# Clinical Investigation Plan

## ABT-CIP-10245
## EVIDENT
## Evaluation of the Infinity Deep Brain Stimulation Electrode Screening Mode Tool

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|---|---|
| Version Number | Ver. D |
| Date | 08 April 2020 |
| Planned Number of Sites and Region(s) | Up to 5 sites in the United States |
| Clinical Study Type | Prospective, non-randomized, single-arm, multi-center, post-market clinical study |
| Abbott Medical Expert | Dr. Binith Cheeran |
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| CIP Author of Current Version | Florence Defresne |

# Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Site Principal Investigator

| |
|---|
| Printed name: |
| Signature: |
| Date: |

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**COMPLIANCE STATEMENT:**

This clinical study will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56,21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11and 45 CFR part 46). The conduct of the clinical study will be approved by the appropriate Institutional Review Board (IRB) of the respective investigational site.

# Clinical Investigation Plan

## 1.0 INTRODUCTION

This document is a clinical investigation plan (CIP) for the clinical study of the Electrode Screening Mode tool, hereafter referred to as the Informity™ tool, on Abbott's Clinician Programmer for the Infinity™ deep brain stimulation (DBS) system. This clinical study is intended to characterize the clinical performance of the Informity tool in programming Infinity DBS systems in patients with Parkinson's disease (PD) or essential tremor (ET). This clinical study is sponsored by Abbott.

This clinical study will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

## 1.1 Background and Rationale

### 1.1.1 Background

Deep brain stimulation (DBS) has become an indispensable therapeutic tool for treating Parkinson's disease, essential tremor, and dystonia, and provides significant symptom relief and quality of life improvement with minimal risk [1]. It is preferred over other surgical treatments due to its adjustability, reversibility, durability, and robust clinical effectiveness and safety.

DBS modulates dysfunctional circuits in the brain so that the brain can function more effectively. This is accomplished by sending continuous electrical signals to specific target areas of the brain, which overrides neural activity that causes neurological dysfunctions. These targets include the subthalamic nucleus (STN), globus pallidus interna (GPi), and ventral intermediate (Vim) nucleus of the thalamus.

Patients with DBS experience considerable improvements in their motor symptoms and are able to greatly reduce their medications [2-4]. DBS allows for both unilateral and bilateral coverage of symptoms, can be tailored to a patient's clinical status by adjusting stimulation parameters, and can provide continuous symptom control 24 hours a day with minimum patient and clinician involvement. The electrodes and electrical systems that provide stimulation are generally very well tolerated with no significant changes in surrounding brain tissue [5].

Despite the proven efficacy of DBS, the benefit of this therapy is highly dependent on the location of the DBS lead and the distribution of the stimulation field within the brain anatomy. DBS requires millimeter accuracy in targeting of specific deep brain nuclei, and precise control over the volume of tissue activated (VTA) via programming of stimulation parameters. When the lead is misplaced or the system is incorrectly programmed, this may cause electrical current to spread to the surrounding associative, motor and limbic areas running near the target nuclei, which can lead to side effects. Common side effects include cognitive impairment, memory deficits, difficulties with speech, disequilibrium, dysphagia, and motor and sensory disturbances [6].

Conventional DBS leads use omnidirectional electrodes that disperse current axially and symmetrically around the activated contacts. Given the radial dispersion of current, a high level of precision is necessary in lead placement to ensure effective therapy [7, 8]. Clinical studies have indicated that accurate placement of DBS leads is correlated to clinical efficacy [9, 10]. Further, limitations in the omnidirectional electrode design translate to restrictions in the ability to sculpt the shape and size of the VTA, resulting in inadequate activated tissue volumes or inaccurate targeting of therapeutic regions [9, 11, 12].

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Recently, the development of directional DBS leads with segmented electrodes allows for focal current steering and improved clinical effectiveness [7, 11, 13, 14]. Computational modeling studies have shown that segmentation of the electrodes allows for expanded programming options, which could potentially reduce side effects, widen the therapeutic range, and lower the therapeutic current [12, 13, 15]. By using segmented electrodes to control the shape of the VTA, the delivered stimulation field better fits the anatomy of the therapeutic target (Figure 1). Based on a computational model developed by Keane et al, smaller directionally segmented electrodes demonstrated superior targeting of the cerebello-thalamo-cortical pathway, especially in cases of misaligned DBS leads [7]. Modelling also suggests that segmentation of the electrode allows for an increase in magnitude of the activating function and electrode impedance while lowering the required stimulation intensity; thus, creating a greater radial distance of the VTA when compared to standard electrodes [13, 14]. The targeted areas within anatomical structures (STN, GPi, and Vim thalamus) have restricted sizes that are associated with effective treatment. Figure 2 depicts a relative illustration of the DBS targets and the target areas within anatomic structures associated with effective treatment. Shaping the VTA with respect to the position of the electrode segment and target structure allows for improved therapeutic outcomes.

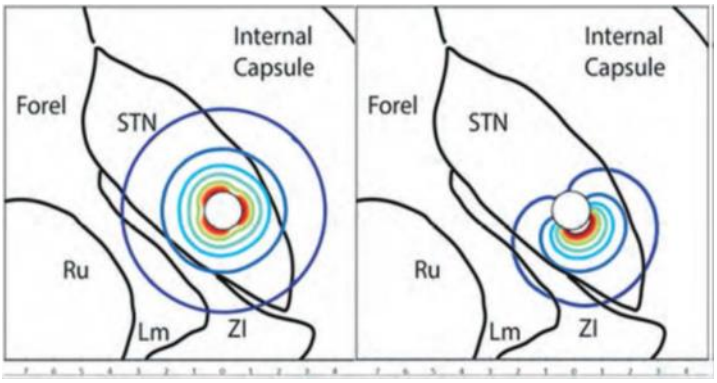


**Figure 1:** Finite element model comparison of (A) omnidirectional stimulation versus (B) unidirectional stimulation using segmented electrodes.

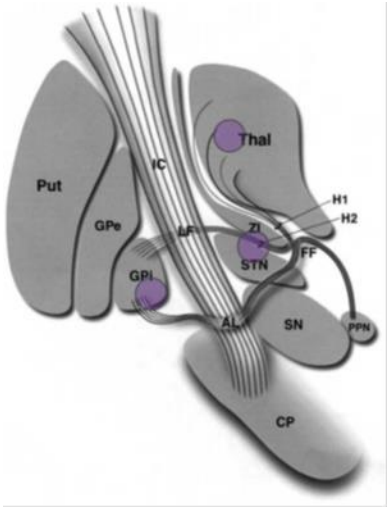


**Figure 2:** DBS targets [8]

The 8 channel Infinity DBS system incorporates this concept of segmentation and directionality. This system includes directional leads, extensions, implanted pulse generators, clinician programmers, and patient controllers. Numerous publications with similar DBS systems and the market experience associated with the currently marketed Infinity DBS system demonstrate the safety and performance of the 8 channel directional DBS leads, extensions and related accessories for treatment of movement disorders.

The efficacy of directional DBS (dDBS) for the treatment of patients with movement disorders is supported with data from three prospective clinical studies. Pollo et al (2014) conducted a prospective, single-center acute study to assess the effectiveness of dDBS in PD and tremor patients [9]. Compared to omnidirectional mode, directional stimulation in the best direction had a therapeutic window (current difference between side effects and therapeutic benefit) that was 41.3% wider than omnidirectional stimulation, and a therapeutic amplitude that was 43% lower than omnidirectional stimulation. Having a wider therapeutic window allows for expanded programming options, especially in cases of lead migration or brain shift, without a need for surgical intervention to regain therapeutic benefit. No adverse events were observed during the implantation of and stimulation using the dDBS lead. An acute evaluation of a dDBS lead was also conducted by Contarino et al (2014) [16]. Directional stimulation proved effective in this study in that it reduced the appearance of side effects, while widening the therapeutic window by redirecting the field of stimulation away from the anatomical structures responsible for the unwanted stimulation effects. No unexpected adverse events were observed during the implantation of and stimulation using the dDBS lead. Finally, Steigerwald et al (2016) performed an assessment of dDBS leads in Parkinson's disease patients, and found that directional current steering increased the therapeutic window size compared to omnidirectional stimulation, although in a highly patient-specific manner [17]. No unexpected adverse events were reported with the use of the dDBS lead.

The full benefits of dDBS are only realized if the stimulation parameters are selected appropriately to focus the VTA within the targeted brain area and avoid non-targeted brain regions. The Informity tool, available within the Clinician Programmer iPad application (Artemis version 3.7 or later), provides a standardized workflow to guide clinicians or trained healthcare providers through the DBS monopolar review screening process. This process involves assessment of the stimulation amplitudes that produce partial or complete therapeutic benefits and transient or sustained side effects, and is performed by individually testing each of the different electrodes on the dDBS lead. The Informity tool enables the neurologist to simultaneously perform this testing on a patient and record the results (Figure 3). Moreover, the tool allows the neurologist to review the results in different formats to aid in the selection of the best contact configuration for that patient (Figure 4). The selection of the best contact configuration is made on the basis of maximizing the width of the therapeutic window and minimizing stimulation power (total electrical energy delivered [TEED]).

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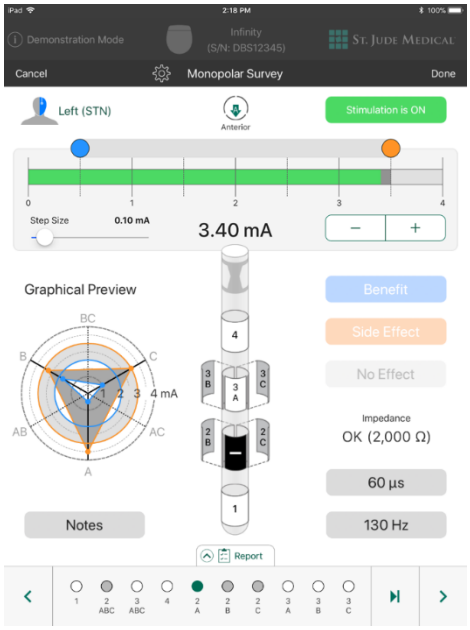


**Figure 3:** Interface of the Informity tool during the monopolar review screening process.

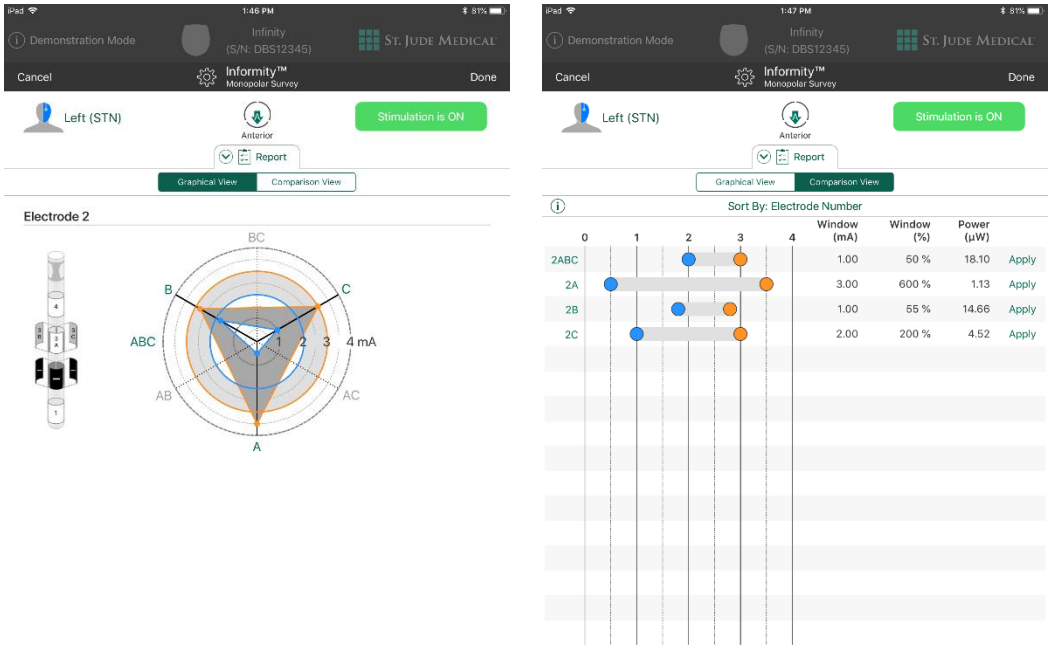


**Figure 4:** Interface of the Informity tool showing the results of the monopolar review screening process in a graphical view (left) and a comparison table view (right).

### 1.1.2 Rationale for Conducting this Clinical Study

The purpose of this post-market clinical study is to characterize the clinical performance of the Informity tool in programming Infinity DBS systems in patients with PD or ET.

# Clinical Investigation Plan

## 2.0 CLINICAL STUDY OVERVIEW

### 2.1 Clinical Study Objective

#### 2.1.1 Primary objective

The objective of this clinical study is to characterize the clinical performance of the Informity tool in programming the Infinity DBS system for treatment of Parkinson's disease and essential tremor.

### 2.2 Device(s) To Be Used in the Clinical Study

#### 2.2.1 Name of the Device(s) Under Investigation

| Device name | Model/ Type | Serial/Lot Controlled | Manufacturer | Region/ Country | Investigational or Market Released | MRI Status |
|---|---|---|---|---|---|---|
| Infinity IPG | 6660, 6662 | Serial Controlled | St. Jude Medical* | USA | Market Released | MR Conditional |
| Directional Lead for the Infinity DBS System | 6170, 6171, 6172, 6173 | Lot Controlled | St. Jude Medical* | USA | Market Released | MR Conditional |
| Infinity DBS System 8 Channel Flex Extension | 6371, 6372, 6373 | Lot Controlled | St. Jude Medical* | USA | Market Released | MR Conditional: 6371, 6372<br>MR Unsafe: 6373 |
| Clinician Programmer App (Artemis™ version 3.7 or later) | 3874 | Serial Controlled | St. Jude Medical* | USA | Market Released | Not applicable |
| Patient Controller App | 3875 | Serial Controlled | St. Jude Medical* | USA | Market Released | Not applicable |

* St. Jude Medical is an Abbott company

This post-market study is investigating the Informity tool on the Clinician Programmer App (Artemis version 3.7 or later), which is illustrated in Figures 3 and 4 of Section 1.1.1. Further details about the Clinician Programmer App are provided in the Instructions for Use (IFU).

#### 2.2.2 Indications for Use

The indications for use of the Clinician Programmer App (Artemis version 3.7 or later) and other devices to be used in this study are bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive

therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease that are not adequately controlled by medications, and unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability.

### 2.2.3 Description of the Device(s) Under Investigation

Please refer to the respective IFU for the list of anticipated adverse effects and additional information regarding the device used in this clinical study.

## 3.0 CLINICAL STUDY DESIGN

This is a prospective, non-randomized, single-arm, multi-center, post-market clinical study designed to evaluate Abbott's Informity tool for Infinity DBS systems.

This clinical study will be conducted at up to 5 centers in the United States.

Up to 40 patients will be enrolled in the study. Of these subjects, up to 20 will have PD and up to 20 will have ET. All patients will have received DBS systems prior to enrolling in the study.

The primary and secondary endpoints will be evaluated when all subjects have completed their 6-month follow-up visit.

## 3.1 Clinical Study Procedures and Follow-up Schedule

The flow chart and the follow-up requirements of this clinical study are described below.

## Clinical Investigation Plan

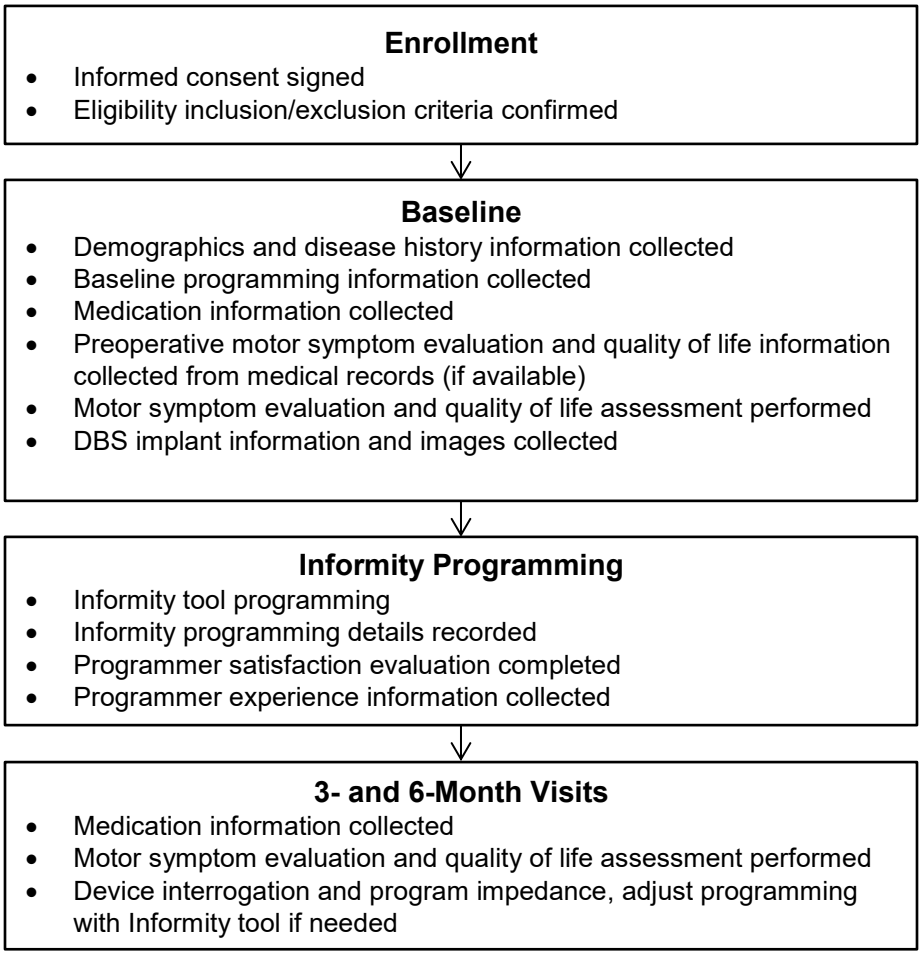


**Figure 5**: Clinical Study Flow Chart

Patients who currently have an Infinity DBS system and meet the standard requirements will be approached to participate in the study. The patient will be informed about the study to determine if he/she is interested in participating. If the patient provides informed consent, then he/she will be screened according to the inclusion/exclusion criteria. If the patient meets the study inclusion criteria and none of the exclusion criteria, he/she is enrolled in the study and becomes a study subject.

At the baseline visit following enrollment, information will be collected on subject demographics and disease history, baseline programming parameters, medication, preoperative motor symptom and quality of life assessments, and DBS implant details. A motor symptom evaluation and quality of life assessment will also be performed at baseline. Subsequently, subjects will undergo Informity programming with the Informity tool, and programming details, programmer experience and programmer satisfaction will be recorded. Follow-up visits will be conducted at 3 and 6 months after the Informity programming visit, for collection of medication information, motor symptom evaluation and quality of life assessment, and recording of programming details. In addition, the subjects will be assessed for any adverse events that should be documented and submitted to the Sponsor.

### 3.2 Measures Taken to Avoid and Minimize Bias

There are several measures that will be taken in this study to minimize bias. First, the person who uses the Informity tool to program a patient in the study must be different from the person who programmed the settings used at baseline. Second, the motor symptom evaluation will be evaluated by a blinded assessor.

Since this study design is open-label and non-controlled, there is a possibility of bias from placebo response following programming with the Informity tool.

### 3.3 Suspension or Early Termination of the Clinical Study

No formal statistical rule for early termination of the clinical study for insufficient effectiveness of the device under investigation is defined.

The Sponsor reserves the right to discontinue the clinical study at any stage or reduce the follow-up period with suitable written notice to the investigator.

Should the clinical study be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per commercial reporting requirements. No additional subject follow-ups will be required following an early termination or suspension.

Should this occur, the investigator shall return all clinical study materials to the Sponsor, and provide a written statement as to why the premature termination has taken place to the IRB (if applicable). All applicable clinical study documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

A Principal Investigator, IRB or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical study at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

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

## 4.0 ENDPOINTS

### 4.1 Primary Endpoints and Rationale

1) Change in therapeutic window size at the Informity programming visit compared to baseline
2) Change in TEED at the Informity programming visit compared to baseline

The primary endpoints were selected because it is hypothesized that they will be significantly improved following Infinity tool programming. Specifically, it is hypothesized that therapeutic window size will increase and TEED will decrease at the Informity programming visit compared to baseline.

### 4.2 Secondary Endpoints

1) Change in UPDRS III for PD subjects or Fahn-Tolosa-Marin tremor rating scale for ET subjects at 3- and 6-month follow-up visits compared to baseline
2) Change in quality of life measurement as measured by the PDQ-39 for PD subjects or QUEST for ET subjects at the 3- and 6-month follow-up visits compared to baseline
3) Duration of programming at the Informity programming visit compared to the most recent programming session prior to enrollment
4) Change in TEED at the 3- and 6-month follow-up visits compared to baseline

### 4.3 Descriptive Endpoint(s)

1) Evaluation of adverse events
2) Evaluation of programmer satisfaction with the Informity tool at the Informity programming visit
3) Change in medication usage at 3- and 6-month follow-up visits compared to baseline
4) Current (amplitude) at which first transient side effect is noted with each contact configuration tested by the Informity tool
5) Current at which first sustained side effect is noted with each contact configuration tested by the Informity tool
6) Current at which first partial therapeutic benefit is noted with each contact configuration tested by the Informity tool
7) Current at which first complete therapeutic benefit is noted with each contact configuration tested by the Informity tool
8) Programmer experience with DBS programming prior to testing Informity tool

## 5.0 SUBJECT SELECTION AND WITHDRAWAL

### 5.1 Subject Population

This clinical study will enroll male and female subjects between the ages of 18 and 80 years who have been diagnosed with PD or ET, and currently have an Infinity DBS system. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any study-specific procedures not considered standard of care.

### 5.2 Subject Screening and Informed Consent

#### 5.2.1 Subject Screening

Potential patients presenting at the clinical sites will be fully informed about the clinical study, following the established Informed Consent process (described in Section 5.2.2). Once a duly dated and signed Informed Consent form is obtained, the clinical study-specific screening procedures may begin.

The following assessments are performed as part of the screening process:

- Review of patient's medical records
- Review of patient's Infinity DBS system using the Clinician Programmer
- Interview with the patient

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Subjects must be screened for clinical study eligibility by a member of the site's clinical study team (physician and/or research coordinator) previously trained to the CIP, and if applicable will be entered into a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical study personnel will record the screening failure on a screening log as required.

Subject data will be collected following enrollment into the clinical study.

### 5.2.2 Informed Consent

The Investigator or his/her authorized designee will conduct the informed consent process, as required by applicable regulations and the center's IRB. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate, such as details of clinical study procedures, anticipated benefits, and potential risks of clinical study participation. Subjects must be informed about their right to withdraw from the clinical study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical study will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's IRB. The subject shall have adequate time to review, ask questions and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical study-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical study enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB according to the IRB's reporting requirements.

If, during the clinical study, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

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

## 5.3 Eligibility Criteria

### 5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site, review of a candidate patient's Infinity DBS system using the Clinician Programmer, and interview with a candidate patient. If some of the clinical tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical study. If ANY of the exclusion criteria are met, the patient is excluded from the clinical study and cannot be enrolled.

### 5.3.2 Inclusion Criteria

#### 5.3.2.1 General Inclusion Criteria

##### 5.3.2.1.1 Parkinson's disease patients

1. Patient must provide written informed consent prior to any clinical study related procedure.
2. Patient is 18 to 80 years of age.
3. Patient is diagnosed with Parkinson's disease for at least 4 years according to standard practice.
4. Patient is willing to maintain a constant dose of anti-Parkinson's disease medication indicated as best medical management for at least 1 month prior to study enrollment.
5. Patient is willing and able to comply with the follow-up schedule for the length of the study.
6. Patient has been implanted with an 8-channel directional Infinity deep brain stimulation system in the subthalamic nucleus (STN) within the last 12 months.
7. Patient has had stable deep brain stimulation programming settings for at least 1 month prior to study enrollment.

##### 5.3.2.1.2 Essential tremor patients

1. Patient must provide written informed consent prior to any clinical study related procedure.
2. Patient is 18 to 80 years of age.
3. Patient is diagnosed with essential tremor for at least 4 years according to standard practice.
4. Patient is willing to maintain a constant dose of anti-tremor medication indicated as best medical management for at least 1 month prior to study enrollment.
5. Patient is willing and able to comply with the follow-up schedule for the length of the study.
6. Patient has been implanted with an 8-channel directional Infinity deep brain stimulation system in the ventral intermediate (Vim) thalamus within the last 12 months.
7. Patient has had stable deep brain stimulation programming settings for at least 1 month prior to study enrollment.

### 5.3.3 Exclusion Criteria

#### 5.3.3.1 General Exclusion Criteria

1. Individuals unable to make the decision to participate in a clinical investigation on their own.
2. Patient is currently programmed with segmented electrodes, and cannot tolerate omnidirectional programming.
3. Patient is being evaluated for a lead revision.

4. Patient has untreated clinically significant depression.
5. Patient has dementia that interferes with their ability to co-operate or comply with study requirements or comprehend the informed consent, as determined by the investigator.
6. Patient abuses drugs or alcohol.
7. Patient is currently enrolled or plans to enroll in another concurrent study that may confound the results of this clinical investigation.
8. Patient has a confirmation of diagnosis of a terminal illness associated with survival <12 months.
9. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the patient's ability to participate in the clinical study or to comply with follow-up requirements, or impact the scientific soundness of the clinical study results.
10. Pregnant or nursing patients and those who plan pregnancy during the clinical study follow-up period.

## 5.4 Subject Enrollment

A patient is considered enrolled in the clinical study from the moment the patient provides written informed consent and has been confirmed to meet all inclusion criteria and none of the exclusion criteria. Omnidirectional programming should be used from the time of enrollment to the Baseline visit.

## 5.5 Subject Withdrawal

Each enrolled subject shall remain in the clinical study until completion of the required follow-up period; however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to Section 3.3.
- Subject undergoes a DBS system revision or DBS system explant
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons
- Subject's non-compliance
- Subject's participation is terminated by the PI or investigator, although the subject consented, since participation is no longer medically appropriate

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB as defined by their institution's procedure(s).

No additional follow-up will be required or data recorded from subjects once withdrawn from the clinical study. Subjects who withdraw will not be replaced by additional study subjects.

Before the subject is withdrawn from the study, the site should make attempts to schedule the subject for a final clinical study visit. At this final follow-up visit, the subject will undergo the following assessments:

- Motor symptom evaluation (stimulation ON/medication ON) performed by a blinded assessor
- Quality of life assessment
- Medication (only PD or ET medications)- indicate the drug category the subject is currently taking on a long term basis, i.e. no short term medication

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a certified letter should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

**Note:** Telephone contact with general practitioner, non-clinical investigation neurologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

## 5.6 Total Expected Duration of the Clinical Study

The total expected duration of the study is expected to be 24 months. Site activation and subject enrollment timelines can be difficult to predict, therefore the total duration of the study may end up being either shorter or longer than estimated.

## 5.7 Expected Duration of Each Subject's Participation

The total expected duration of each subject's participation in the clinical study is approximately 6 months.

## 5.8 Number of Subjects

Up to 40 subjects will be enrolled in the clinical study in order to analyze the primary endpoints.

## 5.9 Estimated Time Needed to Select Required Number of Subjects

The expected duration of enrollment is approximately 18 months.

# 6.0 TREATMENT AND EVALUATION OF ENDPOINTS

## 6.1 Baseline

### 6.1.1 Baseline Assessments

Subjects should have omnidirectional stimulation in use at the time of the Baseline visit. Informity should not be used. The following assessments and information will be collected at the Baseline visit:

- Demographics- subject's age and gender
- Disease history- subject's year of PD or ET symptom onset, year of initial PD or ET diagnosis, subject's impression of worst symptom (PD subjects only)
- Baseline programming- subject's current DBS programming parameters
- Therapeutic window of current parameter set
- TEED of current parameter set
- Duration of the most recent programming session preceding enrollment from the Clinician Programmer session logs (if available)
- Medication dosage (only PD or ET medications)- indicate the drug category the subject is currently taking on a long term basis, i.e. no short term medication
- Preoperative motor symptom evaluation (medication ON) from medical records (if available)
- Preoperative quality of life assessment from medical records (if available)
- DBS implant information
- Pre-op MRI and post-op CT images

An encrypted thumb drive containing de-identified MRI and CT images for all study subjects will be provided to sites and images will be sent to the Sponsor.

The following activities will be performed at the Baseline visit:

- Quality of life assessment
- Motor symptom evaluation (stimulation ON/medication ON) performed by a blinded assessor

The quality of life assessment must be performed prior to the motor symptom evaluation. Quality of life assessments will be performed using PDQ-39 for PD subjects, and QUEST for ET subjects (see Section 6.3.2). Quality of life assessment does not need to be collected if a patient was reprogrammed to omnidirectional stimulation on the same day as the Baseline visit. Motor symptom evaluation will be performed using UPDRS part III for PD subjects and Fahn-Tolosa-Marin tremor rating scale for ET subjects. For both evaluations, responses are rated on a 0 to 4-point scale where 0 indicates 'none' and 4 indicates 'severe' symptom. Motor symptom evaluation will be performed by a blinded assessor, who will not be aware of the subject's programming.

The Baseline visit can occur on the same day as the Enrollment visit, or on a separate day following the Enrollment visit. It should be ensured that the patient is programmed with omnidirectional stimulation upon enrollment. If the Baseline visit occurs on the same day, it is not necessary to collect quality of life measurements. The duration from the Enrollment visit to the Baseline visit must be less than or equal to 30 days.

## 6.2 Informity Programming Procedure

### 6.2.1 Procedures Involved in the Use of the Device Under Investigation

At the Informity Programming visit, the subject's Infinity DBS system will be programmed by a trained programmer (clinician or trained healthcare provider) using the Informity tool. The Clinician Programmer App IFU provides specific instructions for use of the Informity tool.

Subjects are to be instructed not to take their medication the night prior to or the morning of the Informity Programming visit; or depending on the type of medication the subject is taking (i.e. extended release or long acting) the investigator can use their clinical judgement to determine an adequate length of time that the subject should be off medication prior to the testing.

Using the Informity tool, multiple electrode contact configurations on each lead will be assessed by a programmer for therapeutic effects followed by assessment of side effects. The Best Segmented level (BSL) should be determined. Once the BSL has been determined, at a minimum, the three single segments at the BSL must be assessed. As the amplitude is increased by the programmer, the therapeutic effect on the motor symptoms will be based on the programmer's clinical judgement of partial and complete therapeutic benefit seen for the subject's primary motor symptoms. Once first therapeutic effect is determined, the programmer will test for transient and sustained side effects.

The width of the therapeutic window is defined as the electrical current at which a side effect appeared minus the electrical current at which complete therapeutic benefit was obtained. The TEED is defined as the total energy delivered by the system over an arbitrary period of time, and is determined from the programmed stimulation parameters and measured program impedance.

The programmer will review the results of the Informity tool to aid in selection of the electrode contact configuration that they will program the subject. The Balance Threshold or TW% ranking options must be evaluated in the decision process. The Informity Tool Programming Guidance document provides step-by-step instructions for using the Informity tool to select the electrode contact configuration. Subjects are expected to remain programmed with this configuration from the Informity Programming visit until the 3-month visit.

The programmer should use their clinical judgement to determine the amount of time required to rest between each electrode contact configuration evaluation. It is suggested to allow at least a 2-minute rest period between each electrode contact/segment tested. If desired by the subject or programmer, Informity Programming can be separated into two visits performed on back-to-back days in which the left-side or right-side DBS leads are separately programmed and evaluated (if the patient has bilateral DBS leads). If Informity Programming is performed over back-to-back days, then the programmer satisfaction survey is assessed on the second day.

The programmer who performs Informity tool programming must be different from the person who previously programmed that subject's DBS system.

The subject may be given a Patient Controller after the Informity Programming procedure, dependent on the clinician's recommendation for patient care.

The duration from the Baseline visit to the Informity Programming visit must be 21±7 days.

### 6.2.2 Assessments

The following will be collected during the Informity Programming visit:

- Informity programming data, programming parameters, duration of programming and program impedance.
- Programmer satisfaction survey
- Programmer Experience

## 6.3 Follow-up Assessments

### 6.3.1 Follow-up for All Subjects (Site Visit)

Follow-up visits are scheduled at 3 and 6 months after the Informity Programming visit. If Informity Programming is performed over back-to-back days, then follow-up visit timing is based on the date of the second day of programming.

At each visit, the following procedures and assessments must be completed:

- Quality of life assessment
- Motor symptom evaluation (stimulation ON/medication ON) performed by a blinded assessor
- Medication (only PD or ET medications)- indicate the drug category the subject is currently taking on a long-term basis, i.e. no short-term medication
- Interrogation of programmed settings and program impedance.

The quality of life assessment must be performed prior to the motor symptom evaluation. Motor symptom evaluation will be performed by a blinded assessor, who will not be aware of the subject's programming.

If in the Investigator's opinion, the selected DBS electrode contact configuration does not provide adequate therapy for the subject at a follow-up visit, the subject's DBS system parameters can be adjusted. by re-programming with the Informity tool. This re-programming should be performed using the same procedure detailed in Section 6.2.1, and by the same programmer who programmed the patient during the Informity Programming visit. If re-programming is performed, motor symptom evaluation must be performed before and after re-programming at the follow-up visit.

An unscheduled visit is defined as any visit that occurs outside of a specified study visit related to an adverse event or withdrawal of the patient from the study. Any routine programming that occurs outside of a study visit will be captured at the subsequent study visit. Any unscheduled visit needs to be documented by completing the Unscheduled Visit form and other appropriate forms if applicable (Adverse Event, Withdrawal, Programming, and Medication).

### 6.3.2 Patient Reported Outcome (PRO) Measures

The coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following PRO measures will be collected according to the CIP requirements (Sections 6.1.1 and 6.3.1):

- Parkinson's Disease Questionnaire (PDQ-39)

- Quality of Life in Essential Tremor Questionnaire (QUEST)

The Parkinson's Disease Questionnaire (PDQ-39) is a widely used validated questionnaire used to measure PD specific health status [18]. The self-administered questionnaire consists of 39 questions and takes approximately 10-20 minutes to complete with paper & pencil. The subject is instructed to answer one of five response categories depending on how often (from never to always) they have experienced the problem addressed by each item during the past month due to PD. There is a total of 8 dimensions that represent mobility, activities of daily living, emotional well-being, social support, cognition, communication and bodily discomfort. For each question, a 5-point ordinal scoring system is assigned (0 to 4), and the results are summed across all questions and scaled to a 100-point system. Lower scores reflect a better quality of life.

The Quality of Life in Essential Tremor Questionnaire (QUEST) is a disease-specific assessment used to measure the quality of life of ET patients [19]. The self-administered questionnaire consists of 30 questions and is completed with paper & pencil. The subject is instructed to answer one of five response categories depending on the frequency (from never to always) with which tremor was found to impact functional activity or was associated with specific feelings. For each question, a 5-point ordinal scoring system is assigned (0 to 4). The 30 items are divided into five sub-scales (physical/ADL, psychosocial, communication, hobbies/leisure, and work/finances), and the score for each sub-scale is expressed as a percentage of the total score possible for that sub-scale. Lower scores reflect less dissatisfaction or disability due to essential tremor.

### 6.3.3 Schedule of Events

| CIP Activity | Enrollment | Baseline | Informity Programming (21±7 days since Baseline) | 3 Months (±30 days) since Informity Programming | 6 Months (±30 days) since Informity Programming |
|---|---|---|---|---|---|
| Informed Consent Signed | X | | | | |
| Inclusion/Exclusion Criteria Check | X | | | | |
| Subject Demographics | | X | | | |
| Disease History | | X | | | |
| Baseline Programming | | X | | | |
| Programmer Experience | | | X | | |
| Medication | | X | | X | X |
| Motor Symptom Evaluation | | X | | X | X |
| Quality of Life Evaluation | | X | | X | X |
| Implant Information | | X | | | |
| Images Collected | | X | | | |
| Informity Programming | | | X | | |
| Satisfaction | | | X | | |
| Device interrogation and impedance measurement | | | | X | X |
| Adverse Event | If applicable | | | | |
| Deviation | | | | | |

| | |
|---|---|
| Withdrawal | |
| Product Out of Service | |

## 7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical study adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

### 7.1 Definition

#### 7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

**Note 1:** This definition includes events related to the medical device under investigation.

**Note 2:** This definition includes events related to the procedures involved.

**Note 3:** For users or other persons, this definition is restricted to events related to medical devices under investigation.

#### 7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or
    4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
    5. chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

**Note:** A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

### 7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships,

evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

## 7.3 Adverse Event

### 7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical study. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical study or the subject withdraws from the clinical study. All applicable adverse event data will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

All reportable adverse events will be collected on each subject through the 6-month follow-up visit, when each subject's participation in the study ends.

| Clinical Site | Reporting timelines |
|---|---|
| All Sites | Serious adverse events must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined. |

The date the site staff became aware the event met the criteria of an SAE per protocol must be recorded in the source document. The Investigator will further report the SAE to the local IRB according to the institution's IRB reporting requirements.

Records related to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

Reportable events to sponsor are considered:

- All adverse events related to the device, stimulation, and/or procedure regardless if serious or non-serious
- All death events

For unexpected failure modes or unexpected AEs, the site should follow their standard reporting practices for medical device reporting (MDR). As defined in 21 CFR 803, a MDR reportable event (or reportable event) is an event that device user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury. A device user facility must report deaths and serious injuries that a device has or may have caused or contributed to; establish and maintain AE files, and submit summary annual reports to FDA.

**Complaints reporting:** A complaint is defined as a deficiency related to its identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution. All device complaints/malfunctions should be reported to the Sponsor's Customer Service Department.

If the complaint does not involve an AE, the investigator must notify the Abbott Post Market Surveillance Department by submitting the complaint information via email to CCoordinators@abbott.com or by phone 972.309.8000 as soon as possible after becoming aware of the complaint.

### 7.3.2 Procedure for Recording and Reporting Subject Death

Should death occur, the investigator is requested to record death information in the hospital records and document the information on the Adverse Event CRF and submit to Sponsor per the serious adverse events reporting requirements stated in the 'Adverse Event Reporting Requirements' section (7.3.1).

- All efforts to obtain the details about the circumstances surrounding the patient death should be made by the Investigator.

The subject's death is an early conclusion of the subject's participation in the clinical investigation. Therefore, the Investigator is required to complete the Withdrawal CRF.

## 8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical study. Additional details on statistical analyses, including justification of clinical study design, sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoints, may be maintained in a separate Statistical Analysis Plan (SAP).

## 8.1 Statistical Analyses

### 8.1.1 Primary Effectiveness Endpoint Analyses

The hypotheses for the primary endpoints are that the Informity tool will identify DBS parameters that:

1. Have a larger therapeutic window size compared to programmed parameters at baseline
2. Have a lower TEED compared to programmed parameters at baseline

A comparison of therapeutic window and TEED will be performed for the contact configuration used at baseline, and the contact configuration used after Informity programming with the Informity tool, using a paired t-test. All statistical analyses will be conducted assuming a type-1 error rate of 0.05 unless specifically stated otherwise. The change in TEED from baseline to Informity programming will be used to calculate a corresponding battery longevity projection.

### 8.1.2 Secondary Effectiveness Endpoint Analyses

The hypotheses for the secondary endpoints are:

1. The Informity tool will identify DBS parameters that improve motor symptom scores compared to baseline
2. The Informity tool will identify DBS parameters that improve quality of life measurements compared to baseline.

The time required for programming with the Informity tool is shorter than that of the most recent programming session prior to enrollment.

For the change in motor symptom scores, a repeated measure analysis of variance (RMANOVA) will be conducted to determine statistical differences from baseline. Post-hoc Tukey's pairwise comparisons will follow to determine specific differences between follow-up visits. The change in quality of life measurement will also be analyzed using a RMANOVA followed by Tukey's pairwise comparisons. A comparison of the duration of programming will be performed for the programming session preceding enrollment, and the Informity programming session with the Informity tool, using a paired t-test. All statistical analyses will be conducted assuming a type-1 error rate of 0.05 unless specifically stated otherwise.

## 8.2 Timing of Analysis

The dataset will be frozen for analysis when all subjects have completed the 6-month follow-up visit and have evaluable primary endpoint data at the 6-month follow-up visit.

## 8.3 Subgroup Analysis

Subgroup analysis will be performed on the basis of diagnosis (Parkinson's disease or essential tremor). Subgroup analysis will also be performed for those subjects who were programmed with DBS contact 2 or 3 (full ring or individual segments) as a cathode at the Baseline visit.

## 8.4 Multiplicity

All statistical tests will be performed with a type-1 error rate 0.05, unless otherwise stated. Family-wise error for RMANOVA will be addressed using Tukey's pairwise post-hoc comparisons.

## 8.5 Procedures for Accounting for Missing Data

Missing data will be reported at each visit for each outcome. No imputations will be performed for missing data. If the session log data for the programming session prior to enrollment is missing or corrupted for a given subject, then this subject will not be included in the statistical analysis for the time required for programming.

## 8.6 Planned Interim Analysis

Interim analyses may be conducted after all subjects have completed the 3-month follow-up visit, and when all subjects in a diagnosis subgroup (Parkinson's disease or essential tremor) complete the 6-month follow-up visit.

## 8.7 Statistical Criteria for Termination

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

## 8.8 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

## 9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical study-related monitoring, audits, IRB review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this clinical study. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

## 10.0 QUALITY CONTROL AND QUALITY ASSURANCE

### 10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical study. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical study.

### 10.2 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

### 10.3 Training

#### 10.3.1 Site Training

All Investigators and clinical study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical study personnel will include, but is not limited to, the CIP requirements, investigational device usage, and clinical study personnel responsibilities. All Investigators and clinical study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical study personnel must not perform any CIP-related activities that are not considered standard of care at the site.

### 10.4 Monitoring

Sponsor and/or designee will monitor the clinical study over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical study according to the CIP and applicable regulations and has signed the Investigator Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical study and should have access to an adequate number of appropriate subjects to conduct the clinical study.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical study-related documents.

## 10.5 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB or equivalent committee of all CIP deviations in accordance with their specific IRB or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical study may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical study.

## 10.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical study records, including source documentation, for inspection during a Quality Assurance audit.

# Clinical Investigation Plan

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical study, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical study (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

## 11.0 DATA HANDLING AND RECORD KEEPING

For the duration of the clinical study, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical study progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB and clinical study monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical study.

### 11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient’s medical condition, treatment, dates of treatment, etc., into Sponsor’s data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

### 11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical study. All revisions will be tracked and document controlled.

### 11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical study:

- Medical history/physical condition of the subject before involvement in the clinical study sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical study referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, clinic notes, office notes, and any other pertinent patient records, including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs
- Subject's condition upon completion of or withdrawal from the clinical study
- Any other data required to substantiate data entered into the CRF

### 11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical study.

### 11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical study as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical study records.

## 12.0 ETHICAL CONSIDERATION

### 12.1 Institutional Review Board Review and Approval

Institutional Review Board (IRB) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical study. The approval letter must be received prior to the start of this clinical study and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to each institution's IRB requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical study is completed, the Investigator will advise his/her IRB of the progress of this clinical study, per IRB requirements. Written approval must be obtained from the IRB yearly to continue the clinical study, or according to each institution's IRB requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB and the Sponsor.

## 13.0 CLINICAL STUDY CONCLUSION

The clinical study will be concluded when:

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

## 14.0 PUBLICATION POLICY

The data and results from the clinical study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical study. The Investigators will not use this clinical study-related data without the written consent of the Sponsor for any purpose other than for clinical study completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will be responsible for determining whether to register the clinical study on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the clinical study should be registered, Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical study.

## 15.0 RISK ANALYSIS

### 15.1 Anticipated Clinical Benefits

If patients agree to take part in this study, there may or may not be direct medical benefits to an individual patient. A patient may receive improved therapy from the Infinity DBS system for treatment of the symptoms of Parkinson's disease or essential tremor following Informity programming with the Informity tool, but there is no guarantee that this will happen. The information gathered in this study will add to the understanding of treatment options for patients with Parkinson's disease or essential tremor. The scientific use of the data, which is gathered from this study, may help researchers discover better ways of programming DBS systems for treatment of Parkinson's disease or essential tremor and improving quality of life of patients with these movement disorders.

## 15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure are described in the IFUs. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

Deep brain stimulation complications, include, but are not limited to, the following:

- Device-related complications
  - Undesirable changes in stimulation related to cellular changes in tissue around the electrodes, changes in the electrode position, loose electrical connections, or lead fracture
  - Loss of therapeutic benefit as a result of change in electrode positions, loose electrical connections, or lead or extension fracture
  - Initial jolt or tingling during stimulation; jolting or shocking sensations
  - Infection
  - Paresthesia
  - Lead fracture, migration, or dislodgement
  - Misplaced lead
  - Extension malfunction, fracture, or disconnect
  - Deep brain stimulation system failure or battery failure within the device
  - Deep brain stimulation system malfunction or dislodgement
  - Spontaneous turning on or off of the IPG
  - Allergic or rejection response to implanted materials
  - Persistent pain, tightness, or redness at the incision sites or general pain
  - General erosion or local skin erosion over the IPG
  - Persistent pain, tightness, or discomfort around the implanted parts (e.g., along the extension path in the neck)
  - Impaired wound healing (e.g., incision site drainage) or abscess formation
  - Additional neurosurgical procedure to manage one of the above complications or to replace a malfunctioning component

- Stimulation-related complications or other complications
  - Worsening of motor impairment and Parkinson's disease symptoms including dyskinesia, rigidity, akinesia or bradykinesia, myoclonus, motor fluctuations, abnormal gait or incoordination, ataxia, tremor, and dysphasia
  - Paresis, asthenia, hemiplegia, or hemiparesis
  - Dystonia
  - Sensory disturbance or impairment including neuropathy, neuralgia, sensory deficit, headache, and hearing and visual disturbance
  - Speech or language impairment including, aphasia, dysphagia, dysarthria, and hypophonia
  - Cognitive impairment including attention deficit, confusion, disorientation, abnormal thinking, hallucinations, amnesia, delusions, dementia, inability to act or make decisions, psychic akinesia, long term memory impairment, psychiatric disturbances, depression, irritability or fatigue, mania or hypomania, psychosis, aggression, emotional lability, sleep

disturbance, anxiety, apathy, drowsiness, alteration of mentation, postural instability and disequilibrium
- Restless leg syndrome
- Supranuclear gaze palsy
- Hypersexuality or increased libido
- Decreased therapeutic response
- Urinary incontinence or retention
- Diarrhea or constipation
- Cardiac dysfunction (e.g., hypotension, heart rate changes, or syncope)
- Difficulty breathing
- Increased salivation
- Weight gain or loss
- Eye disorder including eye apraxia or blepharospasm
- Nausea or vomiting
- Sweating
- Fever
- Hiccups
- Cough
- Cramps
- Worsening existing medical conditions

Some models of this DBS system are Magnetic Resonance (MR) Conditional, and patients with these devices may be scanned safely with MRI when the conditions for safe scanning are met. Scanning under different conditions may cause device malfunction, severe patient injury, or death. For more information about MR Conditional DBS components and systems, including equipment settings, scanning procedures, and a complete list of conditionally approved components, refer to the MRI procedures clinician's manual for DBS systems. The St. Jude Medical MR Conditional neurostimulation system has been designed to minimize the potential adverse events that may cause patient harm. The following potential adverse events may occur in the MRI environment:

- Lead electrode heating resulting in tissue damage or serious patient injury
- IPG heating resulting in tissue damage in the implant pocket or patient discomfort or both
- Induced currents on leads resulting in unpleasant sensations or motor disturbances
- Damage to the IPGs, leads, or extensions causing the system to fail to deliver stimulation or causing the system to deliver overstimulation
- Damage to the functionality or mechanical integrity of the IPG resulting in the inability to communicate with the IPG
- Movement or vibration of the IPGs, leads, or extensions

Do not perform MRI on a patient if they have any model of this DBS system that is MR Unsafe (Section 2.2.1). Even if the neurostimulator has been removed, the patient should not have an MRI if any part of a MR Unsafe model of this DBS system is still implanted.

## 15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

There are no known incremental risks associated with the Informity tool under investigation.

## 15.4 Risks Associated with Participation in this Clinical Study

There may be some discomforts or inconveniences associated with the study tests and procedures. There is a risk of potential anxiety related to the sensitive nature of the questions asked during some of the assessments. Also, there is a risk of inconvenience of travel or the inability to work due to the need to return to the clinic for follow-up visits that are required for this study.

## 15.5 Steps Taken to Control or Mitigate Risks

The devices used in this study are FDA-approved devices in commercial distribution. In-depth recommendations, special precautions and instructions regarding use of the Informity tool are included in the IFU.

It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, and study monitoring to ensure adherence to the protocol. Stopping rules will be applied for subject safety through enrollment. All adverse events will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

## 15.6 Risk to Benefit Rationale

The risks of participating in this study are similar to the risks of having a DBS system under normal standard of care. Since patients who are enrolled in this study will already have a DBS system implanted, there is minimal additional risk from participating in the study. Moreover, there is potential benefit to the individual patient in receiving improved DBS therapy, and to the entire DBS patient population who may receive better therapy in the future. Therefore, the risk-to-benefit ratio is favorable for undertaking this study.

# Clinical Investigation Plan

## APPENDIX I: SITE CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Sponsor at:

Florence Defresne
Da Vincilaan 11
1935 Zaventem, Belgium
florence.defresne@abbott.com
+32 479 30 21 31

# Clinical Investigation Plan

## APPENDIX II: DEFINITIONS

*Long-term medication usage*: A planned indefinite course of treatment with a specific medication

*Transient side effects*: Side effects of deep brain stimulation that persist for less than 2 minutes

*Persistent side effects*: Side effects of deep brain stimulation that persist indefinitely, and at least 2 minutes during testing

*Partial benefit:* Therapeutic benefit from deep brain stimulation that involves response from only a part of the symptom complex, or does not meet the expected therapeutic response

*Complete benefit*: Therapeutic benefit from deep brain stimulation that meets the expected therapeutic response

# Clinical Investigation Plan

## APPENDIX III: BIBLIOGRAPHY

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## APPENDIX IV: LABELS/ DEVICE MANUALS

Copies of all current labeling and reference/technical manuals, including storage and handling, preparation for use and any intended re-use will be kept under separate cover, and is available upon request.

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## APPENDIX V: CASE REPORT FORMS

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

# Clinical Investigation Plan

## APPENDIX VI: INFORMED CONSENT FORM

The template informed consent form will be kept under a separate cover and is available upon request.

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## APPENDIX VII: MONITORING PLAN

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

# Clinical Investigation Plan

## APPENDIX VIII: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

| Amendment Number | Version | Date | Details | Rationale |
|---|---|---|---|---|
| Not Applicable | A | 20AUG2018 | First release of CIP | N/A |
| Not Applicable | B | 09OCT2018 | Insignificant Changes | N/A |
| Not Applicable | C | 06NOV2018 | Insignificant Changes | N/A |
| Not Applicable | C.3 | 26JUL2019 | 6 and 12 Month Addition | N/A |
| Not Applicable | D | 08APR2020 | Update software, allow previous directional stimulation, remove 1- and 12-month visits | Inclusion criteria were unnecessarily restrictive |

# Clinical Investigation Plan

## APPENDIX IX: CIP SUMMARY

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|---|---|
| **Clinical Study Name and Number** | ABT-CIP-10245<br>EVIDENT |
| **Title** | Evaluation of the Infinity Deep Brain Stimulation Electrode Screening Mode Tool |
| **Objective(s)** | The objective of this clinical study is to characterize the clinical performance of the Informity tool in programming the Infinity DBS system for treatment of Parkinson's disease and essential tremor. |
| **Device Under Investigation** | Informity tool on the Clinician Programmer App (Artemis version 3.7 or later) |
| **Number of Subjects Required for Inclusion in Clinical Study** | Up to 40 subjects with Parkinson's disease (N=20) or essential tremor (N=20) |
| **Clinical Study Design** | Prospective, non-randomized, single-arm, multi-center, post-market clinical study |
| **Primary Endpoints** | 1) Change in therapeutic window size at the Informity programming visit compared to baseline<br>2) Change in TEED at the Informity programming visit compared to baseline |
| **Secondary Endpoints** | 1) Change in UPDRS III for PD subjects or Fahn-Tolosa-Marin tremor rating scale for ET subjects at, 3 and 6 month follow-up visits compared to baseline<br>2) Change in quality of life measurement as measured by the PDQ-39 for PD subjects or QUEST for ET subjects at the 3- and 6-month follow-up visits compared to baseline<br>3) Duration of programming at the Informity programming visit compared to the most recent programming session prior to enrollment<br>4) Change in TEED at the 3- and 6-month follow-up visits compared to baseline |
| **Subject Follow-up** | 3- and 6-month site visits |
| **Inclusion Criteria** | Parkinson's Disease Patients<br>1) Patient must provide written informed consent prior to any clinical study related procedure.<br>2) Patient is 18 to 80 years of age.<br>3) Patient is diagnosed with Parkinson's disease for at least 4 years according to standard practice.<br>4) Patient is willing to maintain a constant dose of anti-Parkinson's disease medication indicated as best medical management for at least 1 month prior to study enrollment.<br>5) Patient is willing and able to comply with the follow-up schedule for the length of the study. |

# Clinical Investigation Plan

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|---|---|
| | 6) Patient has been implanted bilaterally with an 8-channel directional Infinity deep brain stimulation system in the subthalamic nucleus (STN) for a maximum of 12 months prior to study enrollment.<br>7) Patient has had stable deep brain stimulation programming settings for at least 1 month prior to study enrollment.<br><br>Essential Tremor Patients<br>1) Patient must provide written informed consent prior to any clinical study related procedure.<br>2) Patient is 18 to 80 years of age.<br>3) Patient is diagnosed with essential tremor for at least 4 years according to standard practice.<br>4) Patient is willing to maintain a constant dose of anti-tremor medication indicated as best medical management for at least 1 month prior to study enrollment.<br>5) Patient is willing and able to comply with the follow-up schedule for the length of the study.<br>6) Patient has been implanted with an 8-channel directional Infinity deep brain stimulation system in the ventral intermediate (Vim) thalamus for a maximum of 12 months prior to study enrollment.<br>7) Patient has had stable deep brain stimulation programming settings for at least 1 month prior to study enrollment. |
| **Exclusion Criteria** | 1) Individuals unable to make the decision to participate in a clinical investigation on their own.<br>2) Patient is currently programmed with segmented electrodes, and cannot tolerate omnidirectional programming.<br>3) Patient is being evaluated for a lead revision.<br>4) Patient has untreated clinically significant depression.<br>5) Patient has dementia that interferes with their ability to co-operate or comply with study requirements or comprehend the informed consent, as determined by the investigator.<br>6) Patient abuses drugs or alcohol.<br>7) Patient is currently enrolled or plans to enroll in another concurrent study that may confound the results of this clinical investigation.<br>8) Patient has a confirmation of diagnosis of a terminal illness associated with survival <12 months.<br>9) Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the patient's ability to participate in the clinical study or to comply with follow-up requirements, or impact the scientific soundness of the clinical study results.<br>10) Pregnant or nursing patients and those who plan pregnancy during the clinical study follow-up period. |