical care, that information shall be provided to the affected patient(s) in written form via a revised ICF or, in some situations, enrolled patients 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 patient population to be re-consented.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Medical Director will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

23. Suspension or Termination

23.1. *Premature Termination of the Study*

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

23.1.1. Criteria for Premature Termination of the Study

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to patients enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of EC Approval*

Any investigator or EC in the DIRECT-DBS Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3. *Requirements for Documentation and Patient 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 patients 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 patients 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 patients 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 patients.

23.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of patients at a study site at any time after the study initiation visit if no patients have been enrolled for a period beyond 3 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 patients. The EC and regulatory authorities, as applicable, will be notified. All patients enrolled in the study at the site will continue to be followed per standard of care. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. 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 Corporation 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.

25. Reimbursement and Compensation for Patients

25.1. *Patient Reimbursement*

Travel and other expenses incurred by patients as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

25.2. *Compensation for Patient's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study patients, and if required by applicable law.

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27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in **Error! Reference source not found.**.

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CA	Competent Authority
CDRS	Clinical Dyskinesia Rating Scale
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DBS	Deep Brain Stimulation
DFU	Directions for Use
EC	Ethics Committee
EDC	Electronic Data Capture
ETS	External Trial Stimulator
FDA	Food and Drug Administration
GLNT	Great Lakes NeuroTechnologies
HCP	Health Care Personnel
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intent-To-Treat
mA	milliamps
MEDDEV	Medical Device Directives
PC	Primary Cell
PD	Parkinson’s disease
PDQ	Parkinson’s disease Questionnaire
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
STN	Subthalamic nucleus
UADE	Unanticipated Adverse Device Effect
UPDRS III	Unified Parkinson Disease Rating Scale version 3.0, subsection III

27.2. *Definitions*

Terms are defined in **Error! Reference source not found.**.

Table 27.2-1: 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.
Enrollment	A patient is considered to be enrolled as a research subject in the study after informed consent is obtained.
Monopolar review	A process where the therapeutic window for each contact is determined, i.e., measurement of efficacy and side effect thresholds.
Ring Mode	A restriction to device programming where any stimulation delivered is omnidirectional (i.e. all contacts in each directional row have the same amplitude of current being delivered).
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.
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.
Unrestricted Mode	A programming mode without restrictions, used opposite of Ring Mode in the Crossover Phase of the study.
Vercise™ PC	The Vercise™ PC DBS system manufactured by Boston Scientific Neuromodulation

Table 27.2-1: Definitions

Term	Definition
Abbreviations are defined in **Error! Reference source not found.**	