Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT02963259
PREFERENCE-H
Prospective Evaluation comparing the Effects of Constant Current versus Constant Voltage in Deep Brain Stimulation using Hybrid systems
Study Document No: SJM-CIP-10125
Version B
Date: 10-OCT-2016

Sponsor

Abbott/ SJM International, Inc.
The Corporate Village
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Belgium

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Clinical Investigational Plan

Reference:
SJM-CIP-10135

PREFERENCE-H

Prospective Evaluation comparing the Effects of Constant Current versus Constant Voltage in Deep Brain Stimulation using hybrid systems.

Clinical Investigation Plan (CIP)

Sponsor

St. Jude Medical International, Inc.
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PRINICPAL INVESTIGATOR SIGNATURE PAGE

PREFERENCE-H

Reference #: SJM-CIP-10135

Version A

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

SIGNATURE PAGE

PREFERENCE-H
Reference #: SJM-CIP-10135

Version A

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: _____

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1.0 SYNOPSIS

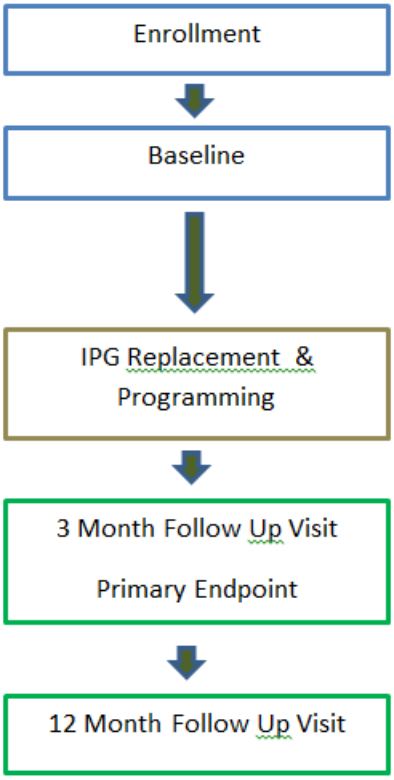
Title:	Prospective evaluation comparing the effects of constant current versus constant voltage in Deep Brain Stimulation using hybrid systems*.
Acronym:	PREFERENCE-H
Purpose:	To evaluate subject's preference for different stimulation modes (i.e. constant voltage and constant current).
Primary Objective:	The primary objective of the study is to demonstrate the subject's preference for a stimulation modality.
Secondary Objective:	The secondary objective of the study is to demonstrate the safety of the hybrid DBS system.
Primary Endpoint:	The primary endpoint is the proportion of subjects who indicate preference on constant current over constant voltage at the 3 Month follow-up visit.
Secondary Endpoint:	The secondary endpoint is the rate of safety events related to battery replacement procedures for hybrid systems.
Descriptive Endpoints:	• The change in Speech Handicap Index at 3 and 12 Months compared to Baseline; • The change in total UPDRS score and the individual UPDRS components at 3 and 12 Months compared to Baseline; • The change in Levodopa medication at 3 and 12 Months compared to Baseline; • The change in Freezing of Gait Questionnaire (FOGQ) scores at 3 and 12 Months compared to Baseline; • The change in Tinetti Test scores at 3 and 12 Months compared to Baseline; • The change in Berg Balance Scale scores at 3 and 12 Months compared to Baseline; • The change in PDQ-39 scores at 3 and 12 Months compared to Baseline; • Proportion of subjects who indicate satisfaction with constant current at 3 and 12 Months; • Proportion of caregivers who indicate satisfaction with constant current at 3 and12 Months; • Proportion of subjects who indicate preference on the constant current over the constant voltage at the 12 Month follow-up visit; • Summary of Health Economic Data for constant current compared to constant voltage.
Design:	Prospective, multicenter, multinational, post-market clinical study. The clinical study will be conducted in approximately 20 centers in Europe, Australia and the United States and approx. 170 subjects will be enrolled. Subjects will be followed for 12 months post battery replacement. The total duration of the study for a subject is expected to be approximately 15-24 months.

Devices used:	• St Jude Medical Infinity™ DBS system • St Jude Medical Brio™ DBS system
Study Population	Subjects who have a diagnosis matching the approved indication and are being considered for an IPG replacement comprise the target population of this study. All subjects who meet the inclusion and none of the exclusion criteria and have signed an Ethics Committee (EC) or Institutional Review Board (IRB) approved informed consent will be considered enrolled in the study.
Inclusion/Exclusion Criteria	Inclusion Criteria: Subjects meeting all the inclusion criteria can be considered for inclusion in the study: • Subject signed the approved Informed Consent; • Subject is ≥18 and ≤ 74 years of age; • Subject is bilaterally treated with deep brain stimulation (DBS) in the subthalamic nucleus (STN) using a constant voltage device (i.e. Soletra™, Itrel™, Kinetra™, ActivaPC™ or ActivaRC™ IPG) and in the Investigator's opinion, is responding satisfactory to CV stimulation; • In the physician's opinion the subject is a suitable candidate for an IPG replacement with different stimulation paradigm; • Subject needs and/or requests an IPG replacement within 12 months after consent and the current IPG has at least 2.6 V output left (i.e. approx. 30% of full battery capacity) at the time of subject enrollment; • PD symptom onset is no longer than 20 years; • Subject has a Hoehn & Yahr score <IV (on stim); • Subject with a normal cognitive function (MMSE ≥ 25); • Subject is fluent speaker (as judged by the investigator) of the language spoken in the country where the investigational site is located. Exclusion Criteria : Subjects will be excluded from the study if they meet any of the following criteria: • IPG battery has less than 30% battery life at the time of consent; • Need to replace or reposition the leads or extensions during the IPG replacement procedure; • Subject had >10 recurrent falls experienced in the 3 months prior to consent; • Subject is unwilling to change to either a St Jude Medical Infinity™ or a St Jude Medical Brio™ DBS system for the IPG replacement; • Subject is unable to attend the study visits.
Data Collection	Data will be collected at Enrollment, Baseline, IPG replacement, 3 Months and 12 Months after IPG replacement. At the Enrollment Visit the Informed Consent procedure will be completed, Inclusion and Exclusion Criteria confirmed, Demographic and Medical History data collected. At the Baseline Visit the following will be collected: Stimulation

	Programming Settings, Medication, Health Economic Data, Speech Handicap Index, Freezing of Gait Questionnaire, Tinetti Test, Berg Balance Scale, Parkinson's Disease Questionnaire, Unified Parkinson's Disease Rating Scale (Part I, II IV On Med/OnStim, Part III On Med/On Stim and On Med/Off Stim), Satisfaction of Therapy Questionnaire for the subject and the caregiver, Adverse Events or Withdrawal (if applicable) At the IPG Replacement Visit the implanted Medtronic® IPG will be explanted and replaced by a SJM Infinity™ DBS IPG or a SJM Brio™ DBS system according to the standard surgical procedures and instructions for use. The time point for the replacement will be decided by the physician according to their standard procedure. Intra-operative assessments and the initial CC programming session will be performed according to each individual site's standard procedure. The frequency, pulse width and number of contacts (monopolar/bipolar) of the stimulation should be kept constant between the constant voltage and the constant current stimulation. The following data will be collected: Implant Information, Initial Programming Information, Adverse Events or Withdrawal (if applicable) At the 3 Months Visit the following will be collected: Stimulation Programming Settings, Medication, Speech Handicap Index, Freezing of Gait Questionnaire, Tinetti Test, Berg Balance Scale, Parkinson's Disease Questionnaire, Unified Parkinson's Disease Rating Scale (Part I, II, IV On Med/OnStim, Part III On Med/On Stim and On Med/Off Stim), Satisfaction of Therapy Questionnaire for the subject and the caregiver, Subject's Preference, Adverse Events or Withdrawal (if applicable) At the 12 Months Visit the following will be collected: Stimulation Programming Settings, Medication, Speech Handicap Index, Freezing of Gait Questionnaire, Tinetti Test, Berg Balance Scale, Parkinson's Disease Questionnaire, Unified Parkinson's Disease Rating Scale (Part I, II, IV On Med/OnStim, Part III On Med/On Stim and On Med/Off Stim), Satisfaction of Therapy Questionnaire for the subject and the caregiver, Health Economic Data, Subject's Preference, Adverse Events or Withdrawal (if applicable).

*Hybrid systems are systems that use device components from different manufacturers (e.g. St Jude Medical and Medtronic).

1.1 STUDY FLOW CHART



1.2 STUDY CONTACTS

[redacted]

[redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Deep brain stimulation (DBS) is widely used to treat motor symptoms in patients with advanced Parkinson's disease (PD) (Aström, Stereotact Funct Neurosurg 2010). DBS is the surgical treatment of choice for Parkinson's disease (PD) patients with medication resistant motor fluctuations, dyskinesias and refractory tremor (Krack, N Engl J Med. 2003; Lang, Mov Disord. 2006; Lang, Mov Disord. 2002) DBS of the subthalamic nucleus (STN) has been shown to improve not only the primary motor symptoms of PD and levodopa-induced motor complications, but also overall quality of life. DBS is an adjustable treatment, with the potential to optimize the treatment through implantable pulse generator (IPG) programming options, by changing the polarity, amplitude (V or mA), pulse width (µsec), and frequency (Hz) of the device.

As problematic side effects after initiation of DBS therapy with first generation unregulated DBS devices have included difficulties in speech, gait and some features of cognition (C Daniels, Movement Disorders 2010; Krack; N Engl Med. 2003). It has been shown that DBS treatment in the Subtalamic Nucleus (STN) can affect some aspects of intelligibility of speech depending on different IPG programming parameters. A particular cognitive side-effect most frequently observed after surgery can be a decline in the verbal fluency tasks in both the phonemic and semantic domain (Castelli, J Neurology 2007). Parameter settings shown to induce significant reduction of PD symptoms may in some cases result in either uninfluenced or intelligibility of speech. (Törnqvist, Movement Disorder 2005). A hypothesis explaining the worsening effect of STN-DBS on speech indicates the decline is related to the influence of the stimulation (current spread) on sounding neural pathways and this system includes cognitive circuits (Tripoliti, Movement Disorders 2008; Woods Neuropsychology Review, 2002)

Large similarities between gait patterns and speech involvement in PD and their response to STN-DBS and levodopa treatment have been demonstrated. The walking cadence and speech index of velocity tend to be lower in patients and are not significantly improved by STN-DBS or levodopa (Cantiniaux J Neurol Neurosurg Psychiatry 2010).

DBS is widely performed using voltage-controlled devices, which were refined from those utilized in cardiac pacing (Cheung & Tagliati, 2010). Such electrical stimulation can be supplied to the brain either using a constant current or a constant voltage power source. A constant current source provides a consistent current to the tissue by adjusting the voltage in response to the tissues impedance. A constant voltage source adjusts the current in response to a change in impedance thereby maintaining the voltage constant. There is evidence that constant current stimulation may provide more accurate control of the electrical field spread produced by these devices through adjustments for the heterogeneity in tissue impedance (Lempka, 2010).

Published research investigating the influence of DBS on parkinsonian patient's speech, gait and cognition has been performed applying constant voltage implantable impulse generators (IPGs). Patients, previously implanted with constant voltage devices and re-implanted (at IPG end of life) with a Brio™ constant current system have reported post-operative improvements in speech according to the feedback received from their implanting physicians.

This post-marketing evaluation has been designed to consistently investigate the subject's preference when switching from a Medtronic® constant voltage or constant current device to a St Jude Medical Infinity™ or St Jude Medical Brio™ constant current system. As electrodes will not be re-positioned,

differences in subject's preference are to be explained by the difference in shape of the delivered pulse or waveform between the two systems.

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

3.1 DESCRIPTION OF SUBJECT POPULATION

The subject population enrolled in this investigation will be comprised of male and female subjects. Subjects have to meet the specific eligibility criteria in order to participate in the study.

3.2 ANTICIPATED CLINICAL BENEFITS

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

3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

The replacement of a DBS IPG involves risks. In addition to those risks commonly associated with surgery, the following risks are also associated with implantation and / or use of the device:

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 the 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.

Complications may occur leading in some cases to surgical revision or explant of the system.

Possible 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 due to a change in electrode positions, loose electrical connections, or lead or extension fraction
- 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 with 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 PD 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 and language impairment including aphasia, dysphagia, dysarthria and hypophonia
- Cognitive impairment including attention deficit, disorientation, abnormal thinking, hallucinations, amnesia, delusions, dementia, inability to act or make decisions, physic 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 PD and essential tremor that is reversible, and adaptable.

The targeted study population consists of subjects who have been previously implanted with a Medtronic® DBS device and re-implanted at the IPG's end of life with a St Jude Medical Infinity™ DBS or St Jude Medical Brio™ DBS constant current system. Subject's preference will be collected for the 2 stimulation modes (i.e. constant voltage and constant current).

Effects of the DBS with constant current as well as with a constant voltage device are considered safe, non-destructive and reversible. The frequency and severity of procedural risks and complications related to the replacement of a Medtronic® device (constant voltage or constant current) by an Infinity™ device or Brio™ device (constant current) are expected to be similar to those 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

There are no known possible interactions with concomitant medical treatments. The following procedures are contra-indicated for patients that have been implanted with this device:

- Diathermy (short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy)
- MR imaging is contra-indicated for patients with an implanted neurostimulation system.

Please refer to the Infinity™ and Brio™ 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 additional risks for the subjects expected in 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 clinical study is to evaluate subject's preference for different stimulation modes (i.e. constant voltage and constant current).

4.2 STUDY DESIGN AND SCOPE

This post-marketing evaluation has been designed to consistently investigate the subject's preference when switching from a Medtronic® device (constant voltage) to a St Jude Medical Infinity™ device or a St Jude Medical Brio™ DBS system (constant current system). As electrodes are not re-positioned, differences in subject's preference are to be explained by the difference in shape of the delivered pulse or waveform between the two systems.

This is the first known study to evaluate the effects of constant voltage versus constant current between 2 manufacturers in PD subjects with regards to subject's preference and symptom control.

Subjects currently implanted with a Medtronic® device, who have been recommended as a candidate for IPG replacement by the Investigator 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 the study inclusion criteria and none of the exclusion criteria, he/she will be informed about the study to determine if he/she is interested in participating. After the subject signs the informed consent, he/she is considered enrolled in the study. The IPG replacement will be done according to the routine time point for IPG replacements.

During the surgery, the leads and extensions will not be re-positioned/revised. The IPG will be implanted according to the physician's standard operating procedures. The IPG will be activated and programmed using the Clinician Programmer by trained personnel. The subject may be given a Patient Controller, dependent on the physician's recommendation for patient care. Subjects will return for evaluation at 3 and 12 months post-implant for follow-up visits. This study is for data collection purposes and there are no additional risks to subjects that participate in this study than those risks associated with deep brain IPG replacement.

The study will be conducted in approximately 20 centers in Europe, Australia and the United States.

4.2.1 Number of subjects required to be included in the study

Approximately 170 subjects will be enrolled in the study.

4.2.2 Estimated time needed to enroll this subject population

[redacted]

4.3 OBJECTIVES

4.3.1 Primary Objective

The primary objective of the study is to demonstrate subject's preference for a stimulation modality.

4.3.2 Secondary Objective

The secondary objective of the study is to demonstrate the safety of the hybrid DBS system.

4.4 ENDPOINTS

4.4.1 Primary Endpoint

The primary endpoint is the proportion of subjects who indicate preference on constant current over constant voltage at the 3 Month follow-up visit.

4.4.2 Secondary Endpoint

The secondary endpoint is the rate of safety events related to battery replacement procedures for hybrid systems.

4.4.3 Descriptive Endpoints

The following data will be collected:

- The change in Speech Handicap Index at 3 and 12 Months compared to Baseline;
- The change in total UPDRS score and the individual UPDRS components at 3 and 12 Months compared to Baseline;
- The change in Levodopa medication at 3 and 12 Months compared to Baseline;
- The change in FOGQ scores at 3 and 12 Months compared to Baseline;
- The change in Tinetti Test scores at 3 and 12 Months compared to Baseline;
- The change in Berg Balance Scale scores at 3 and 12 Months compared to Baseline;
- The change in PDQ-39 scores at 3 and 12 Months compared to Baseline;
- Proportion of subjects who indicate satisfaction with constant current at 3 and 12 Months;
- Proportion of caregivers who indicate satisfaction with constant current at 3 and12 Months;
- Proportion of subjects who indicate preference on constant current over constant voltage at 12 Months;
- Summary of Health Economic Data between constant current and constant voltage.

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 his/her 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

- Subject (and caregiver,if applicable) signed the approved Informed Consent;
- Subject is ≥ 18 and ≤ 74 years of age;
- Subject is bilaterally treated with deep brain stimulation (DBS) in the subthalamic nucleus (STN) using a constant voltage device (i.e. Soletra™, Itrel™, Kinetra™, ActivaPC™ or ActivaRC™ IPG) and is responding satisfactory to CV stimulation in the Investigators opinion;
- In the physician's opinion, the subject is a suitable candidate for an IPG replacement with different stimulation paradigm;
- Subject needs and/or requests an IPG replacement within 12 months after consent and the current IPG has at least 2.6 V output left (i.e. approx. 30% of full battery capacity) at the time of subject enrollment;
- PD symptom onset is no longer than 20 years;

- Subject has a Hoehn & Yahr score <IV (on stim);
- Subject with a normal cognitive function (MMSE ≥25);
- Subject is fluent speaker (as judged by the investigator) of the language spoken in the country where the investigational site is located.

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

4.5.2 Exclusion Criteria

- IPG battery has less than 30% battery life at the time of consent;
- Need to replace or reposition the leads or extensions during the IPG replacement procedure;
- Subject had >10 recurrent falls experienced in the 3 months prior to consent;
- Subject is unwilling to change to a St Jude Medical Infinity™ or Brio™ DBS system for the IPG replacement;
- Subject is unable to attend the study visits.

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.

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 consented, as required by applicable regulations and the center's IRB/EC. Informed consent must be obtained from each subject, and in case they have a caregiver, also from the caregiver prior to any study related procedures. The consent form must be signed and dated by the subject, the caregiver (if applicable), and by the person obtaining the consent.

The principal investigator or his/her 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 relevant to the subject's decision to participate in the clinical study.

The subject (and the caregiver, if applicable) shall be provided with the informed consent form that is written in a language that is understandable to the subject (and the caregiver, if applicable) and has been approved by the center's IRB/EC. 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 IRB/EC/ consistent with the center's IRB/EC reporting requirements.

5.0 DEVICE UNDER INVESTIGATION AND CONTROL/COMPARATORS

5.1 DEVICE DESCRIPTION

In this study, the commercial available Infinity ™ IPG with compatible header, the Brio™ IPG and the pocket adapter that are compatible with the Medtronic® extensions will be used in this study.
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. Physicians use the clinician programmer to create and modify a program for a patient. Subjects use the patient controller to control their prescribed programs. The patient magnet can turn the IPG on and off if the physician enables this functionality.

The Infinity™ 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 '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. The models to be used in this study contain a header that is designed to allow the IPG to connect to Medtronic® extensions and/or leads that meet the compatibility guidelines.

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 the stimulation settings for a subject.

The patient controller is an off-the-shelf touch screen device (iPod Touch) with a SJM designed mobile Application software. Subjects use the patient controller to control their prescribed programs.
Description of the devices and instructions for use can be found in the User's Manual.

The components of the Brio™ DBS IPG to be used in this study include Brio™ DBS rechargeable IPG, a Pocket Adaptor™, a trial stimulator, a clinician programmer and a patient controller.
Description of the devices and instructions for use can be found in the User's Manual.

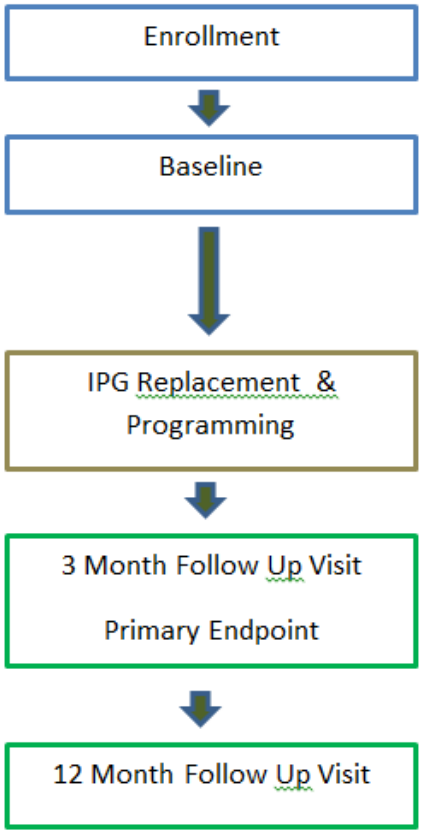
5.2 DEVICE HANDLING AND STORAGE

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

Figure 2: Flow Chart



6.2 PROCEDURES

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 IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).

Table 1: List of all study specific activities/procedures

Procedure	Enrollment	Baseline	IPG replacement & Programming	3 M FU (+-30 days)	12 M FU (+-30 days)
IC signed (Subject & Caregiver)**	X				
Inclusion/Exclusion Criteria	X				
Demographics		X			
Medical History		X			
Medication Review		X		X	X
Health Economic Data		X			X
(S)ADEs			X**	X**	X**
Withdrawal		X**	X**	X**	
Subject's Preference				X	X
QUESTIONNAIRES					
UPDRS I,II,III,IV On Med On Stim		X		X	X
UPDRS Part III On Med Off Stim		X		X	X
Satisfaction of Therapy (Subject & Caregiver)**		X		X	X
PDQ-39		X		X	X
TESTS					
Speech Handicap Index		X		X	X
Gait: 1.Tinetti 2. Freezing of Gait 3. Berg Balance Scale		X		X	X
PROGRAMMING					
Programming Settings		X*		X*	X*
Initial testing/programming			X		
SURGERY/IMPLANT					
Implant Information			X		

Unscheduled Visit: is defined as a follow up that is not explicitly requested by the protocol. Subjects may be asked to return to the clinic for unscheduled study visit. The following information will be recorded: Reason for visit, Action taken, Record program settings (when re-programming has been done).

*Before the questionnaires and the tests, the program settings for the subject should be recorded. After the questionnaires and the tests, the program settings for the subject may be optimized. The evaluator will decide when the settings are optimum. This might take several sessions.
**If applicable

Informed Consent Procedure and Inclusion/Exclusion Criteria:
Subject's eligibility criteria and Informed consent Procedure is performed at the Enrollment visit.

Subject Demographics:
Subject's Age, Weight, Height and Gender; will be collected at the Baseline 1 visit.

Medical History:
Diagnosis, 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.

Medication:
Subject's current medications for the indication will be collected at the Baseline visit and at the 3 and 12 Month Follow- Up visit.

Subject Data:
- Subject's Preference will be collected at 3 and 12 Month Follow-Up visit.
- UPDRS I (Mentation, Behavior and Mood), UPDRS II (Activities of Daily Living), UPDRS III (Motor exam) and UPDRS IV (Complications of Therapy) total scores 'On Medication/On Stimulation' will be collected at Baseline visit, 3 and 12 Month Follow- Up visits;
- UPDRS III Motor exam 'On Medication/Off Stimulation' will be collected at Baseline visit, 3 and 12 Month Follow- Up visit;
- Parkinson's Disease Questionnaire PDQ-39 (Quality of Life) will be completed at Baseline, 3 and 12 Month Follow- Up visit;
- Speech Handicap Index (SHI) will be collected at Baseline, 3 and 12 Month Follow- Up visit;
- Freezing of Gait Questionnaire (FOGQ) will be completed at Baseline, 3 and 12 Month Follow - Up visit;
- Tinetti Test will be assessed at Baseline, 3 and 12 Month Follow- Up visit;
- Berg Balance Scale will be assessed at Baseline, 3 and 12 Month Follow-Up visit;
- Satisfaction of Therapy Questionnaire for the subject will be completed at Baseline, 3 and 12 Month Follow- Up visit.

Caregiver:
Satisfaction of Therapy Questionnaire for the caregiver will be completed at Baseline, 3 and 12 Month Follow- Up visit (if subject has a caregiver).

Health Economic data:
Health Economic data will be collected at Baseline and 12 Month Follow- Up visit.

Programming:
Stimulation settings will be collected at each visit.
Initial programming parameters and settings will be collected at the IPG Replacement visit.
The frequency, pulse width and # of contacts (monopolar/bipolar) of the stimulation should be kept constant between the constant voltage and the constant current stimulation.
Additional programming sessions may be required during the study to optimize the therapy,

Implant:
Implant data will be collected at the IPG Replacement visit.

Please find here below a summary description of the questionnaires and tests:

Speech Handicap Index (SHI):
The SHI is a validated questionnaire with 30 items on speech related problems in daily life.

The Unified Parkinson's Disease Rating Scale (UPDRS):
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 Examination 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.

Freezing of Gait Questionnaire (FOGQ):
The FOGQ is a validated questionnaire with the purpose of identifying the freezing of gait.

Tinetti Test:
A measurement of functional ability that incorporates observation of performance of 13 activities with a focus on gait and balance. The activities include sitting, rising from a chair, standing, turning, reaching up, and bending down. The rating scale is normal, adaptive, or abnormal and is often used to assess the risk of falling.

Berg Balance Scale (BBS):
The test comprises a set of 14 simple balance related tasks, ranging from standing up from a sitting position, to standing on one foot. The degree of success in achieving each task is given a score of zero (unable) to four (independent), and the final measure is the sum of all of the scores

Parkinson's Disease Questionnaire (PDQ-39):
A disease specific instrument designed to measure aspects of health that are relevant to subjects with PD, and which may not be included in general health status questionnaires. The PDQ-39 is a self-administered questionnaire, which comprises 39 questions addressing eight dimensions of health that subjects consider to be adversely affected by the disease.

Satisfaction of Therapy Questionnaire:
Subject and caregiver (if applicable) will be asked to subjectively assess the rate of satisfaction with the deep brain stimulation therapy by completing a questionnaire.

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 subjects to determine subject eligibility for the study
- The inclusion/exclusion criteria will be verified.

- If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and cannot be enrolled.
- The subject is enrolled in the study when the subject signs the EC/IRB approved consent form.

Record enrollment information (name of the study, date of consent and inclusion/exclusion information) in the hospital records and complete the Enrollment form electronically in a timely manner (preferably within 5 days after enrollment).

As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines in this CIP.

In case the subject was consented to participate in the study, but does not meet inclusion/exclusion criteria, and did not receive an IPG replacement, the subject should be withdrawn and a withdrawal form must be completed. The subject will resume his/her regular standard of care with his/her physician.

In case the subject was consented to participate in the study, but does not meet inclusion/exclusion criteria, and did receive an IPG replacement, then this is considered a protocol deviation. A protocol deviation form needs to be completed and the Sponsor must be informed. The EC/IRB and Competent Authority (CA), if applicable, should be notified appropriately about any deviations with regard to the violation of inclusion/exclusion criteria.

The following data will be collected:

- Informed Consent signed (Subject & Caregiver [if applicable])
- Inclusion/Exclusion Criteria
- Demographics
- Medical History

6.4 BASELINE VISIT

The following information will be collected at the Baseline visit.

Baseline visit can be combined with Enrollment visit.

The following data will be collected:

- Medication
- Health Economic Data
- Speech Handicap (SHI)
- Unified Parkinson's Disease Rating Scale 'On Med/On stim'. ("On" state is defined as approximately 30 minutes after a subject takes anti-Parkinson medication when both the clinician and the subject indicate that the medication dose is effective.)
- Unified Parkinson's Disease Rating Scale part III 'On Med/Off Stim'
- Freezing of Gait Questionnaire (FOGQ)
- Tinetti Test
- Berg Balance Scale (BBS)
- Parkinson's Disease Questionnaire (PDQ-39)
- Satisfaction of Therapy Questionnaire for the subject
- Satisfaction of Therapy Questionnaire for the caregiver, if applicable
- Record programming settings

- Adverse events or Withdrawal (if applicable)

6.5 IPG REPLACEMENT VISIT & PROGRAMMING

The implanted Medtronic® IPG will be explanted and replaced by a SJM Infinity™ DBS IPG or a SJM Brio™ DBS system according to the standard surgical procedures and instructions for use. The time point for the replacement will be decided by the physician according to their standard procedure.

Intra-operative assessments and the initial CC programming session will be performed according to each individual site's standard procedure.

The frequency, pulse width and number of contacts (monopolar/bipolar) of the stimulation should be kept constant between the constant voltage and the constant current stimulation.

Additional programming sessions may be required to optimize the therapy.

The following data will be collected:

- Implant information
- Initial programming information
- Adverse Events or Withdrawal (if applicable)

6.6 3 MONTH FOLLOW UP VISIT (3 months +/- 30 days after IPG replacement)

The current programming settings will be recorded before the questionnaires and tests.

The following data will be collected:

- Subject's Preference
- Speech Handicap Index (SHI)
- Unified Parkinson's Disease Rating Scale 'On Med/On Stim' ("On" state is defined as approximately 30 minutes after a subject takes anti-Parkinson medication when both the clinician and the subject indicate that the medication dose is effective.)
- Unified Parkinson's Disease Rating Scale part III 'On Med/Off Stim'
- Freezing of Gait Questionnaire (FOGQ)
- Tinetti Test
- Berg Balance Scale (BBS)
- Parkinson's Disease Questionnaire (PDQ-39)
- Satisfaction of Therapy Questionnaire for the subject
- Satisfaction of Therapy Questionnaire for the caregiver, if applicable
- Medication
- Adverse events or Withdrawal (if applicable)

After the questionnaires and the tests, the SJM Infinity ™ or Brio™ DBS system parameters shall be optimized if needed. The optimized settings will be recorded.

6.7 12 MONTH FOLLOW UP VISIT (12 months +/- 30 days after IPG replacement)

This visit will also serve as the end-of-study assessment.
The current programming settings will be recorded before the questionnaires and tests.

The following data will be collected:

- Subject's Preference
- Unified Parkinson's Disease Rating Scale 'On Med/On Stim' ("On" state is defined as approximately 30 minutes after a subject takes anti-Parkinson medication when both the clinician and the subject indicate that the medication dose is effective.)
- Unified Parkinson's Disease Rating Scale part III 'On Med/Off Stim'
- Freezing of Gait Questionnaire (FOGQ)
- Tinetti Test
- Berg Balance Scale
- Parkinson's Disease Questionnaire (PDQ-39)
- Satisfaction of Therapy Questionnaire for the subject
- Satisfaction of Therapy Questionnaire for the caregiver, if applicable
- Medication
- Health Care Economic Data
- Adverse events or Withdrawal (if applicable)

6.8 UNSCHEDULED VISIT

An Unscheduled Visit is defined as a follow up that is not explicitly requested by the protocol. Subjects may be asked to return to the clinic for unscheduled study visit.

The following information will be recorded:

- Reason for visit
- Action taken
- Record program settings (when re-programming has been done)

No specific assessment is required for this visit. If applicable, the AE or Withdrawal will be documented.

6.9 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 the study visits.

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 or the subject in completion of the questionnaires

6.10 SUBJECT STUDY COMPLETION

When the subject completes the 12-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.

6.11 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 clinical study design and well-defined subject selection criteria.

Subject 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 subject visit calendars.

6.12 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

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 needs an unplanned revision of the leads and/or extensions during IPG replacement
- 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 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 therefore 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.

When subject withdrawal from the clinical study is due to an adverse event the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. 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 IRB/EC 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 IRB/EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an IRB/EC, 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, IRB/EC 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 IRB/EC [as required] 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. Such deviations shall be documented and reported to the sponsor and the EC 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).

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 EVENTS

8.1 DEFINITIONS

8.1.1 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,

- Investigation, replacement, modification, or support of the anatomy or of a physiological process,
- Supporting or sustaining life,
- Control of conception,
- Disinfection of medical devices and

- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

8.1.2 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 investigational medical device under study.

This definition includes events related to the investigational medical device or the comparator.
This definition includes events related to the procedures involved.

8.1.3 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
  - A malignant tumor (in applicable countries only)
- Fetal distress, fetal death or a congenital abnormality or birth defect

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

8.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

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 investigational medical device.

8.1.5 Serious Adverse Device Effect (SADE)

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

For **unexpected failure modes** or unexpected adverse events, the site should follow their standard reporting practices for **medical device reporting (MDR)/ Vigilance reporting** for medical devices per the regulations.

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

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). The safety surveillance and the safety reporting will continue until the last investigational 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.

Adverse event data as well as deaths will be collected throughout the clinical study and will be reported to the Sponsor through the EDC system. The Investigator will record adverse events on the appropriate case report forms.

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

The investigator will report the event to the IRB/EC per their reporting requirements.

For this study, reportable events to sponsor are considered:
All procedure or device related Adverse Events (whether or not the event is considered serious).

- ADEs (procedure/device related)
- SADEs (procedure/device related)

These events will be reported to the Sponsor, as soon as possible in accordance to the local laws and regulations.

The Sponsor will ensure that all events 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/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 effects in section 3.3 are associated with a DBS System.

Events that will not be considered as SADE/ADE for the purposes of this study and should not be recorded in the AE CRF are as follows:

- Hospital admission for the planned replacement of the IPG due to normal battery end of life.
- Events directly linked to optimization/programming during the optimization/programming sessions.

8.3 SUBJECT DEATH

8.3.1 Procedure for recording and reporting subject death

Investigators must report deaths to the sponsor as soon as possible in accordance to the local laws and regulations.
Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the Death case report form and submit to Sponsor through the electronic data capture (EDC) system deployed by St. Jude Medical.

Subject death may be an outcome of a SAE:
- Death is therefore related to an SAE: all efforts to obtain the SAE details should be made and the AE form must be completed or updated accordingly.
- The subject's death is an early conclusion of the subject's participation in the study. Therefore, the investigator is requested to complete the Withdrawal form.
- The investigator must notify the EC/IRB, if appropriate, in accordance with national and local laws and regulations.

8.4 DEVICE DEFICIENCY (DD) / COMPLAINTS

The devices used in this study are CE-marked; therefore, the Device Deficiencies/ Complaints will not be collected through dedicated CRFs.

For sites located outside of the United States:
A **Device Deficiency** is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device Deficiencies include malfunctions, use errors and inadequate labeling. Device Deficiencies in St. Jude Medical market-released products must be reported per St. Jude Medical product surveillance process. This product is a commercially released product; therefore, all Device Deficiencies need to be submitted through this process as well. The investigator or designee should notify the SJM Post market Surveillance Department by e-mailing the information about the Device Deficiency to [redacted].

For sites located in the United States:
A **Complaint** is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Complaints include malfunctions, use errors and inadequate labeling. Complaints in St. Jude Medical market-released products must be reported per St. Jude Medical product surveillance process. This product is a commercially released product; therefore, all Complaints need to be submitted through this process as well. The investigator or designee should notify the SJM post market Surveillance Department by e-mailing the information about the Complaint to [redacted]

9.0 DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling.

The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

[redacted]

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 that we collect or maintain for this clinical trial. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical trial. 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, IRB/EC 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 CRFs 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 CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

No data can be recorded directly in the CRFs.

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

10.0 MONITORING

Monitoring will be conducted according to St. Jude Medical's Clinical Monitoring work instruction.
Prior to beginning the clinical investigation, the Sponsor will contact the investigator or designee to discuss the clinical investigation and data requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator shall make subject and clinical investigation 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 IRB/EC have not been submitted or are incomplete, inaccurate, false or misleading.

12.0 STATISTICAL CONSIDERATIONS

12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

The primary endpoint is the proportion of subjects who indicate preference on constant current over constant voltage at the 3 Month follow-up visit.

12.1.1 Primary Endpoint

[redacted]

12.1.2 Secondary Endpoint

The rate of safety events related to battery replacement procedures for hybrid systems.

[redacted]

The event rate will be summarized as (1) # events per patient-year of follow up and (2) incidence rate. The number of events per patient-year of follow-up will be calculated as the total number of safety events related to battery replacement procedures for hybrid systems divided by total follow-up duration from IPG replacement visit to either 12M visit or withdrawal visit (patient-years). The incidence rate (%) will be calculated as number of subjects who undergo IPG replacement and encounter safety events related to battery replacement procedure for hybrid system divided by total subjects who undergo IPG replacement.

12.1.3 Descriptive Endpoints

The following descriptive endpoints will be reported:

- The change in Speech Handicap Index at 3 and 12 Months compared to Baseline;
- The change in total UPDRS score and the individual UPDRS components at 3 and 12 Months compared to Baseline;
- The change in Levodopa medication at 3 and 12 Months compared to Baseline;
- The change in FOGQ scores at 3 and 12 Months compared to Baseline;
- The change in Tinetti Test scores at 3 and 12 Months compared to Baseline;
- The change in Berg Balance Scale scores at 3 and 12 Months compared to Baseline;
- The change in PDQ-39 Quality of Life scores 3 and 12 Months compared to Baseline;
- Proportion of subjects who indicate satisfaction with constant current at 3 and 12 Months;
- Proportion of caregivers who indicate satisfaction with constant current at 3 and 12 Months;
- Proportion of subjects who indicate preference on constant current over constant voltage at the 12 Month follow-up visit.
- Summary of Health Economic Data for constant current compared to constant voltage.

12.2 SAMPLE SIZE

[redacted]The target number of subjects for enrollment is 170 and the target number of subjects for the primary endpoint analysis is 115.

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

Any deviation from the statistical plan will be documented and reported.

12.4 THE SPECIFICATION OF SUBGROUPS FOR ANALYSIS

No subgroup analyses are planned for this study.

12.5 PROCEDURES THAT TAKE INTO ACCOUNT ALL THE DATA

All reported data will be used in the analysis for relevant endpoints. Missing data will be excluded from the respective endpoint analysis.

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

Analyses of each endpoint will be performed in subjects who provide complete data for each endpoint. Subject accountability for enrolled subjects will be performed prior to analyses of the primary and secondary endpoints. 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.

12.7 THE EXCLUSION OF PARTICULAR INFORMATION FOR THE TESTING OF THE HYPOTHESIS, if relevant

There is no intent to exclude particular information for the testing of hypotheses.

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

Each participating will enroll at least one subject to a maximum of 30 subjects.

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 minimum 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 coordinating investigator (if applicable).

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB/EC 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 subject needs an unplanned revision of the lead and/or extension during the IPG replacement
- 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(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the current Declaration of Helsinki
- 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 IRB/EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, IRB/EC 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 IRB/EC 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 IRB/EC 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 IRB/EC 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, IRB/EC, 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 IRB/EC or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them 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

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.

17.0 BIBLIOGRAPHY

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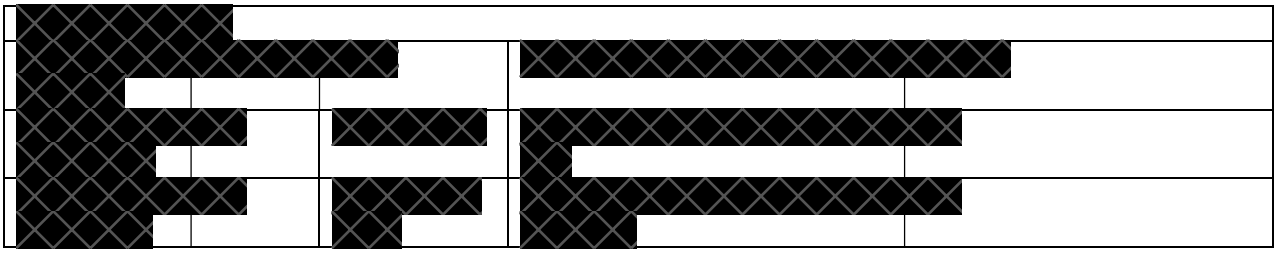
APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CCI	Clinical Coordination Investigator
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
DD	Device Deficiency
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
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
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MMSE	Mini-mental state examination
MP	Monitoring Plan
NA	Not Applicable
PD	Parkinson's Disease
PI	Principal Investigator
POA	Power of Attorney
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

APPENDIX B: CIP REVISION HISTORY



Appendix C: DECLARATION OF HELSINKI

The most current version of the document will be followed.

Appendix D: DEVICE MANUAL

A copy of the device manuals will be kept under a separate cover and is available upon request.

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

A list of Clinical Investigational sites and IRB/EC will be kept under a separate cover and is available upon request.

Appendix F: SAMPLE INFORMED CONSENT

The informed consent will be kept under a separate cover and are available upon request.

Appendix G: CASE REPORT FORMS

The case report forms will be kept under a separate cover and are available upon request.