Abbott	Clinical Investigation Plan Cover Page

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PROGRESS
Post-Market Clinical Follow Up Evaluating the Infinity Deep Brain Stimulation Implantable Pulse Generator System
Study Document No: [redacted]
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Date: 25-NOV-2019

Sponsor

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Clinical Investigational Plan

Reference: [redacted]

"PROGRESS"

Post Market Clinical Follow Up Evaluating the Infinity Deep Brain Stimulation Implantable Pulse Generator System

Clinical Investigation Plan (CIP)

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROGRESS

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Reference #: [redacted]

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

Principal Investigator

Printed name: _____

Signature:_____

Date: _____

Coordinating Investigator/National Investigator/Medical Advisor

SIGNATURE PAGE

PROGRESS

[redacted]

Reference #: [redacted]

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

Coordinating Investigator:

Printed name: _____

Signature: _____

Date: _____

Co-Coordinating Investigator:

Printed name: _____

Signature: _____

Date: _____

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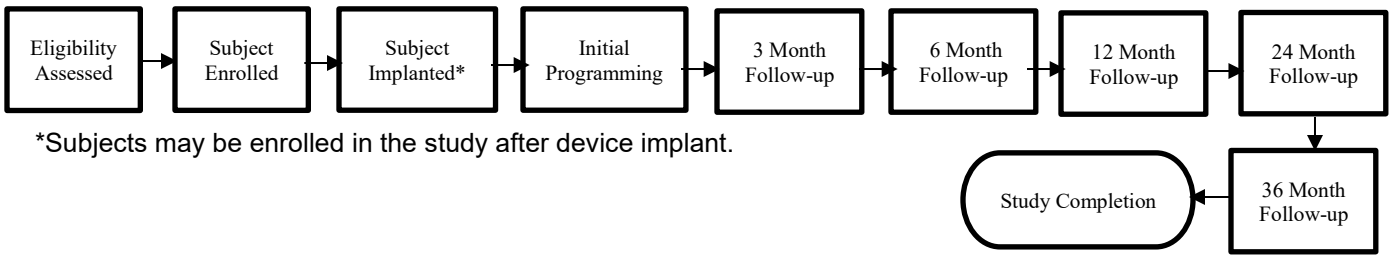
1.0 SYNOPSIS

Title	Post Market Clinical Follow Up Evaluating the Infinity Deep Brain Stimulation Implantable Pulse Generator System
Acronym	PROGRESS
Purpose	The purpose of this post market study is to characterize the clinical performance of the Infinity Deep Brain Stimulation (DBS) Implantable Pulse Generator (IPG), DBS leads, extensions and related system components.
Primary Objective	Demonstrate superiority of the directional lead DBS therapeutic window to the omnidirectional lead DBS therapeutic window.
Secondary Objectives	Demonstrate non-inferiority of the directional lead DBS therapeutic window to the omnidirectional lead DBS therapeutic window and compare Unified Parkinson's disease Rating Scale (UPDRS part III motor examination) at 3 and 6 months to evaluate therapeutic differences in omnidirectional vs directional stimulation.
Primary Endpoint	The proportion of subjects for which at least one lead's therapeutic window (evaluated by a blinded evaluator) is greater using directional stimulation than omnidirectional stimulation, tested against a performance goal of 60% at the 3-month follow-up visit.
Secondary Endpoints	If primary endpoint not met, the proportion of subjects with a therapeutic window (evaluated by a blinded evaluator) which is larger under directional stimulation than omnidirectional stimulation tested against a performance goal of 40% at the 3 month follow-up visit; Comparison of 3-month vs. 6-month UPDRS part III motor examination scores (evaluated by a blinded evaluator) to assess therapeutic differences in omnidirectional vs. directional stimulation.
Descriptive Endpoints	Evaluation of subject and clinician stimulation preference at 6-month follow-up visit; Change in therapeutic effectiveness measured by UPDRS part III motor examination at the 12-month follow-up visit from baseline visit; Change in Activities of Daily Living (ADLs) measurement as determined from the UPDRS part II ADLs at the 3-, 6-, and 12-month follow-up visits from baseline visit; Change in quality-of-life measurement as measured by the Parkinson's Disease Questionnaire (PDQ-39) at the 3-, 6-, and 12-month follow-up visits from baseline visit; Evaluation of device-related adverse events; Evaluation of subject and programmer satisfaction with product usability at the 12-month follow-up visit; Comparison of mean values of therapeutic window with directional and omnidirectional stimulation; Current (amplitude) at which first sustainable side effect is observed with directional and omnidirectional stimulation; Current (amplitude) at which first sustainable stimulation-induced side effect is observed with directional and omnidirectional stimulation; Minimum therapeutic current with directional and omnidirectional stimulation; Optimal therapeutic current with directional and omnidirectional stimulation;

	Total amount of time required for each study visit and programming. Long-term outcomes evaluated by change compared to baseline in UPDRS part III motor examination, UPDRS part II ADLs and PDQ-39, at the 36-month follow-up visit.
Design	This study is designed as a prospective, blinded-subject, blinded-evaluator, observational, multi-center 36 month post market clinical follow up study. The total duration of this study is expected to be 60 months. The clinical study will be conducted at up to 60 centers in the European Union, United States, Latin America, and Australia. Up to 350 subjects will be enrolled. The primary endpoint analysis will be performed when 66 subjects have completed 12 months of follow-up and have evaluable primary endpoint at the 3-month follow-up visit. Interim annual progress reports will be reported to comply with Post-Market Clinical Follow-up (PMCF) requirements. Baseline data can be collected from the subject's medical records to compare to follow-up visits. Data will be collected 3, 6, 12, 24 and 36 months after initial programming for comparison to baseline. A subset of subjects enrolled in this study will be used to meet the PMCF requirement for CE mark. Once this subset of subjects is enrolled and followed for 12 months and have evaluable primary endpoint at the 3-month follow-up visit, a report will be submitted indicating completion of this requirement.
Devices Used	The following devices will be used in the study: Infinity DBS System Infinity DBS system including Implantable Pulse Generator (IPG), the 4 and 8 channel leads and accessories Infinity Clinician Programmer App and Patient Controller App
Study Population	Subjects who have a diagnosis matching the approved indication and are being considered for a DBS implant or who have been implanted with an Infinity system comprise the target population for this study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria, and who have signed a statement of informed consent approved by an Ethics Committee (EC) or Institutional Review Board (IRB), will be enrolled in the study. The PMCF requirement will be complete when 66 subjects have been followed for 12 months and have evaluable primary endpoint at the 3-month follow-up visit.
Inclusion/ Exclusion Criteria	<u>Inclusion Criteria</u> Subject is able to provide informed consent; Subject is diagnosed with Parkinson's disease (PD) and has been recommended to receive a bilateral DBS implant in the Subthalamic Nucleus (STN), or has been implanted bilaterally with an Infinity system in the STN; Subject must be available for follow-up visits. <u>Exclusion Criteria</u> Subject is not a surgical candidate; In the investigator's opinion, the subject is unable to tolerate multiple programming sessions within a single setting;

	Subject is unable to comply with the follow-up schedule.
Data Collection	Data will be collected at baseline, initial programming, and 3 months, 6 months, 12 months, 24 months and 36 months after initial programming date. Retrospective chart review or prospective completion of the baseline study evaluations may be conducted for each subject. Retrospective collection of the most recently documented UPDRS part II ADLs and UPDRS part III motor scores (on and off medication) can be used as baseline data for comparison to 3-, 6-, 12- and 36-month data. Subjects will undergo DBS system implantation in accordance with the physicians' standard operating procedures. Subjects will return for the initial programming visit according to the site's normal standard of care. The initial programming date will be classified as "Day 0". At the initial programming visit, the leads will be tested according to the site's standard monopolar review followed by omnidirectional testing. After Day 0, subjects will return to the clinic for evaluations at 3 months (±30 days), 6 months (±30 days), 12 months (±60 days), 24 months (±90 days) and 36 months (±90days). At the 3- and 6-month visits, Parkinson's disease symptoms will be evaluated by a blinded evaluator using the UPDRS part III motor examination. At the 3-, 6- 12- and 36-month visits, subjects will be evaluated using the UPDRS part II for the ability to perform activities of daily living in the Stimulation On state, and will complete the PDQ-39 to evaluate quality-of-life. At the 3-, 12- and 36-month visits, a detailed omnidirectional and directional programming assessment will be performed. The right and left lead will be tested independently in multiple programming configurations. Amplitude will be increased slowly by the programmer until first meaningful therapeutic effect is confirmed by the blinded evaluator. Amplitude will continue to be increased slowly by the programmer until the first sustainable side effect is observed by the blinded evaluator. The subject and programmer will also complete the System Usability Scale (SUS) at the 12-month visit to assess the ease of use of the device. The PMCF requirement will be met when 66 subjects have been followed for 12 months and have evaluable primary endpoint at the 3-month follow-up visit.

1.1 STUDY FLOW CHART



*Subjects may be enrolled in the study after device implant.

1.2 STUDY CONTACTS

[redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Deep Brain Stimulation (DBS) has become an indispensable therapeutic tool for treating Parkinson's disease, dystonia and tremor, which provides an opportunity for significant symptom relief and quality of life improvement with minimal risk [1]. It is preferred over surgical treatment due to its adjustability, reversibility, long lasting and robust clinical effectiveness and safety.

DBS is intended to modulate 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 block the impulses that cause neurological dysfunctions. Targets include the globus pallidus internus (GPi) and the subthalamic nucleus (STN). Patients with DBS experience considerable improvements in their motor symptoms and are sometimes able reduce medication usage [2-4].

Despite the proven efficacy of DBS, the benefit of this therapy is highly dependent on the distribution of the stimulation field within the brain anatomy. Due to the omnidirectional nature of lead design combined with the complex functional anatomy of DBS brain targets, today's DBS leads offer limited control over the area of stimulation delivery. As a result, the propagation of current beyond the specific brain target stimulation-induced side effects are very common with 4 electrode lead designs. Common side effects include cognitive impairment, memory deficits, difficulties with speech, disequilibrium, dysphagia, and motor and sensory disturbances [5]. The effects are most frequently related to suboptimal lead placement and an inability to finely control the volume of tissue activated (VTA). Additionally, the non-spherically shaped targets of DBS indicate a need for programming that allows for the ability to shape the electrical field and potentially reduce the spread of current to unintended areas of the brain.

In addition to the surgical procedure, a critical aspect of successful DBS is programming of the system such that optimal stimulation for alleviation of clinical symptoms is accomplished without the introduction of unwanted side effects.

The advantages of DBS is that it allows for both unilateral and/or bilateral coverage of symptoms, it is reversible as well as can be tailored to a patient's clinical status (parameters are adjustable allowing for minimization of stimulation induced side effects and improvements in efficacy over time), and the system can provide continuous symptom control 24 hours a day with minimum patient and physician involvement. The electrodes and electrical systems that provide stimulation are generally very well tolerated with no significant changes in surrounding brain tissue [6].

However, DBS requires millimeter accuracy in targeting of specific deep brain nuclei and when misplaced may cause electrical current to spread to the surrounding associative, motor and limbic areas running through the target nuclei which can lead to serious adverse effects. Recently, literature indicates that controlling the directionality of the current in DBS more precisely could lead to improved effectiveness and/or reduced side effects [7, 8, 9, 10]. Like DBS, Spinal Cord Stimulation (SCS) utilizes leads to deliver electric impulses to target areas to alleviate clinical symptoms. However, technological advancements in SCS leads that allow for the ability to steer current into the dorsal horns and away from the dorsal roots have led to improved long-term outcomes and an expanded indication for SCS for chronic back pain. This is accomplished through the multitude of electrode configurations, sizes, quantity and shapes which afford physicians an ability to customize lead selection to each patient and control the stimulation delivered to the intended target. Such advancements are being evaluated but have not yet been made commercially available for DBS.

Consequently, both computational modeling studies and clinical 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 [8, 11, 12]. By using segmented electrodes to control the shape of the VTA, the stimulation field delivered would be better fitted to the anatomy of the therapeutic target. 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[13]. 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 [8, 11]. Shaping the VTA with respect to the position of the electrode segment and target structure allows for more selective control of the stimulation field which may yield improved therapeutic outcomes for some patients. In DBS, the target areas, the STN, Vim and Gpi for PD, tremor and dystonia respectively, have a restricted size within these functional structures that are associated with effective treatment. Figure 1 depicts a relative illustration of the DBS targets and the target areas within anatomic structures associated with effective treatment.

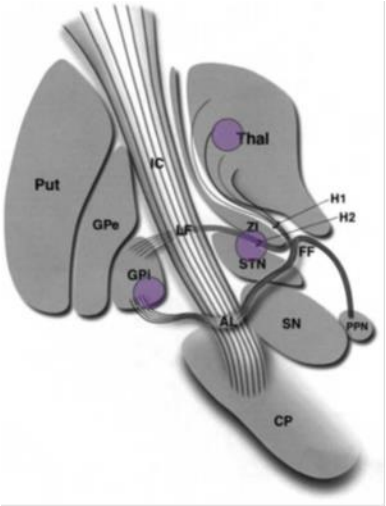


Figure 1: DBS Targets[14]

The side effects from recruiting unintended neural structures vary depending on the original target and placement of the DBS lead. The proximity of the surrounding structures that correspond to disabling side effects such as tonic muscular contraction, dysarthria conjugate eye deviation, paresthesia or gait imbalance make it difficult to target the specific areas without the introduction of adverse effects. It has also been reported that spillover of stimulation to non-motor portions of the subthalamic nucleus may induce behavioral impairment and limbic side effects such as depression and impulsivity. DBS in the Vim that spans to adjacent structures can induce paresthesia side-effects by stimulating neurons within the sensory pathway of the ventral caudal (Vc) nucleus of thalamus. To date, physicians utilize electrode placement and stimulation parameter settings to control the stimulation delivered to the appropriate anatomic areas. Finite element modeling using actual patient anatomy has been studied to understand the electric field generated by DBS electrodes and its correlation to the volume of tissue activated. Standard DBS electrodes provide stimulation by dispersing current axially and symmetrically around the activated contacts (Figure 2). Because of this dispersion, the volume of tissue activated (VTA) by the stimulation prevents the excitation of neuronal tissue in a defined direction.

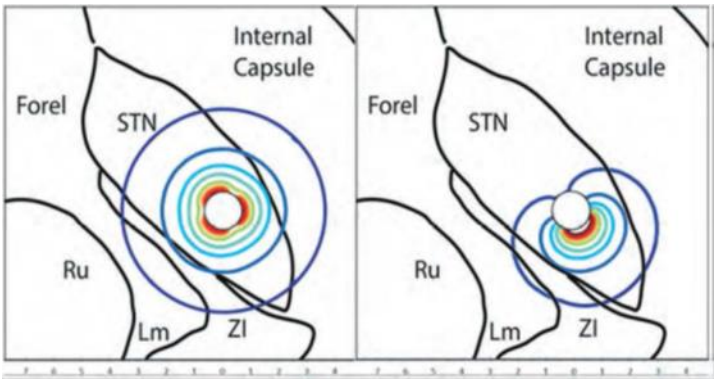


Figure 2: Finite element model comparison of (A) omnidirectional stimulation versus (B) unidirectional stimulation using segmented electrodes

These models have led to an understanding of the occurrence of side effects associated with lead placement and electrode size or configuration. Specifically, given the radial dispersion of current, a high level of precision is necessary in placement to assure an effective therapeutic range [7, 14]. Clinical studies have further bolstered that accurate placement of DBS leads is correlated to the best clinical efficacy [15, 16]. Further, limitations in the current electrode size, translates to an inability to sculpt the shape and size of the VTA resulting in inadequate activated tissue volumes or inaccurate targeting of therapeutic regions [15, 10, 12].

In addition to current design limitations of existing DBS electrodes, post-operative migration of the lead can result in decreased clinical benefit of DBS. In cases of clinically relevant migration, the physician is afforded two options: 1) reprogramming and 2) additional surgery to relocate the lead to an adequate area. With current lead designs, reprogramming is limited due to the finite size of the therapeutic brain target or inability to shape the field due to the lead design [17]. More often than not, additional surgery is required to reposition the lead to regain adequate stimulation coverage. Additional surgery resulting from DBS lead misplacement or migration may be minimized through the use of a lead that allows for directional control of the current. The 8 channel SJM lead incorporates the concept of segmentation and directionality to allow for flexibility of reprogramming, compensating for loss of stimulation at the optimal brain target. The 8 channel lead will provide multiple avenues for redirecting the stimulation through sculpting the electric field and controlling the VTA. Directional DBS (dDBS) models have shown that current steering can activate different proportions of neural populations without surgically modifying the position of the electrode. Additionally, implantation of leads with a larger number of small surface area contacts could also help focus stimulation on the intended target resulting in finer control over the VTA [14].

DBS provides an opportunity for significant symptom relief and quality of life improvement with clinically acceptable risk. The 8 channel Infinity™ DBS System including leads, extensions, and the related accessories demonstrate the same safety and efficacy profile as the SJM currently marketed DBS Systems. Numerous publications with similar DBS systems and the market experience associated with the currently marketed SJM DBS system demonstrate the safety and performance of the equivalent 8 channel DBS leads, extensions and related accessories for treatment of Parkinson's disease, dystonia, and tremor.

The efficacy of the use of directional DBS (dDBS) for the treatment of patients with movement disorders is supported with data from 2 prospective single center acute clinical studies. Pollo et al (2014) conducted a prospective, single center acute study to assess the effectiveness of dDBS in PD and

tremor patients [15]. Compared to omnidirectional mode, the directional stimulation in the best direction was 41.3% wider with a therapeutic current necessary to produce meaningful stimulation that was 43% lower. The benefit of having a wider window for therapeutic stimulation 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) [18]. Directional stimulation proved effective in this study in that it reduced the appearance of side effects; while, widening the therapeutic window by redirection of 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.

The purpose of this post market clinical follow up (PMCF) study is to support the chronic clinical performance of the Infinity DBS IPG, leads, extensions and related system components. In addition, the study is to demonstrate that the 8 Channel leads and IPGs will allow the implanter to gain better control over the stimulation field as well as to expand the available programming options.

A sub-set of subjects enrolled in this study will be used to meet the Post Market Clinical Follow-Up (PMCF) requirement for CE mark. Once this sub-set of patients is enrolled and followed for 12 months and have evaluable endpoint data at the 3-month follow-up visit, a report will be submitted indicating completion of this requirement.

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

There are no additional anticipated risks associated with the use of the Infinity system than from those identified for currently available DBS systems.

3.1 DESCRIPTION OF SUBJECT POPULATION

Subjects who have a diagnosis matching the approved indication (Parkinson's disease) and are being considered for a DBS implant with leads placed at the Subthalamic Nucleus (STN), or who have been implanted with an Infinity system for Parkinson's disease with leads placed at the STN, comprise the target population for this study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria, and who have signed a statement of informed consent approved by an Ethics Committee (EC) or Institutional Review Board (IRB), will be enrolled in the study.

3.2 ANTICIPATED CLINICAL BENEFITS

The Infinity system with the directional lead provides additional programming options not available in other market-approved DBS systems.

If patients agree to take part in this study, there may or may not be direct medical benefits to the individual patient. The scientific use of the data, which is gathered from this study, may help researchers discover better ways of programming DBS patients and improving quality-of-life.

3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Deep brain stimulation potentially has the following adverse effects:

Possible surgical complications. Surgical complications include, but are not limited to, the following: intracranial hemorrhage (which can lead to stroke, paralysis, or death); subcutaneous hemorrhage or seroma; hematoma; cerebrospinal fluid leakage or cerebrospinal fluid abnormality; brain contusion; infection or inflammation; antibiotic anaphylaxis; skin disorder; edema; persistent pain at surgery site or IPG site; erosion; brachial plexus injury (nerves to chest, shoulder and arm); postoperative pain, stress, or discomfort; neuropathy (nerve degeneration); hemiparesis (muscular weakness or partial paralysis on one side of body); ballism or hemiballism (uncontrollable movements on both or only one side of the body); confusion—transient, nocturnal or ongoing; cognitive impairment, including delirium, dementia, disorientation, psychosis and speech difficulties; aphasia; deep vein thrombosis; complications from anesthesia; phlebitis (vein inflammation); pulmonary embolism (sudden blood vessel obstruction); aborted procedures (air embolism, unable to find target, surgical complication, etc.); complications from unusual physiological variations in patients, including foreign body rejection phenomena; pneumonia, seizure or convulsions; paralysis (loss of motor function, inability to move); stroke and death.

Possible deep brain stimulation complications. 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

3.4 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE UNDER INVESTIGATION, AS IDENTIFIED IN THE RISK ANALYSIS REPORT

DBS refers to the electrical stimulation of structures deep within the brain. DBS is considered an effective treatment for Parkinson's disease, tremor and dystonia that is reversible, and adaptable.

The targeted study population consists of subjects who have been implanted with or are being considered for implant of an Infinity DBS system. Standard outcome measures will be used to evaluate Parkinson's disease symptoms.

Effects of the DBS are considered safe, non-destructive and reversible. The frequency and severity of procedural risks and complications related to the implant of the Infinity system are expected to be similar to those that are cited in the current literature.

3.5 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

There are no study-related additional risks expected within this study.

3.6 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS AND/OR CONCURRENT MEDICAL INTERVENTIONS

Diathermy therapy is contraindicated for subjects who have been implanted with the Infinity system. Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (all now referred to as diathermy) on subjects implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in a severe injury or death. Diathermy is further prohibited because it may also damage the neurostimulation system components. This damage could result in loss of therapy, requiring additional surgery for system replacement. Injury or damage can occur during

diathermy treatment whether the neurostimulation system is turned on or off. All subjects are advised to inform their healthcare professional that they should not be exposed to diathermy treatment.

Magnetic resonance imaging (MRI) may be contraindicated for subjects implanted with the Infinity system. If the Infinity system has MRI Conditional labelling, MRI may be performed with imaging settings descried in Abbott's DBS MRI Procedures Manual. If the Infinity system does not have MRI Conditional labelling, do not use a full body radiofrequency (RF) coil or other extremity coils on subjects implanted with a neurostimulation system. Because energy from MRI can be transferred through the implanted system, the potential for heat generation at the location of the electrodes exists. This isolated temperature rise may cause tissue damage at the location of the implanted electrodes, possibly resulting in severe injury or death. Injury can occur during MRI treatment whether the neurostimulation system is turned on or off. Patients with a neuromodulation system that does not have MRI Conditional labelling are advised to inform their healthcare professional that they should not be exposed to MRI.

Please refer to the Infinity IPG clinician manual/instructions for use regarding warnings and precautions.

3.7 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

There are no study-related additional risks expected within this study.

3.8 RISK-TO-BENEFIT RATIONALE

There are no study-related additional risks expected within this study.

3.9 DESCRIPTION OF HISTORY OF MODIFICATIONS OR RECALL IN RELATION TO SAFETY AND CLINICAL PERFORMANCE FOR DEVICE UNDER INVESTIGATION

This is a newly approved device and no device modifications have been reported to date. No device recalls have been issued concerning this product.

4.0 STUDY DESIGN

4.1 PURPOSE

The purpose of this post market study is to characterize the clinical performance of the Infinity DBS system including IPG, leads, extensions and related system components.

The PMCF requirement for this study will be to demonstrate superiority of directional stimulation compared to omnidirectional stimulation, as measured by therapeutic window. The primary endpoint will be evaluated for the first 66 subjects who complete the 12-month follow-up visit and have evaluable primary endpoint at the 3-month follow-up visit.

4.2 STUDY DESIGN AND SCOPE

This study is a post-market clinical follow-up study designed as a prospective, blinded-subject, blinded-evaluator, observational, multi-center evaluation of the Infinity DBS system. The clinical study will be conducted in up to 60 centers from the European Union, United States, Latin America, and Australia.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

Subjects who currently have an Infinity DBS system or have been recommended by the investigator for implantation of a DBS system and meet the standard requirements will be approached to participate in the study. Each subject will be screened according to the inclusion/exclusion criteria. If the subject meets all of the study inclusion criteria and none of the exclusion criteria, the subject will be informed about the study to determine if the subject is interested in participating. Baseline data may be collected from the subject's medical record. After the subject signs the informed consent and is enrolled in the study, the subject will undergo an Infinity DBS system implant if the Infinity DBS system is not already implanted.

During the surgery, the leads will be implanted according to the physician's standard operating procedures. The neurosurgeon will be instructed to implant the hourglass-shaped radiopaque marker facing posterior or toward the implanter during insertion (toward the back of the subject's head) so that contact/segments are easily identifiable. The orientation of the contacts will be collected. In addition, neurosurgeons will be instructed to plan placement to target between contacts 2 and 3. A pre-operative and post-operative image (Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT)) will be obtained to assist with lead location data. The IPG will be activated according to the site's standard of care and will be programmed by trained personnel using the Clinician Programmer. The subject may be given a Patient Controller, dependent on the physician's recommendation for patient care. Subjects will return for evaluation 3, 6, and 12 months post-initial programming for follow-up visits. An optional long-term follow-up will collect additional information 24 months after initial programming, optionally by telephone, and at a 36-month follow-up visit. This study is for data collection purposes and there are no additional risks to patients who participate in this study other than those risks of having a deep brain stimulation system implanted.

A comparison of the therapeutic window using directional stimulation to the therapeutic window using omnidirectional stimulation will be performed for each lead on each subject. Subjects will be considered to have a greater therapeutic window with direction stimulation if one or both leads has a larger therapeutic window with directional stimulation than omnidirectional stimulation.

A blinded evaluator will be used in this study to minimize study bias. The blinded evaluator will assess the therapeutic window for each subject at initial programming, the 3-month visit and the 12-month visit. The UPDRS part III motor examination for each subject will also be assessed by the blinded evaluator at the 3-month and 6-month visits. The blinded evaluator will not be aware of the subject's programming or device settings at the time of the evaluation. In addition, subjects will be unaware of their programmed parameters for the first 6 months.

All serious adverse events (SAEs), serious procedure-related events (and procedure-related AEs lasting longer than 30 days) and device-related adverse events will be recorded throughout the subject's participation in the study.

[redacted]

4.2.1 Number of subjects required to be included in the study

Up to 350 subjects will be enrolled in the study (refer to section 12.0).

A subset of subjects enrolled in this study will be used to meet the Post-Market Clinical Follow-Up (PMCF) requirement for CE mark. Once this subset of subjects is enrolled and followed for 12 months

and have evaluable primary endpoint data at the 3-month follow-up visit, a report will be submitted indicating completion of this requirement. The primary endpoint analysis will be performed when 66 subjects have completed 12 months of follow-up and have evaluable primary endpoint data at the 3-month follow-up visit.

4.2.2 Estimated time needed to enroll this subject population

[redacted]

4.3 OBJECTIVES

4.3.1 Primary Objective

Demonstrate superiority of the directional lead DBS therapeutic window to the omnidirectional lead DBS therapeutic window.

4.3.2 Secondary Objective

Demonstrate non-inferiority of the directional lead DBS therapeutic window to the omnidirectional lead DBS therapeutic window and comparison of UPDRS part III motor examination scores at 3 and 6 months to evaluate therapeutic differences in omnidirectional vs directional stimulation.

4.4 ENDPOINTS

4.4.1 Primary Endpoint

The proportion of subjects for which at least one lead's therapeutic window (evaluated by a blinded evaluator) is greater using directional stimulation than omnidirectional stimulation, tested against a performance goal of 60%, at the 3-month follow-up visit. The directional segment with the widest therapeutic window will be compared to omnidirectional stimulation.

4.4.2 Secondary Endpoint

If primary endpoint not met, the proportion of subjects with a therapeutic window (evaluated by a blinded evaluator) which is larger under directional stimulation than omnidirectional stimulation tested against a performance goal of 40% at the 3 month follow-up visit; Comparison of 3-month vs. 6-month UPDRS part III motor examination scores (evaluated by a blinded evaluator) to assess omnidirectional vs. directional stimulation.

4.4.3 Descriptive Endpoints

The following data will be collected:
Evaluation of subject and clinician stimulation preference at 6-month follow-up visit;
Change in therapeutic effectiveness measured by UPDRS part III motor examination at the 12-month follow-up visit from baseline visit;
Change in ADLs as determined from the UPDRS part II ADLs at the 3-, 6-, and 12-month follow-up visits from baseline visit;
Change in quality-of-life as measured by the PDQ-39 at the 3-, 6-, and 12-month follow-up visits from baseline visit;
Evaluation of device-related adverse events;
Evaluation of subject and programmer satisfaction with product usability at the 12-month follow-up visit.
Comparison of mean values of therapeutic window with directional and omnidirectional stimulation;

Current (amplitude) at which first sustainable side effect is observed with directional and omnidirectional stimulation;
Current (amplitude) at which first sustainable stimulation-induced side effect is observed with directional and omnidirectional stimulation;
Minimum therapeutic current with directional and omnidirectional stimulation;
Optimal therapeutic current with directional and omnidirectional stimulation;
Total amount of time required for programming and each study visit.
Long-term outcomes evaluated by change compared to baseline in UPDRS part III motor examination, UPDRS part II ADLs and PDQ-39, at the 36-month follow-up visit.

4.5 INCLUSION AND EXCLUSION CRITERIA

A subject who meets all of the inclusion criteria and none of the exclusion criteria is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code linked to their names, alternative identification or contact information.

This log will be kept up to date throughout the clinical study by the principal investigator or an authorized designee. To ensure subject privacy and confidentiality of data, this log must be maintained throughout the clinical study at the clinical site.

To participate in this clinical subject, the subject must meet all of the following inclusion criteria:

4.5.1 Inclusion Criteria

1) Subject is able to provide informed consent;
2) Subject is diagnosed with Parkinson's disease (PD) and has been recommended to receive an Infinity DBS system with a bilateral DBS implant in the Subthalamic Nucleus (STN), or has received an implant of an Infinity system with bilateral lead implants in the STN;
3) Subject must be available for follow-up visits.

A subject is not eligible for clinical study participation if the subject meets any of the following exclusion criteria:

4.5.2 Exclusion Criteria

1) Subject is not a surgical candidate;
2) In the investigator's opinion, the subject is unable to tolerate multiple programming sessions within a single setting;
3) Subject is unable to comply with the follow-up schedule.

4.6 SUBJECT POPULATION

4.6.1 Subject Screening

All subjects presenting at the investigational site can be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate in the study. In case the subject agrees, a duly signed and dated Patient Informed Consent will be obtained.

4.6.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent. (Refer to section 4.7 for the informed consent process). Although subjects exit the study after completion of the 12-month visit, subjects who provide written informed consent by signing the informed consent addendum for long-term follow-up may participate in 24- and 36-month follow-up visits.Follow-up visits will be scheduled based on date of initial programming.

4.6.3 Enrollment of Medicare Beneficiaries

In the United States, subjects enrolled in the clinical study are expected to be consistent with the Medicare population based on age and as such, the study results are expected to be generalizable to the Medicare population.

4.7 INFORMED CONSENT PROCESS

4.7.1 General process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be required to provide informed consent, as required by applicable regulations and the center's EC or IRB. Informed consent must be obtained from each subject prior to any study-related procedures. The consent form must be signed and dated by the subject and by the person obtaining the consent.

The principal investigator or an authorized designee will conduct the informed consent process. 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 in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's EC or IRB. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing center's EC or IRB consistent with the center's EC or IRB reporting requirements.

5.0 DEVICE UNDER INVESTIGATION AND CONTROL/COMPARATORS (IF APPLICABLE)

5.1 DEVICE DESCRIPTION

Infinity DBS system:

In this study, commercially available St. Jude Medical (SJM) Infinity DBS system components will be used. This neurostimulation system is designed to deliver electrical stimulation to targets in the brain. The neurostimulation system includes the following primary components:

- Implantable pulse generator (IPG)
- Leads
- Extensions
- Clinician programmer
- Patient controller

The IPG connects to the implanted extensions, which connect to the leads implanted in the brain. The IPG delivers electrical pulses through the extensions and leads to electrodes at a selected target in the brain in order to provide therapeutic stimulation. The patient magnet can turn the IPG on and off, if the physician enabled this functionality. Physicians use the clinician programmer to create and modify a program for a patient. Patients use the patient controller to control their prescribed programs. Components of the Infinity DBS system and model numbers are included in Appendix D.

Infinity Implantable Pulse Generator
This IPG is an electronic device designed to be connected to one or two extensions. It is powered by a hermetically sealed battery within a titanium case and uses microelectronic circuitry to generate constant-current electrical stimulation. The IPG is conductive on all sides, which allows the IPG case (also called a “can”) to be used as an anode for monopolar stimulation. The IPG communicates wirelessly with system programmers and controllers, and IPGs are available in small and large sizes to accommodate different power needs. The IPG can receive software upgrades after implantation to provide patients with additional features as approved by the respective regulatory agencies. To upgrade features on the IPG, a system programmer is needed.

Leads
St. Jude Medical DBS leads are designed for introduction into the brain using standard stereotactic neurosurgical techniques. Leads feature electrodes on a stiff distal end with an inactive lead tip. The proximal end of the lead contains contact bands that correspond with each of the distal electrodes and an inactive band that functions as a contact for a setscrew when connecting to a compatible extension. Additionally, the leads have colored bands that can help during implantation to differentiate between the right and left sides of the body. Two types of leads are available: 4 channel and 8 channel. The 4-channel leads contain cylindrical electrodes that provide stimulation in all directions around the lead. The 8-channel leads contain cylindrical and segmented electrodes. The segmented electrodes can be

activated independently to focus stimulation in one direction to help exclusively target desired neurological structures.

Extensions
St. Jude Medical DBS extensions are designed to connect the lead to the IPG. One end of the extension is designed to receive the proximal end of the lead, and the opposite end of the extension is designed for insertion and connection with the IPG.

Clinician Programmer
The Clinician Programmer Application is a software application running on an iPad which is used by a clinician to wirelessly connect to Infinity IPGs to establish or modify a patient's stimulation prescription.

Patient Controller
The Patient Controller is a component of the Infinity system. It is an off-the-shelf touch screen device (iPod Touch) with SJM-designed mobile Application Software.

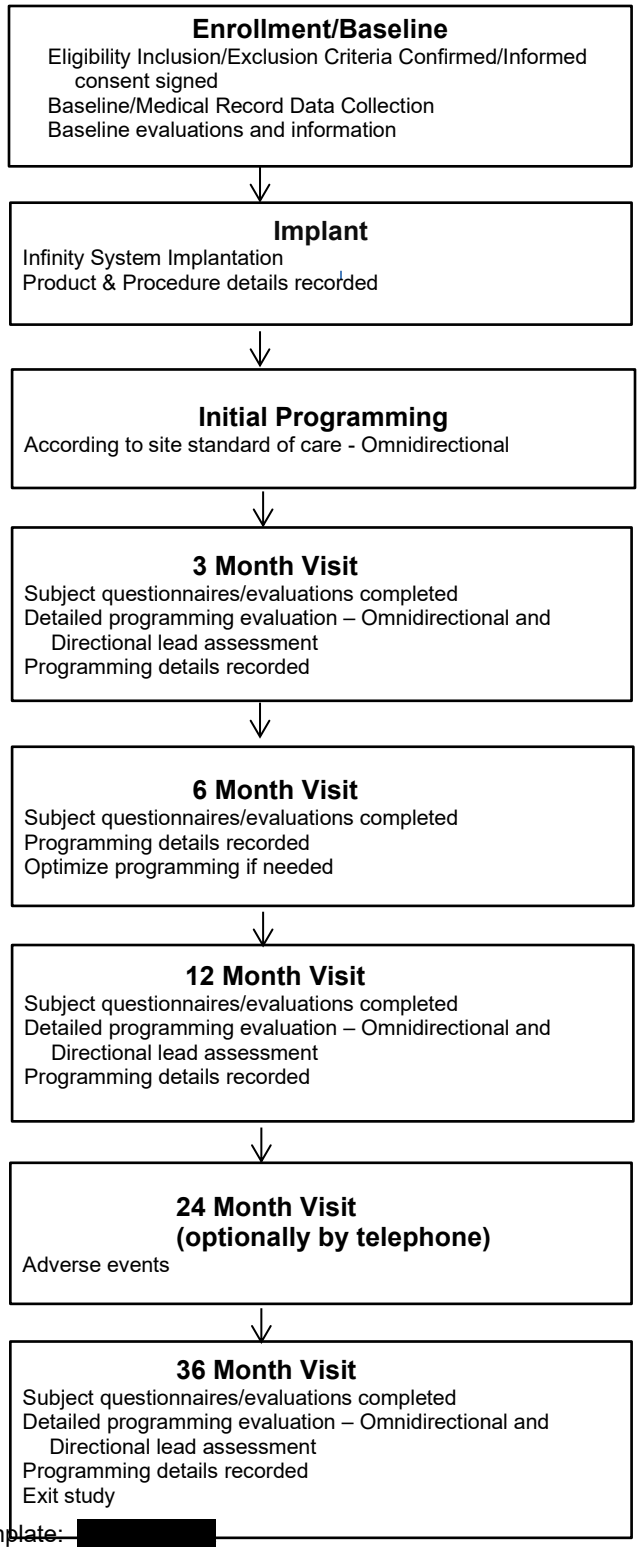
5.2 DEVICE HANDLING AND STORAGE

Only regulatory approved and commercially available shelf-stock will be used within commercially approved indications for the investigation. No specific device traceability is required.

6.0 PROCEDURES

6.1 STUDY FLOW CHART

Subjects may be enrolled after device implant



6.2 STUDY VISITS

The clinical study will be conducted in accordance with the CIP. All parties participating 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.

The clinical study will not commence until St. Jude Medical receives written approval from the EC or IRB and relevant regulatory authorities and all required documents have been collected from the site(s).

Table 1: List of all study specific activities/procedures

Visit / Study Activity	Enrollment Baseline	Implant	Initial Programming site standard of care – Omnidirectional (Day 0)***	3 Month 3 months ± 30 days since Initial Programming – Directional	6 Month 6 months ±30 days since Initial Programming	12 Month 12 months ± 60 days since Initial Programming	24 Month 24 months ±90 days since Initial Programming	36 Month 36 months ±90 days since Initial Programming
Inclusion/Exclusion Criteria check	X							
Informed Consent Process	X							
Subject Demographics	X							
Parkinson's Disease History	X							
Parkinson's Disease Medication Current	X					X		X
UPDRS Section II and III Off Medication	X							
UPDRS Section II and III On Medication	X							
UPDRS Section II (On Med On Stim)				X	X	X		X
UPDRS Section III (Off Medication / On Stim)				X*		X		X
UPDRS Section III (Off Medication / Off Stim				X*		X		X
UPDRS Section III (On Med On Stim)				X*	X*	X		X
UPDRS Section III (On Med Off Stim)				X*	X*	X		X
PDQ-39	X			X	X	X		X
Implant Information		X						
Pre- and Post-Operative Image Collected		X						
Initial testing/ programming data/session data			X*					
Subject Preference					X**			
Clinician Preference					X			

Visit / Study Activity	Enrollment Baseline	Implant	Initial Programming site standard of care – Omnidirectional (Day 0)***	3 Month 3 months ± 30 days since Initial Programming – Directional	6 Month 6 months +30 days since Initial Programming	12 Month 12 months ± 60 days since Initial Programming	24 Month 24 months ±90 days since Initial Programming	36 Month 36 months ±90 days since Initial Programming
System Usability Scale (SUS) Subject						X		
System Usability Scale (SUS) Programmer						X		
Device Testing/ Programming data /session data				X*	X	X*		X
Adverse Event Check		(X)	(X)	(X)	(X)	(X)	(X)	(X)
System Revision Check				(X)	(X)	(X)		(X)
Deviation		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Termination/Exit		(X)	(X)	(X)	(X)	(X)	(X)	(X)

*Blinded Evaluation ** Blinded Subject (X) if applicable
***For subjects implanted with the Infinity DBS System at the time of enrollment, "Day 0" will be the date of consent.

Baseline and implant information may be retrospectively collected from the subject's medical records after enrollment.

Informed Consent Procedure and Inclusion/Exclusion Criteria:
Patient's eligibility criteria will be evaluated and informed consent will be obtained at the Baseline/Enrollment visit.

Subject Demographics:
Subject's Age, Weight, Height and Gender will be collected at the Baseline visit.

Parkinson's Disease History:
Subject's year of symptom onset, year of initial diagnosis, length of diagnosis, subject's impression of worst symptom, will be collected at the Baseline visit.

Parkinson's Disease Medication:
Subject's current medications for PD will be collected at the Baseline visit, at the 12-month and 36-month follow-up visits.

Subject Data:
Baseline PDQ-39, UPDRS part II ADLs and part III motor examination scores may be collected from the subject's medical record. PDQ-39, UPDRS part II ADLs On Medication/On Stimulation, and UPDRS part III motor examination On Medication and On and Off Stimulation will be collected at 3, 6,12 and 36 Month Follow-Up visits. UPDRS part III Off Medication will also be collected at 3-, 12-, and 36-month

follow-up visits. In addition, subject/programmer satisfaction and data device usage will be collected at the 12-Month Follow-Up visit.

Unified Parkinson's Disease Rating Scale/Section II and Section III:
In order to assess the subject's activities of daily living and Parkinson's disease symptoms, Section II and III of the UPDRS questionnaire will be completed at Baseline, 3-, 6-, 12- and 36-Month Follow-Up visits.
The UPDRS is a rating tool to follow the longitudinal course of Parkinson's disease. It is made up of the following sections: I) Mentation (mental status), Behavior, and Mood, II) Activities of Daily Living (ADL), III) Motor sections and IV) Complications of Therapy, which are evaluated by interviewing the patient. All responses are rated on a 0 to 4-point scale where 0 indicates 'none' and 4 indicates 'severe' symptom.

Parkinson's Disease Questionnaire:
In order to assess the subject's quality of Life the PDQ-39 will be completed at Baseline, 3-, 6-, 12- and 36-Month Follow-Up visits. The PDQ-39 is a disease specific instrument designed to measure aspects of health that are relevant to patients with PD, and which may not be included in general health status questionnaires. The PDQ-39 is a self-administered questionnaire, which comprises 39 items addressing eight domains of health that patients consider to be adversely affected by the disease.

Implanted System Information:
Information regarding the implanted system will be collected during the permanent implantation procedure and in case of additional surgery or from the medical records if patient was already implanted with the Infinity System.

Programming Interrogation/Data:
Programming data and parameters, including program impedance, will be collected during initial programming, at the 3-, 6-, 12- and 36-Month Follow-Up visits. Device session data should be sent to the Sponsor.

Evaluation of Programming/Device Testing:
Detailed device testing will be done at the Initial programming, 3-month follow-up visit, 12-month follow-up visit and 36-month follow-up visit.

System Usability Scale/SUS:
In order to assess the subjects and site programmer's use of the system, a System Usability Scale (SUS), a simple, ten-item scale giving a global view of subjective assessments of usability will be completed by the subject and programmer at the 12 Month Follow-Up visit.

Adverse Events:
Please refer to Section 8.0 of this protocol.

6.3 ENROLLMENT VISIT

The following enrollment activities are performed after the subject has been screened and must occur before any study evaluation /visit.

- The principal or delegated investigator is responsible for screening all potential patients to determine patient eligibility for the study.

- If a patient meets all inclusion criteria and does not meet any of the exclusion criteria, the patient is eligible for the study.
- The patient is enrolled in the study when the patient signed the EC- or IRB-approved consent form.

Site personnel should record enrollment information (name of the study, date of consent and Inclusion/exclusion information) from the hospital records and complete the Enrollment form electronically in a timely manner (preferably within 5 days after enrollment).

Beginning when the patient signs the Patient Informed Consent form, AEs must be reported according to the guidelines mentioned in this CIP.

In case the subject was consented to participate in the study, but does not meet inclusion/exclusion criteria, and was not implanted, the subject should be withdrawn and a withdrawal form must be completed. The patient will resume regular standard of care with the patient's physician.
In case the subject was consented to participate in the study and was implanted but does not meet inclusion/exclusion criteria, then this is considered a protocol violation. A protocol deviation form needs to be completed and the Sponsor must be informed. The EC or IRB and Competent Authority, if applicable, should be notified appropriately about any deviations with regard to the violation of inclusion/exclusion criteria.

6.4 BASELINE VISIT

The following information will be collected at the baseline visit (baseline data can be collected on the same day as enrollment/informed consent). Baseline information can be retrospectively collected from the subject's medical records after enrollment:
Demographics
Parkinson's disease history and medication

The following may be collected retrospectively from the subject's medical record. The retrospective data should be collected from the most recent assessments completed prior to the implant date but not greater than 12 months prior:

- UPDRS Off and On Medication – Most recently documented UPDRS
- PDQ-39 – Most recently documented PDQ-39

6.5 IMPLANT/PROCEDURE

Subjects will be permanently implanted with the Infinity™ neuromodulation system according to standard operating procedures. It is suggested that the neurosurgeon implant the hourglass shaped radiopaque marker facing posterior or toward them during insertion (toward the back of the subject's head) so that contact/segments are easily identifiable. The orientation of the contacts will be collected. In addition, neurosurgeons will be instructed to plan placement to target between contacts 2 and 3. A pre-operative and post-operative image (MRI/CT) will be obtained to capture lead location data. Subjects will receive a patient programmer if the physician does this as part of his standard of care and will be instructed on the use of the system. Subjects will be unaware of their programmed parameters for the first 6 months.

Following system implantation, the stimulator will be activated and programmed by trained personnel in accordance with the physician's and hospital's standard operating procedures.

The following information will be collected at the Implantation visit (implant information can be retrospectively collected from the subject's medical records if enrollment occurs after implant):
Lead/extension and IPG data
Pre-operative and post-operative images
AE and/or protocol deviation (if applicable)

6.6 SCHEDULED FOLLOW-UPS

Blinded Evaluation

A blinded evaluator will be used in this study to minimize study bias. The blinded evaluator will assess the therapeutic window for each subject at the initial programming, the 3-month visit and at the 12-month visit. The UPDRS part III motor examination for each subject will also be assessed by the blinded evaluator at the 3-month and 6-month visits. This evaluator will not be aware of the subject's programming or device settings. It is recommended that the blinded evaluator assessing the therapeutic window and the UPDRS part III motor examination should be the same person; however, it is not required. In addition, subjects will be unaware of their programmed parameters for the first 6 months.

Subjects are to be instructed not to take medication the night prior to or the morning of the study visit. This is defined as the Off Medication state. Upon taking appropriate medication, subject is considered to be in the On Medication state.

Initial Programming (to be completed according to site's standard of care)
The following will be collected:
- Monopolar review
- AE and/or protocol deviation (if applicable).
- Omnidirectional testing – Off Medication (See Evaluation of Programming)
- Initial programming parameters – Sites will program each lead in an omnidirectional configuration to be used for the first 3 months. If omnidirectional stimulation does not provide adequate therapy or is not tolerated by the subject, any other programming is allowed.

Initial programming information can be retrospectively collected from the subject's medical records if enrollment occurs after implant. For these subjects, the omnidirectional testing by the programmer and blinded evaluator will be completed on the date of consent/enrollment.

3-Month Follow-Up Visit (3 months ± 30 days since initial programming or consent date)
The following information will be collected at the 3-month follow-up visit:
- PDQ-39;
- UPDRS part II ADLs On Medication / On Stimulation;
- UPDRS part III motor examination Off Medication/Off and On Stimulation assessed by a blinded evaluator;
- UPDRS part III motor examination On Medication/ Off and On Stimulation assessed by a blinded evaluator;
- Omnidirectional testing – Off Medication (See Evaluation of Programming)
- Detailed directional lead testing as tolerated by the subject – Off Medication (see Evaluation of Programming); sites are to program each lead to the optimal directional segment;
- Programming parameters; device session data;
- Unscheduled visits (if applicable);

- AE, system revision, and/or protocol deviation (if applicable).

6-Month Follow-Up Visit (6 months ± 30 days since initial programming or consent date)
The following information will be collected at the 6-month follow-up visit:
- PDQ-39;
- UPDRS part II ADLs On Medication / On Stimulation;
- UPDRS part III motor examination On Medication/ Off and On Stimulation assessed by a blinded evaluator;
- Programming parameters; device session data;
- Subject and clinician preference;
- Unscheduled visits (if applicable);
- AE, system revision, and/or protocol deviation (if applicable).

12-Month Follow-Up Visit (12 months ± 60 days since initial programming or consent date)
The following information will be collected at the 12-month follow-up visit:
- PDQ-39;
- Patient SUS questionnaire
- UPDRS part II ADLs On Medication / On Stimulation;
- UPDRS part III motor examination Off Medication/Off and On Stimulation;
- UPDRS part III motor examination On Medication/ Off and On Stimulation;
- Omnidirectional and directional testing - Off Medication;
- Programming parameters; device session data;
- Programmer SUS questionnaire;
- Unscheduled visits (if applicable);
- Current Parkinson's Disease medication;
- AE, system revision, and/or protocol deviation (if applicable).

24-Month Follow-Up Visit (24 months ± 90 days since initial programming)
The following information will be collected at the 24-month follow-up visit:
- AE and/or protocol deviation (if applicable). Adverse events will be reported on subjects who consent for participation in the long-term follow-up. The start date for reporting events will be the day of the previous PROGRESS follow-up visit, to ensure that all adverse events are reported. Adverse events will continue to be reported for the duration of the subject's participation in the long-term follow-up.

The 24-month visit may be performed in person or by telephone, at investigator decision. If consent for the long-term follow-up occurs after window for the 24-month follow-up visit has passed, it will be considered a missed visit with no protocol deviation required. The subject will be scheduled for the 36-month visit based on initial programming date.

36-Month Follow-Up Visit (36 months ± 90 days since initial programming)
The following information will be collected at the 36-month follow-up visit:
- PDQ-39;
- UPDRS part II ADLs On Medication / On Stimulation;
- UPDRS part III motor examination Off Medication/Off and On Stimulation;
- UPDRS part III motor examination On Medication/ Off and On Stimulation.
- Omnidirectional and directional testing - Off Medication;
- Programming parameters; device session data;

- Unscheduled visits (if applicable);
- Current Parkinson's Disease medication;
- AE, system revision, and/or protocol deviation (if applicable).

Evaluation of Programming/Device Testing:
Device testing is to be completed with the subject in the Off Medication state.
Subjects are to be instructed not to take their medication the night prior to or the morning of the study visit; or depending on the type of levodopa medication the subject is taking (i.e.; extended release or long acting) the investigator can use clinical judgement to determine an adequate length of time that the subject should be off medication prior to the testing.

In order to minimize programming bias, each site will have a designated programmer and a designated blinded evaluator during the omnidirectional and directional device testing. The blinded evaluator will be unaware of the specific program changes made to the device parameters during each testing.

Initial Programming Visit
Each site will perform their standard monopolar review of each lead to determine the best contact selection for the subject followed by:

Omnidirectional Testing – Assessment of the contact that has been selected as providing the best clinical benefit. Omnidirectional testing is defined as:
- Any of the contacts on a 4 channel lead (1-4); or
- All 3 segments (A, B, and C) are activated on contact 2 or 3 of the 8 channel lead; or
- Contact 1 or 4 active on the 8 channel lead

Each lead will be assessed by a blinded evaluator for first meaningful therapeutic effect followed by assessment of first sustainable side effects.

As the amplitude is increased by the programmer, the therapeutic effect on the motor symptoms will be based on the blinded evaluator's clinical judgement.
First meaningful therapeutic effect will be determined by the blinded evaluator's clinical judgement of the benefit seen for the subject's primary motor symptoms (i.e.; first benefit seen in at least one of the cardinal symptoms of PD (Tremor, Rigidity, or Bradykinesia or other).

Once first therapeutic effect is determined, the site will test for side effects. The amplitude will continue to be increased slowly by the programmer until the first sustainable side effect is observed by the blinded evaluator.
Side effects will be documented based on the determination of the blinded evaluator.

The width of the therapeutic window is defined as the electrical current at which a sustained side effect appeared minus the electrical current at which a meaningful therapeutic benefit was obtained.

Subjects are to be programmed and remain programmed in an omnidirectional configuration from the initial programming visit until the 3-month visit. If in the investigator's opinion, omnidirectional

configuration does not provide adequate therapy for the subject, the investigator may change the programming to allow the use of a directional configuration.

3-Month Visit - Device testing is to be completed with the subject in the Off Medication state.
In order minimize bias and maintain the blind as much as possible for the blinded evaluator, the site's designated programmer will be asked to flip a coin to determine which testing configuration will be completed first ("heads" will be designated as omnidirectional and "tails" will be designated directional). This is so that the testing is not always completed in the same order.

Omnidirectional testing will be repeated according to the instructions above.

A detailed directional lead/contact testing will also occur as tolerated by the subject. The testing will be completed in 2 steps for a total of 6 assessments. Each programming/detailed device testing can be performed over multiple days (within the same calendar week). Each lead will be assessed for first meaningful therapeutic effect followed by assessment of first sustainable side effects by the blinded evaluator.

Directional Testing:
Step 1: 8 Channel Lead – Directional assessment of each individual segment of the contact (2 or 3) that has been selected as providing the best clinical benefit. Testing will be completed in the following configurations:

- Segment 2 or 3A; followed by;
- Segment 2 or 3B; followed by;
- Segment 2 or 3C.

Step 2 (optional): 8-Channel Lead - Directional testing of 2 segments on the same contact. Two segments may be activated together: Each of the following configurations may be tested for a total of 3 separate tests. Select contact 2 or contact 3 for testing based on the best clinical benefit from testing in Step 1:

- A and B activated; followed by;
- B and C activated; followed by;
- A and C activated.

For each of the above steps, the amplitude will be increased slowly by the programmer until the blinded evaluator confirms first therapeutic effect. As the amplitude is increased, the first therapeutic effect on the motor symptoms will be based on the blinded evaluator's clinical judgement..
First meaningful therapeutic effect will be determined by the blinded evaluator's clinical judgement of the benefit seen for the subjects primary motor symptoms (i.e.; first benefit seen in at least one of the cardinal symptoms of PD (Tremor, Rigidity, or Bradykinesia or other)). Once first therapeutic effect is determined, the site will test for side effects. The amplitude will continue to be increased slowly by the programmer until the first sustainable side effect is observed by the blinded evaluator. Side effects will be documented based on the determination of the blinded evaluator.

Clinicians should use clinical judgement to determine the amount of time required to rest between each lead segment evaluation. It is suggested to allow a minimum of at least a 2-minute rest period between each contact/segment testing. During the testing session the clinician will also rate the subject's fatigue level.

The width of the therapeutic window is defined as the electrical current at which a sustained side effect appeared minus the electrical current at which a meaningful therapeutic benefit was obtained.

At the conclusion of the 3-month visit, the site physician should select the directional program that provides the best clinical benefit for the subject based on the detailed device testing that was completed and the subject should remain programmed using a directional configuration until the 6-month visit. If in the investigator's opinion, the directional configuration does not provide adequate therapy for the subject, the investigator may change the programming to allow the use of an omnidirectional configuration. Subjects who are implanted with the 4 channel lead will only have the omnidirectional testing at the initial programming visit to determine therapeutic window and first side effect. At the 3-month visit these subjects will complete the omnidirectional testing, will have the programming parameters collected and will complete the visit evaluations.

12-Month Visit - Device testing is to be completed with the subject in the Off Medication state. Omnidirectional and directional testing will be repeated according to the instructions above.

36-Month Visit - Device testing is to be completed with the subject in the Off Medication state. Omnidirectional and directional testing will be repeated according to the instructions above.

6.7 UNSCHEDULED VISITS

An unscheduled visit is defined as any visit that occurs outside of a specified study visit. Only unscheduled visits occurring after the permanent implant (all components implanted) will be recorded.

The visit still needs to be documented by completing the appropriate forms if applicable, Adverse Event, Death and/or Withdrawal.

6.8 DESCRIPTION OF ACTIVITIES PERFORMED BY SPONSOR REPRESENTATIVES

Trained sponsor personnel may perform certain activities to ensure compliance to the clinical investigational plan and may provide technical expertise.

Sponsor personnel may:
Provide technical support to the Investigators during implantation and programming

Sponsor personnel will not:
- Perform the informed consent process
- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of a health care practitioner
- Independently collect clinical investigational data
- Assist the physician in the completion of the UPDRS or subject in the SUS forms completion

6.9 SUBJECT STUDY COMPLETION

When a subject completes the 36-month follow-up visit, the subject's participation in the clinical study is complete. The subject will return to the medical care as per physician's recommendation.

6.10 ANY KNOWN OR FORSEEABLE FACTORS THAT MAY COMPROMISE THE OUTCOME OF THE CLINICAL STUDY OR THE INTERPRETATION OF THE RESULTS

All foreseeable factors that may compromise the outcome have been taken into account by the clinical study design and well-defined subject selection criteria.

Patient recruitment and retention will be monitored throughout the study and include (but are not limited to) the following activities: evaluation of the site and investigators, training of site personnel, developing site support materials, providing patient visit calendars.

6.11 DESCRIPTION OF THE METHODS THAT WILL BE USED TO ADDRESS POTENTIALLY CONFOUNDING FACTORS IN THE CLINICAL STUDY DESIGN (e.g. stratified randomization, statistical analysis, etc.)

Stratified analysis will be used to diagnose potential confounding factors, and multivariable regression will be used to adjust the outcome of the primary endpoint in case confounding factors are identified.

Subject factors including, but are not limited to:
- Subject baseline characteristics
- Concomitant medication
- Use of other medical device

6.12 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Each subject should remain in the study until completion of the required follow-up period; however, a subject's participation in the study may be discontinued at any time. Should this occur, the reason for discontinuation must be documented in the withdrawal form.

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:
- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons.
- Subject undergoes a system revision or system explant
- Subject is deceased (cause must be documented)
- 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
- Subject is lost to follow-up: Subject does not adhere to the scheduled follow-up visits but has not explicitly requested to be withdrawn from the clinical study. (This does not apply to missed visits).

Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow-up visits:

1. A subject will be considered lost to follow-up after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.
2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's hospital records.

Note: If a subject misses one or more of the scheduled follow-up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

If a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation as appropriate.
The status of the subject's condition should be documented at the time of withdrawal.

7.0 COMPLIANCE TO CIP

7.1 STATEMENTS OF COMPLIANCE

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining EC or IRB approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the EC or IRB or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an EC or IRB, and regulatory requirements with respect to the study, that information will be forwarded to St. Jude Medical.

7.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, EC or IRB requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.
In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form. The site will submit the CRF to St. Jude Medical.

Regulations require Investigators obtain approval from St. Jude Medical and the EC or IRB before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC or IRB. Such deviations shall be documented and reported to the sponsor and the EC or IRB as soon as possible, but no later than 5 working days.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported on a CRF.

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

Investigator will notify St. Jude Medical and the reviewing EC or IRB within 5 working days of:
- Any deviation to protect the life or physical well-being of a subject in an emergency
- Any failure to obtain informed consent

Investigators or the designee must notify St. Jude Medical, Inc. as soon as possible and complete the Deviation CRF.

The Investigator is required to adhere to local regulatory requirements for reporting deviations to EC or IRB.

7.3 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:
- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing

- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

8.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

8.1 DEFINITIONS

8.1.1 Adverse Event (AE)

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 study.

This definition includes events related to the medical device and the procedures involved.

8.1.2 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

8.1.3 Adverse Device Effect (ADE)

An adverse event related to the use of a medical device used in the study.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the medical device.

8.1.4 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DEVICE DEFICIENCIES/COMPLAINTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS, AND SERIOUS ADVERSE DEVICE EFFECTS:

General AE Reporting
Safety surveillance within this study and the safety reporting both performed by the Investigator, starts as soon as the subject is enrolled in this study (date of signature of the informed consent). Safety surveillance and the safety reporting will continue until the last study visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

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

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Records relating 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. All adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

SAE Reporting
The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs 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 must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Reportable events to sponsor are considered:
1) All Serious Adverse Events;
2) All device related Adverse Events (whether or not the event is considered serious).

Procedure related AEs as noted in Section 3.3 that are not identified as Serious Adverse Events should only be reported if they become severe, become reportable as an SAE, or if they continue for greater than 30 days after the surgery date. The following commonly reported procedure related AEs should only be reported as AEs if they continue for longer than 30 days postoperatively:

- Headache
- Persistent pain at surgery site or IPG site
- Post-operative pain, stress, or discomfort

- Confusion (transient, nocturnal, or ongoing)
- Cognitive impairment including delirium, dementia, disorientation, psychosis and speech difficulties
- Complications from anesthesia

The Sponsor will ensure that all events (noted above) are reported to the relevant authorities as per regulations.

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

All adverse events (as noted above) will be reported as per applicable regulatory requirements.

In addition to the adverse events commonly associated with surgery, the potential adverse events in section 3.3 are associated with a DBS system.

8.3 SUBJECT DEATH

8.3.1 Procedure for recording and reporting subject death

Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the AE case report form and submit to Sponsor. The death events must be reported as per the SAE reporting requirements provided in the above section 8.2. 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 outcome of an AE and an early conclusion of the subject's participation in the clinical investigation. Therefore, the Investigator is required to complete the Withdrawal form.

8.4 DEVICE DEFICIENCY (DD)/COMPLAINT REPORTING

During the study, the Investigator will be responsible for reporting all complaints. A complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

If the complaint does not involve an AE, the Investigator must notify the Abbott Post Market Surveillance Department by submitting the information on the device [redacted] as soon as possible after becoming aware of the complaint. This information will not be collected on a CRF for the study.

If the complaint involves an AE, the Investigator must complete an AE CRF, including the information on the complaint and submit to Abbott as soon as possible and in accordance with the local laws and regulations.

9.0 DATA MANAGEMENT

The Sponsor and its affiliates will be responsible for the data handling, and for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information collected or maintained for this clinical study. The privacy of each subject and confidentiality of his/her information will be preserved in reports when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC or IRB review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

9.1 DATA MANAGEMENT PLAN

A detailed Data Management Plan will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.2 DOCUMENT AND DATA CONTROL

9.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the electronic case report forms (eCRFs) and in all required reports.

9.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the eCRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

The CRFs will be signed and validated (eCRF) by the authorized site personnel.

9.2.3 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 transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. 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. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

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.

10.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

11.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment

where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC or IRB have not been submitted or are incomplete, inaccurate, false or misleading.

12.0 STATISTICAL CONSIDERATIONS

12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

A subset of subjects enrolled in this study will be used to meet the Post Market Clinical Follow-Up (PMCF) requirement for CE mark. Once this subset of subjects is enrolled and followed for 12 months and have evaluable endpoint data at the 3-month follow-up visit, a report pertaining to primary endpoint and secondary endpoints analyses will be submitted indicating completion of this requirement.

12.1.1 Primary Endpoint

The proportion of subjects with a therapeutic window (evaluated by a blinded evaluator) which is larger under directional stimulation than omnidirectional stimulation will be tested against a performance goal of 60% at the 3-month follow-up visit.

The width of the therapeutic window is defined as the electrical current at which a sustained side effect appeared minus the electrical current at which a meaningful therapeutic benefit was obtained. The directional segment with the widest therapeutic window will be compared to omnidirectional stimulation.

Hypothesis

The hypothesis is formally expressed as:

H_0: $p \leq 0.60$

H_a: $p > 0.60$

where p is the probability that the therapeutic window under directional stimulation is larger than the therapeutic window under omnidirectional stimulation.

Analysis

The primary endpoint will be tested at the 5% significance level. The analysis population includes subjects who have evaluable therapeutic window using omnidirectional and directional stimulation. The analysis will be carried out by calculating the 95% lower confidence bound (LCB) on the success rate using the Clopper-Pearson exact method. The null hypothesis will be rejected if the 95% lower confidence bound (LCB) for p is greater than 0.60.

12.1.2 Secondary Endpoint

12.1.2.1 Secondary Endpoint 1

If the primary study endpoint is not met, the following hypothesis will be tested to evaluate non-inferiority of therapeutic window with directional stimulation compared to omnidirectional stimulation.

Hypothesis

The hypothesis is formally expressed as:

H_0: $p \leq 0.40$

H_a: $p > 0.40$

where p is the probability that the therapeutic window under directional stimulation is larger than the therapeutic window under omnidirectional stimulation (success).

Analysis

The secondary endpoint will be tested at the 5% significance level. The analysis population includes subjects who have evaluable therapeutic windows under omnidirectional and directional stimulation. The analysis will be carried out by calculating the 95% lower confidence bound (LCB) on the success rate using the Clopper-Pearson exact method. The null hypothesis will be rejected if the 95% lower confidence bound (LCB) for p is greater than 0.40.

12.1.2.2 Secondary Endpoint 2

The endpoint will test whether directional stimulation has greater therapeutic effect than omnidirectional stimulation by comparison of 3- and 6-month UPDRS part III motor examination (as evaluated by a blinded evaluator).

Change in UPDRS part III motor examination within each subject is defined as:

Change in UPDRS part III = UPDRS part III at 3 month (omnidirectional) – UPDRS part III at 6 months (directional)

The following hypothesis will be tested:

H_0: mean change in UPDRS part III motor examination ≤ 0

H_a: mean change in UPDRS part III motor examination > 0

Analysis

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% lower confidence bound (LCB) on the mean change in UPDRS part III motor examination score based on a t-distribution. The null hypothesis will be rejected if the 95% LCB is greater than 0.

12.2 SAMPLE SIZE

The sample size is calculated assuming a success (therapeutic window of directional stimulation is larger than the one of omnidirectional stimulation) rate of 75%. [redacted]

12.3 PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE CLINICAL STUDY

There are no pass/fail criteria to be applied to the results of this clinical study.

12.4 THE PROVISION FOR AN INTERIM ANALYSIS, when applicable

Masked interim analysis will be performed to compare distribution of therapeutic window at 3 months, and to compare UPDRS at 3 and 6 months. Group names will be masked. Masked analysis will also be performed for the subset of subjects enrolled at implant, and for the subset of subjects enrolled after implant. Additional unblinded interim analysis will be conducted after additional subjects reach 3 months of follow-up.

12.5 CRITERIA FOR THE TERMINATION OF THE CLINICAL STUDY ON STATISTICAL GROUNDS

There is no planned termination for the study based on statistical grounds.

12.6 PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any deviations from the statistical analysis plan will be documented.

12.7 THE SPECIFICATION OF SUBGROUPS FOR ANALYSIS

There will be a subgroup analysis of change in UPDRS part III motor examination score from 3 months to 6 months for the subset of subjects using omnidirectional stimulation at 3 months and directional stimulation at 6 months. Subject and clinician preference will be evaluated for the subset who have omnidirectional stimulation for the first 3 months and directional stimulation for the subsequent 3 months. There will also be a subgroup analysis of endpoints for the subset of subjects enrolled at implant, and for the subset of subjects enrolled after implant.

12.8 PROCEDURES THAT TAKE INTO ACCOUNT ALL THE DATA

Analyses will be performed in subjects who have evaluable therapeutic windows for both omnidirectional and directional stimulation for the primary endpoint and the first secondary endpoint. The analysis will be performed in subjects who have 3- and 6-month UPDRS part III motor examination

complete for the second secondary endpoint. Subject accountability for enrolled subjects will be performed prior to analyses of the primary and secondary endpoints.

12.9 THE TREATMENT OF MISSING, UNUSED, OR SPURIOUS DATA, INCLUDING DROP-OUTS AND WITHDRAWALS

There are no plans to perform imputations for missing data, subject dropouts or withdrawals. If spurious data are discovered, these data will be excluded from analyses. Reasons for exclusion of any data from analyses will be summarized.

12.10 THE EXCLUSION OF PARTICULAR INFORMATION FOR THE TESTING OF THE HYPOTHESIS

There are no intent to exclude information for the testing of the hypothesis.

12.11 IN MULTI-CENTER STUDIES, THE MINIMUM AND MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED FOR EACH CENTER

A minimum of 1 subject may be included at each center participating in the study.

12.12 TIMING FOR ANALYSES

The dataset will be frozen for analysis when 66 subjects have completed the 12-month visit and have evaluable primary endpoint at the 3-month follow-up visit to support the minimum requirements to meet the Post Market Clinical Follow-Up (PMCF) requirement for CE mark.

13.0 DOCUMENT RETENTION

St. Jude Medical and the Principal Investigators will maintain the clinical study documents as required by St. Jude Medical, Inc. and applicable regulatory requirements. They will take measures to prevent accidental or premature destruction of these documents. The Principal Investigator or St. Jude Medical may transfer custody of records to another person/party and document the transfer at the investigational site or at St. Jude Medical's facility.

These documents must be retained by the investigational site for a period of 2 years after clinical study conclusion and made available for monitoring or auditing by St. Jude Medical's representative or representatives of the FDA and other applicable regulatory agencies. The Principal Investigator must ensure the availability of source documents from which the information on the case report forms was derived.

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the Investigator Brochure (IB), Report of Prior Investigations (RPI), CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the Steering Committee (if applicable). The Steering Committee is responsible for

overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the EC or IRB and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

15.0 INVESTIGATION SUSPENSION OR TERMINATION

15.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY OR OF THE CLINICAL STUDY IN ONE OR MORE INVESTIGATIONAL SITES

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

Possible reasons for early termination of the study by the sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Recommendation from DSMB to Steering committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee or Institutional Review Board
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 72 hours to St. Jude Medical and the EC
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The study will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor.

Should either of these events occur, the investigator will return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the EC or IRB and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, EC or IRB or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the EC or IRB or regulatory authority, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from EC or IRB or regulatory authority.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the EC or IRB are notified, either by the Principal Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

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

15.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Principal Investigators, EC or IRB, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical study resumes from the EC or IRB or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform subjects of the reasons for resumption.

15.3 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed AND
- The final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure. The final report will be submitted within one year of the end of the investigation.

16.0 PUBLICATION POLICY

The results of the clinical study will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

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APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigational Plan
CRF	Case Report Form
CT	Computed Tomography
DBS	Deep Brain Stimulation
DD	Device Deficiency
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
GP	General Practitioner
IB	Investigator Brochure
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISO	International Organization for Standardization
MDR	Medical Device Reporting
MRI	Magnetic Resonance Imaging
NA	Not Applicable
PI	Principal Investigator
PMCF	Post Market Clinical Follow Up
PD	Parkinson's disease
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
STN	Subthalamic Nucleus
SUS	System Usability Scale
UPDRS	Unified Parkinson's Disease Rating Scale
USADE	Unanticipated Serious Adverse Device Effect

APPENDIX B: CIP REVISION HISTORY

[redacted]

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

Appendix C: DECLARATION OF HELSINKI

The most current version of the document will be followed.

Appendix D: INFINITY DBS SYSTEM COMPONENTS

The Infinity DBS system under investigation includes the following devices and accessories:

Component	Model Number and Name
DBS IPG	6660 Infinity 5 IPG 6662 Infinity 7 IPG
Lead	6170 8-channel directional lead, 30 cm, 0.5 mm spacing 6171 8-channel directional lead, 30 cm, 1.5 mm spacing 6172 8-channel directional lead, 40 cm, 0.5 mm spacing 6173 8-channel directional lead, 40 cm, 1.5 mm spacing 6166 4-channel lead, 30 cm, 0.5 mm spacing 6167 4-channel lead, 30 cm, 1.5 mm spacing 6168 4-channel lead, 40 cm, 0.5 mm spacing 6169 4-channel lead, 40 cm, 1.5 mm spacing
Extension	6371 8-channel flexible extension, 50 cm 6372 8-channel flexible extension, 60 cm 6373 8-channel flexible extension, 90 cm 6355 4-channel flexible extension, 50 cm 6356 4-channel flexible extension, 60 cm 6359 4-channel flexible extension, 90 cm
Accessory	6010 Guardian™ cranial burr hole cover system 6015 Screw, 5 mm 1190 Tunneling tool, 0.125” 1101 Torque wrench 1111 Port plug Large pocket sizer Small pocket sizer 6599 DBS EPG, 16 channel 3014 Multi-lead trial cable 1210 Patient magnet 1803 Lead and extension insertion tool 1140 DBS lead stop
Clinician Programmer	3874 Clinician programmer application
Patient Controller	3875 Patient controller application

Appendix E: LIST OF CLINICAL INVESTIGATION SITES AND IRB/EC

[redacted]

Appendix F: SAMPLE INFORMED CONSENT

[redacted]

Appendix G: CASE REPORT FORMS

[redacted]