Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation

CLOVER-DBS

A4063

CLINICAL INVESTIGATION PLAN

NCT03037398

Sponsored By

Boston Scientific International S.A.
Parc Val Saint-Quentin, Bâtiment H
2 Rue René Caudron
78960 Voisins le Bretonneux
France

and

Boston Scientific Neuromodulation Corporation
Neuromodulation
25155 Rye Canyon Loop
Valencia, CA 91355
United States of America

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. The protocol should be held confidential and maintained in a secure location.

Do not copy or distribute without written permission from Boston Scientific Corporation.

[redacted]

[redacted]

Contact Information

Role	Contact
[redacted]	[redacted]
[redacted]	

[redacted]

Original Release: September, 26, 2016

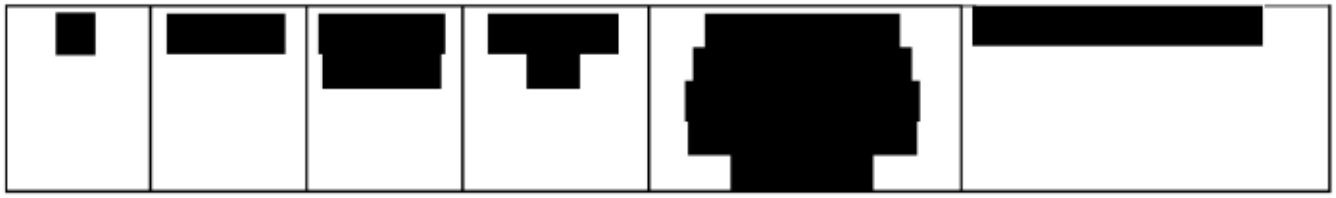
Current Version: November 20, 2023

Revision [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

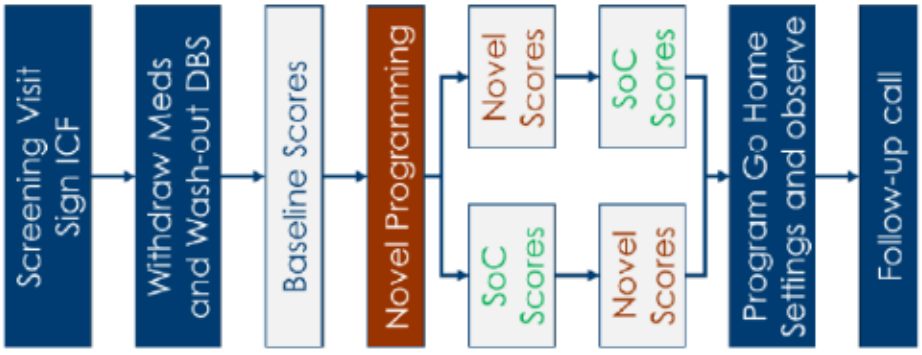
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					new programming method for the Directional Lead.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	







2. Protocol Synopsis

Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation **CLOVER-DBS**	
Study Objective(s)	The first exploratory objective of this study is the evaluation of the performance of a novel Deep Brain stimulation (DBS) programming method compared to standard of care programming (SOC) methods for current and new components of the Vercise System. The second exploratory objective is the further development of the novel DBS programming method based on the gained knowledge.
Indication(s) for Use	Parkinson's Disease.
Commercial Device already implanted	Boston Scientific Neuromodulation (BSN) Vercise™ System.
Control device	None; each subject will serve as their own control.
Study Design	Prospective, multi-center study with randomized and double-blinded evaluation phase. 

Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation **CLOVER-DBS**	
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Primary Endpoint	There will be no primary endpoint as the study is exploratory.
[redacted]	[redacted]

Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation CLOVER-DBS	
	[redacted]
Method of Assigning Subjects to Treatment	All eligible patients who consent to participation and have met all of the inclusion and none of the exclusion criteria will be evaluated using additional stimulation parameters based on novel programming method.
Follow-up Schedule	• Screening (0 to 8 weeks prior to Programming Visit). • Programming Visit. • Follow-up phone call 7±3 days after the Programming Visit. The overall study will be considered complete when the last subject completes their Follow-up phone call 7±3 days after their Programming Visit.
[redacted]	[redacted]

Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation

CLOVER-DBS

[redacted]	[redacted]
Inclusion Criteria	IC1. Implanted bilaterally in STN or GPi with a Vercise™ DBS system for Parkinson's disease, including directional leads, for at least four months and programming optimized according to standard of care with no changes to electrode configuration of primary settings for at least four weeks. IC2. Diagnosis of bilateral idiopathic PD with the presence of at least one of bradykinesia or tremor. IC3. MDS-UPDRS subset III score of ≥25 in the pre-operative meds off state. IC4. DBS must improve PD symptoms by ≥25% in the meds off state, as measured by MDS-UPDRS subset III score. IC5. Able to understand the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed. IC6. Be at least 18 years of age. IC7. [redacted]
Exclusion Criteria	EC1. Any significant psychiatric problems, including unrelated clinically significant depression as determined by the investigator. [redacted] [redacted]
Statistical Methods	

Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation CLOVER-DBS	
Primary Statistical Hypothesis	None
Statistical Test Method	Descriptive statistics for the exploratory endpoints will be generated, stratified by groups of subjects who used the same version of the novel programming method.
Sample Size Parameters	Sample size not determined in a prospective manner.

[redacted]

[redacted]

[redacted]

[redacted]

4. Introduction

4.1. *Background*

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 motor symptoms 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). However, the increase of available options to optimize DBS settings due to technology developments makes it practically impossible to manually explore the clinical benefit of these options on each patient (12). The novel algorithm investigated in this study aims to facilitate and automatize the exploration of the available options to optimize DBS settings, and previous versions of it have already delivered promising acute results (13-15), but longer term results are still missing.

4.2. *Study Rationale*

This study will compare various program settings for the bilateral stimulation of the STN or GPi using the BSC implantable Vercise™ DBS System for the treatment of levodopa-responsive, moderate to severe idiopathic PD.

[redacted]

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

[redacted]

5.3. *Device/Equipment Accountability*

Patients who have already been implanted with the Boston Scientific Vercise™ System are eligible for enrollment. Accountability is therefore not applicable. No investigational equipment will be used as test equipment. Test equipment accountability is required, if applicable.

6. Study Objectives and Endpoints

The first exploratory objective of this study is the evaluation of the performance of a novel DBS programming method compared to standard of care (SOC) programming methods for current and new components of the Vercise System. The second exploratory objective is the further development of the novel DBS programming method based on the gained knowledge.

There will be no primary endpoint as the study is exploratory.

Exploratory endpoints are:

- Difference in the amount of time and number of steps to program using the novel programming method as compared to the SOC programming method.
  - Note: The time and number of steps to program for the SOC method will be estimated by the physician based on subject's interrogation and the subject's medical files.
- Difference in bradykinesia and tremor scores obtained from novel method settings versus from SOC settings (from MDS-UPDRS III questionnaires and/or optionally using external sensors).
- Difference in upper extremity rigidity scores obtained from novel method settings versus from SOC settings (from MDS-UPDRS-III and/or optionally using external sensors).
- Difference in MDS-UPDRS-III scores obtained from novel method settings versus from SOC settings.
- Number of Subjects provided with novel algorithm derived stimulation settings as go-home DBS settings after the Programming Visit.
- Number of Subjects that kept novel algorithm derived stimulation settings as active DBS program at the Follow-up phone call.
- Clinical Global Impression of Change-Clinician (CGIC-C) and Clinical Global Impression of Change-Subject (CGIC-S) outcomes.
- Clinician and Subject DBS settings preference.

7. Study Design

Prospective, multi-center study with randomized and double-blinded evaluation phase.

7.1. *Scale and Duration*

[redacted]

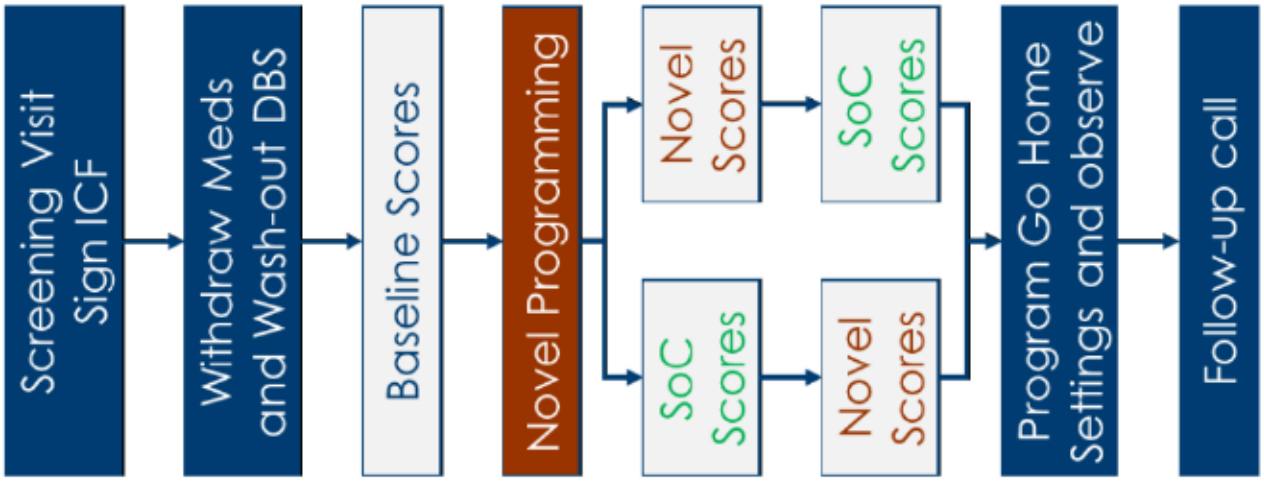


Figure 7.1-1: CLOVER-DBS Study Design

7.2. *Treatment Assignment*

Eligible patients who consent to participation and have met all inclusion and none of the exclusion criteria will be assigned a unique subject identifier. [redacted]

Randomization will take place using sealed envelopes, using a pre-generated randomization table, stratified by site to ensure approximate balance of treatment allocation within each site. [redacted]

[redacted]

8. Subject Selection

8.1. *Study Population and Eligibility*

Up to 100 randomized subjects may be included in the study. Subjects will generally be recruited from physician's practice and will have had a commercially-approved BSC Vercise™ System implanted for at least four months and their programming unchanged for at least 4 weeks.

The following section outlines the specific inclusion and exclusion criteria for the study. Each patient must meet all of the inclusion criteria and have none of the exclusion criteria prior to enrollment.

8.2. *Inclusion Criteria*

Patients 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	IC1. Implanted bilaterally in STN or GPi with a Vercise™ DBS system for Parkinson's disease, [redacted] IC2. Diagnosis of bilateral idiopathic PD with the presence of at least one of bradykinesia or tremor. IC3. [redacted] IC4. DBS must improve PD symptoms by ≥25% in the meds off state, as measured by MDS-UPDRS subset III score. IC5. Able to understand the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed. IC6. Be at least 18 years of age. IC7. [redacted]

8.3. *Exclusion Criteria*

Patients 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. No vulnerable populations will be enrolled in this study. See Section 24 for the definition of a vulnerable patient.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	EC1. Any significant psychiatric problems, including unrelated clinically significant depression as determined by the investigator. [redacted]

9. Subject Accountability

9.1. *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.

9.2. *Withdrawal*

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

Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent; study non-compliance, or death. 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 up to the point of subject withdrawal and a "Subject End of Study" form (or equivalent) must be completed.

If the withdrawal is due to the investigator's discretion, the investigator should return programming to the initial settings and observe the subject for one hour to ensure no adverse events occur.

Additional 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. All open adverse events should be closed or documented as unresolved. Data collected up to the point of subject withdrawal may be used for study analysis, unless local regulations apply.

Withdrawn subjects who have not reached randomization will be replaced.

9.3. *End-of-Study Definition*

A subject is considered to have completed the study if he or she has completed the screening and programming visits as well as the follow-up phone call and the scheduled procedures shown in the Data Collection Schedule.

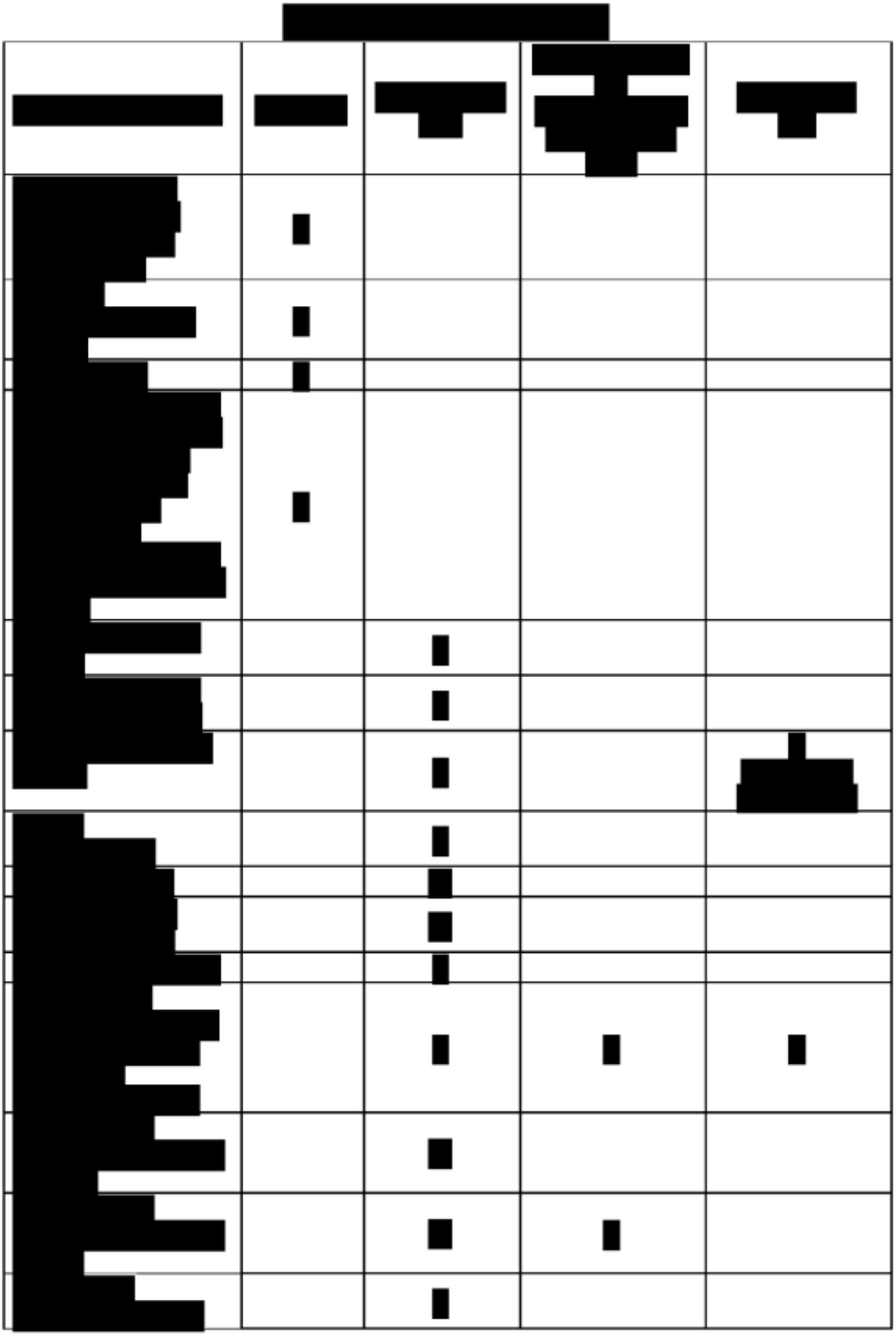
The end of the study is defined as completion of the last visit or procedure shown in the Data Collection Schedule in study globally:

- The maximum number of 100 subjects is randomized.
- The study is terminated at any time, at the Sponsor's discretion.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in Table 10.1-1.



[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

[redacted]

10.2. *Study Candidate Screening*

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

10.3. *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.

10.4. *Screening Visit*

The screening assessments should be completed within 8 weeks prior to the Programming Visit. It can be completed on the same day as the Programming Visit.

[redacted]

10.5. *Programming Visit*

The Programming Visit must be completed within 8 weeks of the screening assessment.

[redacted]

[redacted]

10.6. *Follow-up Phone Call (7±3 days after the Programming visit)*

Each subject will be contacted via phone 7±3 days after the completion of the Programming Visit. [redacted]

10.7. *Unscheduled visit(s)*

Unscheduled visits may occur at any time between the end of the Programming Visit and the Follow-up Phone Call for reprogramming or for evaluation of a possible adverse event (AE). These visits can be in person or via a phone call. [redacted]

10.8. *Study Completion*

Each subject will complete the study after the Follow-up phone call has been done.

10.9. *Source Documents*

Table 10.9-1 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.

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.9-1.

Table 10.9-1: 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 site
Clinician programmer printouts for programming information about trialed settings, clinical responses, and impedance and IFP measurements	Retain at site
Clinician and subject clinical evaluations (e.g. (MDS-UPDRS III, rigidity, Global Impression of Change for clinician and subject, DBS settings preference for clinician and subject)	Retain at site
Novel method derived clinical evaluations (e.g. Clinical Effects Map) and if applicable, external Sensor ratings.	Retain on a cloud-based server
Imaging pre and post implant procedure	Retain at the site, de-identified copies on a cloud-based server

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

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

11.1.1.1. Hypotheses

No formal hypothesis has been defined.

11.1.1.2. Sample Size

The sample size has not been determined in a prospective manner.

11.1.1.3. Statistical Methods

Descriptive statistics for the exploratory endpoints will be generated, stratified by groups of subjects who used the same version of the novel programming method.

11.1.2. Exploratory Endpoints

Several exploratory endpoints are included in this study to explore the effect of treatment on additional outcomes. The exploratory endpoints are intended to generate hypotheses for future studies. Consequently, no correction for multiple testing will be performed for the exploratory endpoints. All exploratory endpoints will be clearly identified as such in study reports.

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

All exploratory endpoints will be analyzed on an intent-to-treat basis.

11.2.2. Control of Systematic Error/Bias

Selection of study candidates will be made from the Investigator's usual patient population. All patients meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be eligible for participation in the study. The reasons for exclusion, for patients who sign an informed consent form but are not included in the study, will be indicated. Subjects who complete the novel programming will be randomly allocated into the two arms of the evaluation phase of the study, minimizing the systematic error.

11.2.3. Number of Subjects per Investigative Site

There are no restrictions to the number of subjects enrolled per investigative site. The enrollment will be competitive until the maximum number of subjects in the study is reached.

11.3. *Data Analyses*

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

11.3.1. Interim Analyses

Throughout the study, there will be ongoing interim analyses where the data collected can be analyzed to determine the efficacy of the novel programming method and improve its performance.

12. Data Management

12.1. *Data Collection, Processing, and Review*

The questionnaires/forms collected on paper will be transmitted from the site via fax or email and stored on the secure server. The investigator provides his/her signature on the appropriate paper case report forms.

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

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

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.

[redacted]

12.3. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements. 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 prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody

must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. Deviations

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

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using paper CRF. Sites may also be required to report deviations to the EC/REB, and the 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 notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

14. Compliance

14.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in the spirit of 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 applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC/REB 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/REB or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of

Helsinki, any conditions of approval imposed by the reviewing EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the 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, and assess (seriousness and relationship to the device/study procedure) every adverse event and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).

- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- 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.

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

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, 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.

14.3. *Ethics Committee / Research Ethics Board*

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

A copy of the written EC/REB 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. 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/REB before the changes are implemented to the study. All changes to the ICF will be EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF.
Annual EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or EC/REB requirements. Copies of the study reports and the EC/REB continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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

14.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during testing required by the protocol. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating study equipment

- Performing lead diagnostic testing and impedance or induced field potential measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from programmers, and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed form
- Print out programming reports directly from the programmer and provide original printouts to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

14.5. *Insurance*

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

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to

have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

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

16. Potential Risks and Benefits

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™ 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.

16.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

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

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

- Subjects may find it difficult, uncomfortable, or tiresome to complete study visits, 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.

16.3. *Possible Interactions with Concomitant Medical Treatments, if applicable*

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.

16.4. *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.

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 subject.
- 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.

16.5. *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 previously determined according to standard of care programming approaches can be identified.

16.6. *Risk to Benefit Rationale*

The purpose of this study is to develop a programming algorithm to support clinicians with efficient programming now that new DBS systems increase the options of programming exponentially. The additional programming that is required for this study has a similar risk-to-benefit ratio as for programming sessions with other DBS systems and is within reason for foreseeable risks. However, studies do not always predict all side effects that may be experienced. Observation of all subjects is required as outlined in the protocol.

17. Safety Reporting

17.1. *Reportable Events by Investigator to Boston Scientific*

After the informed consent is signed and the subject is considered enrolled in the study (as defined in the Subject Accountability section), whether prior to, during, or subsequent to the study procedure, the investigator must record, assess and report the following events to BSC::

- Serious Adverse Device Effects(SADEs)
- Serious Adverse Events (SAEs) related to the Study Procedure
- Adverse Device Effects (ADEs)
- Adverse Events (AEs) related to Study Procedure
- Device Deficiencies (DDs)
- Serious Adverse Events (SAEs) that are unrelated to the Study Device and unrelated to the Study Procedure
- Serious (Public) Health Threats (SPHTs)

The investigator is also responsible for recording, assessing, and reporting new and/or updated information in relation to the already reported events in a timely fashion.

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

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

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

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 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 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated.

Table 17.2-1: Safety Definitions

Term	Definition
	NOTE 1: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other 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 or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated 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 17.2-1: 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**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the device under study.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

NOTES:

- 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.

17.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE to the study device(s) (hardware and stimulation) and study procedure. See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device(s) (Device Under Study) 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 study device or the procedures related to the use of the study 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 study 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 study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases 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 study device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

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

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

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 Procedure Related AEs: AEs that can reasonably be attributed to a study protocol required procedure.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1-1. 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) and Device Deficiencies for each subject during the subject's participation in the study.

Table 17.4-1-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Adverse Event	Complete AE CRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through end of study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Device Effects	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) 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 CRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

Event Classification	Communication Method	Communication Timeline post-market studies* (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Device Effects (including study procedure related events)	Complete AE CRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device. Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Adverse Device Effects : In a timely manner but not later than 30 business days after becoming aware of the information • Reporting required through end of study • Upon request of sponsor

17.5. *Device Deficiencies*

Device deficiencies will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis. Instructions for returning the device(s) are described in the Standard Operating Procedure (SOP) 90149137 Used Medical Device Return Shipment. 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 CRF.

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

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

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

18. Informed Consent

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

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted

by BSC or its delegate (e.g. CRO), and approved by the site's EC/REB, 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/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

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

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject 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 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 (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/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during 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/REB. The new version of the ICF must be approved by the EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC/REB. The EC/REB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

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

20. Suspension or Termination

20.1. *Premature Termination of the Study*

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

20.1.1. Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the EC/REB 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/marketing of the device.

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

Any investigator, or associated 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 ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3. *Requirements for Documentation and Subject Follow-up*

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

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

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

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

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

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled 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 subjects. The EC/REB and regulatory authorities, as applicable, will be notified. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Study Registration and Results

21.1. *Study Registration*

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

21.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, 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.

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

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

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

[redacted]

[redacted]

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

[redacted]

24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in Table 24.1-1.

Table 24.1-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CA	Competent Authority
CRF	Case Report Form
CRO	Contract Research Organization
DBS	Deep Brain Stimulation
DFU	Directions for Use
EC	Ethics Committee
ETS	External Trial Stimulator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPi	Globus Pallidus internus
HCP	Health Care Personnel
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ICMJE	International Comm ittee of Medical Journal Editors
IEC	Independent Ethics Committee
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Standards Organization
mA	milliamps
MEDDEV	Medical Device Directives
PC	Primary Cell
PD	Parkinson's disease
REB	Research Ethics Board
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Effect
STN	Subthalamic nucleus
UADE	Unanticipated Adverse Device Effect
MDS-UPDRS III	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III
USADE	Unanticipated Serious Adverse Device Effects

24.2. *Definitions*

Terms are defined in Table 24.2-1.

Table 24.2-1: Definitions

Term	Definitions
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.
Source Data *Ref: ISO 14155*	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 *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data
Vercise™	The Vercise™ DBS system manufactured by Boston Scientific Neuromodulation
Vulnerable Patients	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response
Abbreviations are defined in Table 24.1-1	