INVENT
Intraoperative Investigation of a Directional Lead and Local Field Potentials for the Optimization of Stimulation Efficacy
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Clinical Investigation Plan (CIP)

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

Principal Investigator

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

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1 Synopsis

1.1 Objective(s)

The current study aims to explore the functional use of LFPs recorded intraoperatively for the optimization of a directional DBS lead programming

Aim-1: To determine whether intraoperative LFPs recorded from the segmented DBS electrode can predict the optimal stimulation parameters.

Aim-2: Compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.

1.2 Devices Used

The following devices will be used in this clinical investigation:

Device name	Model/Type	Manufacturer	Region/ Country	Investigational or Market Released
Infinity IPGs	6660 -3	Abbott	US	Market released
Infinity Directional Leads	6170-3	Abbott	US	Market released
Infinity System Extensions	6371-3	Abbott	US	Market released
Guardian™ Burr Hole Cover	6010	Abbott	US	Market released
Clinician Programmer	3872 & 3874	Abbott	US	Market released
Patient Controller	6883 & 3875	Abbott	US	Market released
DBS EPG	6599	Abbott	US	Market released
8-Channel Adapters	2311 & 2316	Abbott	US	Market released
Multilead Trial Cable	3014	Abbott	US	Market released

1.3 Indications for Use

The Infinity directional leads are indicated for use in DBS as treatment for PD symptoms.

1.4 Design

This is a feasibility study designed to evaluate the usefulness of intraoperative LFP recordings obtained from the implanted DBS lead to predict ideal stimulation parameters.
Additionally this study will compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.

Approximately 8 subjects will be enrolled in this clinical investigation. The clinical investigation will be conducted at 2 centers in the USA.

Subjects participating in this clinical investigation will monitored during DBS implant procedure and programming. The expected duration of enrollment is 8 months. The total duration of the clinical investigation is expected to be 1 year.

1.5 Endpoints

The overall goal of the study is to investigate LFP analysis as a strategic tool in the operating room (OR) setting and to establish the relationship between LFPs and DBS efficacy and side effects.

1.5.1 Primary Endpoints

Concordance between LFP derived predictions and clinically optimized stimulation parameters

1.5.2 Secondary Endpoints

Characteristic of the LFP signals correlating to presence of side effects

1.6 Study Population

In this study we will explore the predictive capacity of LFPs recorded from STN. In total, 8 patients undergoing bilateral STN DBS and part of the PROGRESS study will be enrolled for this investigation over a 1-year period. The current surgical case load at BCM supports this level of enrollment. The details of implantation procedures and blinded trial design are given in the following sections.

1.7 Inclusion/Exclusion Criteria

1.7.1 Inclusion Criteria

- Patient currently enrolled in the PROGRESS study
- Age 18-70 years
- Ability to provide informed consent
- Diagnosis of idiopathic Parkinson's disease, and DBS consensus team review supporting the placement of STN DBS.

1.7.2 Exclusion Criteria

- Subject is not a surgical candidate;
- In the Investigator's opinion the subject unable to tolerate multiple programming sessions within a single setting;
- Subject unable to comply with the follow-up schedule

1.8 Enrollment

A patient becomes a subject once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent.

1.9 Study Assessments

LFP recordings will be collected from the implanted DBS lead at the end of the DBS implantation procedure. Simultaneously other biomedical and physiological signals collected with a variety of sensors, including a 2-channel bipolar electrocardiogram, 4 channel electromyogram (EMG; 2 upper and 2 lower limbs), and two 3-axis accelerometers attached to contra-lateral limbs.

The optimal stimulation parameters, selected using standard clinical programming algorithms, will be collected for comparison with the predictions obtained from the analysis of the data collected during the DBS implant procedure.

2 Introduction

The current study aims to explore the functional use of LFPs recorded intraoperatively for the optimization of a directional DBS lead programming via the following two aims:

Aim-1: To determine whether intraoperative LFPs recorded from the segmented DBS electrode can predict the optimal stimulation parameters.

Aim-2: Compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.

This clinical investigation will be performed in the U.S.A. and is sponsored by Abbott.

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

3 Background and Justification for Clinical Investigation

The efficacy of deep brain stimulation (DBS) has been established and it is now the most commonly used surgical treatment for patients with Parkinson's disease (PD) in the U.S. DBS provides patients with moderate to advanced symptoms a better quality of life than with medication alone (Deuschl et al., 2006; Williams et al., 2010). There is no consensus as to the optimal site for the active electrode of the DBS lead in the subthalamic nucleus (STN). Additionally, patients receive differing therapeutic benefit with varying DBS parameters. Consequently, quantitative and objective methods for determining optimal electrode location and stimulation parameters are needed (Mera et al., 2011). STN stimulation can result in side effects arising from the spread of stimulation to surrounding structures (Richardson, et al., 2009). Moreover, sub-optimal positioning of DBS electrodes accounts for up to 40% of cases of inadequate efficacy of stimulation postoperatively (Okun et al., 2005). Thus, the clinical efficacy of DBS depends critically on accurate localization of the STN and generated stimulation field.

DBS surgery in PD involves the stereotactic implantation of a macroelectrode into a pre-determined target region, selected based on the indication being treated. The indirect, or consensus target coordinates are then modified based on preoperative stereotactic imaging and/or intraoperative electrophysiological techniques. The most commonly employed electrophysiological techniques include microelectrode recording and macrostimulation through the DBS electrode. Microelectrode single unit activity (SUA) recording allows the identification of individual neurons that are characteristic of the target of interest, by virtue of cellular firing rate, amplitude, pattern, and distance from the cortical surface. The DBS electrode, which typically consists of four platinum-iridium contacts, is subsequently implanted based on the microelectrode findings. Implantation of DBS electrodes also makes it possible to assess the neural activity of a population of neurons from deep brain structures. Therefore, local field potentials (LFPs) can be used strategically to study the dynamics of deep brain structures and develop novel technologies for the improvement of DBS therapy in a closed loop fashion.
Our hypothesis are that a) current steering will yield fewer side effects than omnidirectional stimulation and b) the knowledge about the spatial distribution of LFPs assessed with segmented leads can be used to select certain stimulation parameters.

With these motivations we will study the following aims to explore the functional use of LFPs recorded intraoperatively for the optimization of a directional DBS lead programming. A schematic diagram representing our proposed work is also given in Fig.1.

Studies measuring and analyzing the LFPs in the STN indicate that excessive synchronization of oscillatory activity exists in the beta frequency band (8–30Hz) and can be used as a possible pathophysiological marker of the Parkinsonian state in human patients with PD (Brown et al.,2001; Williams et al., 2002; Kuhn et al.,2005). It is well recognized that PD patients in the “off” medication state demonstrate increased power in beta band oscillations at rest in both the STN and the GPi (Brown and Williams, 2005). Levodopa intake, and subsequent motor improvement, correlates with the power decrease of the beta band in both the STN (Kuhn et al, 2009) and GPi (Brown et al, 2001). However, limited research explored the functional use of LFPs for the optimization of DBS in the clinical setting. The latest research executed on a small population of human subjects indicates that the LFP activity recorded post operatively can serve as a neuro-biomarker to predict the optimal contact for stimulation (Ince et al., 2010).

With this motivation, the LFPs recorded from the contacts of the segmented DBS electrode located in the STN will be used to investigate whether the assessed activity during the surgery can be correlated with the magnitude of symptom severity and improvement following stimulation. **Specifically, through a blinded study, we will investigate whether the contacts with excessive LFP activity at various bands seen intra-operatively match the contacts selected clinically for DBS programming. If they do not match, contributing factors will be explored.** A sample dataset representing the predictive capability of intra-operative STN LFPs to select the clinically optimal stimulation contact is given in Fig.2.

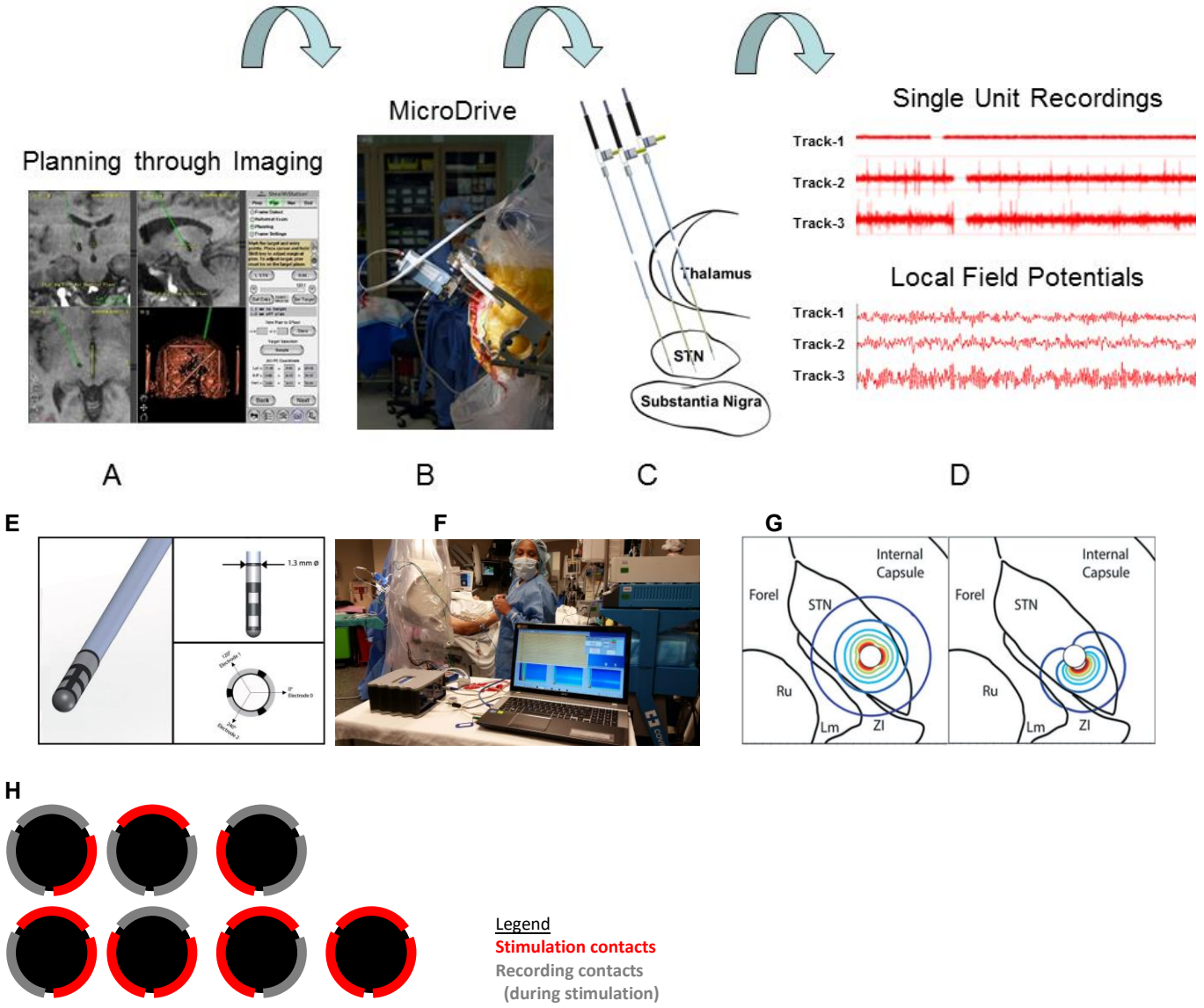

Fig.1. The schematic diagram of our blinded study design is given in the top image. The LFP and SUA recording will be obtained in the OR and information obtained from both modalities will be used for track selection. Intraoperative LFP recordings will be obtained simultaneously with SUA from three trajectories identified by stereotactic imaging (A). The microelectrodes will be inserted towards the estimated target with a Neurodrive (B) to localize characteristic SUA or excessive LFP activity in the STN (D). After the identification of optimal track and depth, a directional DBS electrode (E) with 1-3-3-1 configuration will be implanted temporarily. LFP recordings will be obtained from all 8 contacts of the directional lead and will be processed in real-time intraoperatively with a system developed in Dr. Ince's laboratory. The neurologist will be blinded to these LFP recordings (F). The therapeutic window will be studied with the implanted electrode by generation of the stimulation with 6 unidirectional and one omnidirectional pattern (G and E). The outcome of the unidirectional stimulation will be

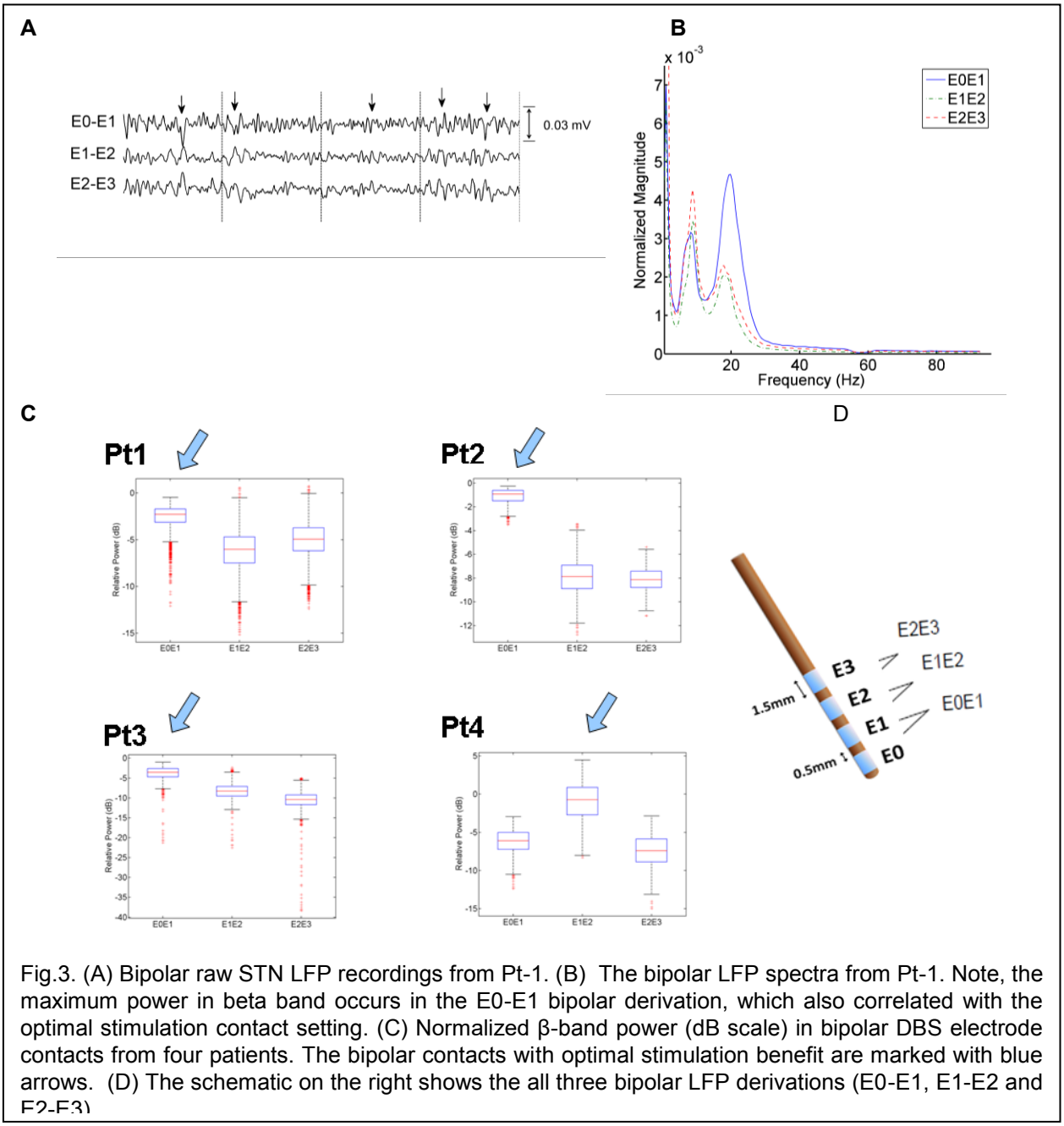

Fig.3. (A) Bipolar raw STN LFP recordings from Pt-1. (B) The bipolar LFP spectra from Pt-1. Note, the maximum power in beta band occurs in the E0-E1 bipolar derivation, which also correlated with the optimal stimulation contact setting. (C) Normalized β-band power (dB scale) in bipolar DBS electrode contacts from four patients. The bipolar contacts with optimal stimulation benefit are marked with blue arrows. (D) The schematic on the right shows the all three bipolar LFP derivations (E0-E1, E1-E2 and E2-E3)

4 Device(s) Under Investigation

4.1 Identification and Description of the Devices under investigation

4.1.1 Identification

No devices are under investigation in this study. In this study we seek to evaluate the feasibility of using LFP recorded during DBS lead implant as support to programming of DBS stimulation parameters. This will be performed using custom software for analysis of electrophysiological data developed by Prof. Ince.

Table 1: Identification of Devices under Investigation

Device name	Model/Type	Manufacturer	Region/ Country	Investigational or Market Released
Infinity IPGs	6660 -3	Abbott	US	Market released
Infinity Directional Leads	6170-3	Abbott	US	Market released
Infinity System Extensions	6371-3	Abbott	US	Market released
Guardian™ Burr Hole Cover	6010	Abbott	US	Market released
Clinician Programmer	3872 & 3874	Abbott	US	Market released
Patient Controller	6883 & 3875	Abbott	US	Market released
DBS EPG	6599	Abbott	US	Market released
8-Channel Adapters	2311 & 2316	Abbott	US	Market released
Multilead Trial Cable	3014	Abbott	US	Market released

4.1.2 Device Description and Intended Purpose

The Infinity device and all the devices indicated in table 1 are indicated for use in the treatment of Parkinson's disease.

4.1.3 Device Handling and Storage

Sponsor requires all investigational products be stored, according to the labeling and Instructions for Use, in a secure area to prevent unauthorized access or use.

4.2 Devices Accountability

Post market study not requiring device accountability.

5 Clinical Investigation Design

5.1 Clinical Investigation Design

This is a prospective single center feasibility trial aimed at evaluating the functional use of LFPs recorded intraoperatively for the optimization of a directional DBS lead programming.
All participants will undergo DBS implant procedure according to standard clinical practice. After lead implant LFP will be recorded from the DBS lead for 1min in resting and hand movement states, together

with additional physiological signals. The efficacy of stimulation will be validated intraoperatively with concurrent testing of parkinsonian features and the absence of stimulation side-effects, per clinical routine.
The recorded data will be converted to Matlab (Mathworks, Natick MA) format, as described previously (Ince et al, 2010) for further analysis. The LFP data will be processed offline, using state-of-the-art signal processing and spectrum estimation techniques, to identify novel neuro-markers that will be used for the prediction of prediction of optimal stimulation contacts and correlation with the symptoms of the patient.

We will quantify the relief of symptoms through steered stimulation by contrasting the UPDRS scores before and after DBS in the outpatient clinical settings according to procedures described in the PROGRESS study for both directional and omnidirectional stimulation, and for identification of the therapeutic window.

In total, 8 patients undergoing bilateral STN DBS and part of the PROGRESS study will be enrolled for this investigation over a 1-year period. The current surgical case load at BCM supports this level of enrollment.
This study will be conducted in two centers in the U.S.A.

5.2 Objectives

5.2.1 Primary Objectives

To determine whether intraoperative LFPs recorded from the segmented DBS electrode can predict the optimal stimulation parameters.
Studies measuring and analyzing the LFPs in the STN indicate that excessive synchronization of oscillatory activity exists in the beta frequency band (8–30Hz) and can be used as a possible pathophysiological marker of the Parkinsonian state in human patients with PD (Brown et al.,2001; Williams et al., 2002; Kuhn et al.,2005). It is well recognized that PD patients in the “off” medication state demonstrate increased power in beta band oscillations at rest in both the STN and the GPi (Brown and Williams, 2005). Levodopa intake, and subsequent motor improvement, correlates with the power decrease of the beta band in both the STN (Kuhn et al, 2009) and GPi (Brown et al, 2001). However, limited research explored the functional use of LFPs for the optimization of DBS in the clinical setting. The latest research executed on a small population of human subjects indicates that the LFP activity recorded post operatively can serve as a neuro-biomarker to predict the optimal contact for stimulation (Ince et al., 2010).
With this motivation, the LFPs recorded from the contacts of the segmented DBS electrode located in the STN will be used to investigate whether the assessed activity during the surgery can be correlated with the magnitude of symptom severity and improvement following stimulation. Specifically, through a blinded study, we will investigate whether the contacts with excessive LFP activity at various bands seen intra-operatively match the contacts selected clinically for DBS programming. If they do not match, contributing factors will be explored. A sample dataset representing the predictive capability of intra-operative STN LFPs to select the clinically optimal stimulation contact is given in Fig.2.

5.2.2 Secondary Objectives

Compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.
As one experimenter adjusts the stimulation parameters, a blinded rater will record the therapeutic window (TW) from the minimum amount of current required to provide a meaningful improvement in motor symptoms to the maximum current that could be delivered without producing adverse effects, such as dysarthria, focal muscle contractions or paraesthesias. The TW of directional stimulation will be compared to omnidirectional stimulation. Using this data (acquired through long-term directional and

omnidirectional programming as part of the PROGRESS study), as well as the 3D distribution of the LFP recordings, we will investigate the relationship between the two when an omnidirectional stimulation field is generated. For example, a side effect may be more likely to occur if the clinical stimulation field includes an area outside the spatial distribution of LFPs with select characteristics.

5.3 Endpoints

There is one primary endpoint and one secondary endpoint in this clinical investigation.

5.3.1 Primary Endpoint

Concordance between LFP derived predictions and clinically optimized stimulation parameters
In this project we will establish the feasibility of recording LFP data intra-operatively from DBS electrode contacts using a multi-channel, high throughput data acquisition system and investigate if patterns in LFP can be used to select the optimal contacts for patient programming. Establishing the role of identifying and localizing LFP patterns intraoperatively can play an essential role in assisting the clinician who is programming the patient to select the optimal contact, especially when electrodes with multiple contacts (>8) are employed during DBS therapy. In this scenario, conventional techniques employing systematic contact evaluations in various combinations will be impractical due to time constraints.
The recently developed directional lead of SJM with 1-3-3-1 configuration offers the possibility of recording LFP activity from multiple directions. The primary utility of the segmented electrode is to steer the stimulation such that the side effects can be minimized. However, multiple contacts (n=8) on the electrode increase the programming complexity. In this project, we aim to determine in a blinded manner whether LFPs can guide programming. The outcomes of this pilot project will establish the scientific basis for whether LFPs recorded from a segmented electrode can be used for clinical decision making and to fine tune stimulation parameters.

5.3.2 Secondary Endpoint

Characteristic of the LFP signals correlating to presence of side effects.

5.4 Study Population

In this study we will explore the predictive capacity of LFPs recorded from STN. In total, 8 patients undergoing bilateral STN DBS and part of the PROGRESS study will be enrolled for this investigation over a 1-year period. The current surgical case load at BCM supports this level of enrollment. The details of implantation procedures and blinded trial design are given in the following sections.

5.4.1 Inclusion Criteria

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

- Patient currently enrolled in the PROGRESS study
- Age 18-70 years
- Ability to provide informed consent
- Diagnosis of idiopathic Parkinson's disease, and DBS consensus team review supporting the placement of STN DBS.

5.4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must be excluded from the clinical investigation:

- Subject is not a surgical candidate;
- In the Investigator's opinion the subject unable to tolerate multiple programming sessions within a single setting;

- Subject unable to comply with the follow-up schedule

6 Procedures

Approval from the Sponsor must be received prior to initiating study procedures.

Enrolled subjects (as defined in section 6.2) will undergo DBS implant with the Infinity device according to standard clinical practice. During implantation procedure LFP will be recorded from the DBS leads contacts together with additional biometric measurements. The efficacy of stimulation will be validated intraoperatively with concurrent testing of parkinsonian features and the absence of stimulation side-effects, per clinical routine.
We will quantify the relief of symptoms through steered stimulation by contrasting the UPDRS scores before and after DBS in the outpatient clinical settings according to procedures described in the PROGRESS study for both directional and omnidirectional stimulation, and for identification of the therapeutic window. All subjects will undergo rigorous rating-scale-based assessment of the severity of their neurologic symptoms “off” and “on” PD medications, using the practically defined off state (CAPSIT-PD). Programming will be performed by an experienced clinical practitioner who is blinded to the LFP recordings and their analysis.
Following completion of this study, patients care will continue according to the PROGRESS study.

The following sections provide a detailed description of procedures required by this CIP.

6.1 Informed Consent Process

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process, as required by applicable regulations and the center’s IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject’s decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject’s legal rights. The subject shall be provided with the informed consent form written in a language that is understandable to the subject and has been approved by the center’s IRB/EC. The subject shall have adequate time to review, ask questions and consider participation.

If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and by the person obtaining the consent. The signed original will be filed in the subject’s hospital or research charts, and a copy will be provided to the subject.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject’s hospital and/or research charts. The date of signature will be entered on an applicable Case Report Form (CRF).

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

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

6.2 Point of Enrollment

Subject is considered enrolled in the clinical investigation from the moment the subject has provided a written Informed Consent and has been confirmed to meet all inclusion criteria and none of the exclusion criteria.

The Principal Investigator or delegated study personnel will record enrollment information (name of the clinical investigation, date of consent and Inclusion/exclusion information) in the hospital records and complete and submit an applicable CRF in a timely manner.

Notification of enrollment to the Sponsor is considered to have occurred when the Sponsor has received the applicable CRF.

6.3 Scheduled Procedures

The Principal Investigator is responsible for ensuring all clinical investigation data is collected as required per CIP scheduled procedures.

6.3.1 Implant/Procedure

All participating subjects will undergo 3.0T MRI and CT scans to be used for surgical planning. The imaging protocol will consist of anatomical imaging using susceptibility-weighted imaging (SWI), T1-, and T2-weighted sequences. The brain MRI (Stealth Station, Medtronic) will be fused in stereotactic space, to the CT to determine the initial electrode trajectory to STN and confirm final electrode location.

Patients will undergo a preoperative stereotactic MRI as described above. On the morning of surgery, patients will undergo placement of the Leksell frame under local anesthesia, and will then undergo a stereotactic CT scan. Three simultaneous microelectrode recording tracks will be performed, with one electrode oriented along the CT/MRI-derived electrode trajectory, one 2-mm anterior, and one 2-mm lateral.

Single unit activity (SUA) and LFP recordings will begin at 20mm above the presumptive target and three microelectrodes will be advanced through the target to a position 3-mm below the intended target, in 1mm increments until 10mm above target. Then reduce increment to less than 0.5mm until the electrode reaches 3mm below the target. The positions of initial 3-microelectrodes will be modified if necessary due to the lack of excessive beta band activity. At each depth, microelectrodes will be used to record both LFP and SUA for 30 seconds.

The neurosurgeon will use standard clinical technique for localizing the STN, via real-time auditory and visual analysis of the SUA. The dorsal, ventral, and posterior borders of the STN will thus be identified, and STN neurons examined for movement-responsive receptive fields. The ventral border of the STN will be selected as the desired depth for the tip of the chronic DBS electrode. Our previous recordings indicate that STN can be identified with an excessive beta band activity of LFPs. Therefore, the optimal trajectory and electrode depth will be selected based on the excessive LFP activity and combination of SUA signal analysis.

Then the directional lead will be implanted and LFP signals will be recorded from all 8 contacts of the macroelectrode with 1-3-3-1 configuration. The LFP signal will be recorded from the target for 1min in resting and hand movement states (Aim-1). During these recordings, the neurologist who will test patient programming will be blinded to LFP data. Therefore, in each patient the optimal stimulation contacts will be selected without any influence from the LFP analysis.

The LFP recordings will be obtained using the gHIamp biosignal amplifier (Gtec, Inc. Austria) at 2.4 kHz and 24 bit resolution. The depth information will be obtained from the Neurodrive (Alpha Omega, Nazareth, Israel), through a custom Ethernet based interface which was previously developed in Dr. Ince's lab. Besides neural activity, we will record other biomedical and physiological signals with a variety of sensors, including a 2-channel bipolar electrocardiogram, 4 channel electromyogram (EMG; 2 upper and 2 lower limbs), and two 3-axis accelerometers attached to contra-lateral limbs. These signals will be entered into the multipurpose neural data acquisition system in order to synchronize behavior with the neural data. Resting and movement periods of the recording will be identified from the EMG and wireless 3-axis accelerometer sensors. The recorded data will be converted to Matlab (Mathworks, Natick MA) format, as described previously (Ince et al, 2010) for further analysis. The LFP data will be processed offline, using state-of-the-art signal processing and spectrum estimation techniques, to identify novel neuro-markers that will be used for the prediction of prediction of optimal stimulation contacts and correlation with the symptoms of the patient.

The efficacy of stimulation will be validated intraoperatively with concurrent testing of parkinsonian features and the absence of stimulation side-effects, per clinical routine. For instance, the presence of low-threshold side effects of stimulation, indicating electrode position too close to an adjacent structure—e.g., internal capsule or medial lemniscus or nucleus of cranial nerve III, when STN is the desired target—would require repositioning in order for the electrode to be clinically useful.

6.3.2 Additional Visits

Quantification of the relief of symptoms and therapeutic window with omnidirectional and directional stimulation will be obtained in the outpatient setting as part and according to the procedures described in the PROGRESS study, during the appropriate follow up visits.

6.4 Unscheduled Visits

These visits will be documented as part of the PROGRESS study.

Table 2: List of all clinical investigation specific tests and procedures

Visit Study Activity	Enrollment & Baseline	Implant Procedure	Initial Programming
Informed Consent Process	X		
Enrollment	X		
Inclusion/Exclusion	X		
DBS implant		X	
Local field potential recordings		X	
Termination	(X)	(X)	(X)
Death	(X)	(X)	(X)

(X) If applicable

6.5 Description of Activities Performed by Sponsor Representatives

While Sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all clinical investigation data is collected as required per CIP.

6.6 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the 12-month visit. Upon completion of subject participation in the clinical investigation, the subject will return to standard of care.

6.7 Subject Withdrawal

Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator. Subjects will be requested to specify the reason for the request to withdraw. The investigator must make all reasonable efforts to retain the subject in the clinical investigation until completion of the clinical investigation.

A subject will be considered 'Lost to Follow-up' after 3 number of missed visit(s) and a minimum of two unsuccessful phone calls from investigational site personnel to the subject or contact to schedule the next follow-up visit. These two phone calls must be documented in the subject's hospital records. If the subject is deemed lost to follow-up a letter should be sent to the subject's last known address or to the subject's general practitioner (GP) and a copy of the letter must be maintained in the subject's hospital records.

In case of subject withdrawal, the site should make attempts to schedule the subject for a final study visit. At this final study visit, the subject will undergo the following assessments:

- Termination

7 Statistical Considerations

The following section describes the statistical methods for the clinical investigation and justification of the design. Additional details on statistical analyses, including sensitivity analyses, poolability analyses,

subgroup analyses and analysis of descriptive endpoint(s) may be maintained in a separate Statistical Analysis Plan (SAP).

7.1 Hypotheses

The current study aims to explore the functional use of LFPs recorded intraoperatively for the optimization of a directional DBS lead programming

Aim-1: To determine whether intraoperative LFPs recorded from the segmented DBS electrode can predict the optimal stimulation parameters.

Aim-2: Compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.

7.1.1 Primary Endpoint Hypothesis

To determine whether intraoperative LFPs recorded from the segmented DBS electrode can predict the optimal stimulation parameters.

7.1.1.1 Analysis Methodology

To identify the location of the DBS electrode and its contacts as well as the directionality of the segmented contacts, the intra-operative and postoperative CT and 1.5T MRI scans will be merged in stereotactic space to the preoperative imaging dataset, using the Cranial Cloud interface.

Artifact-free LFP segments at each depth will be identified by visual inspection of sensor data and video recording, and, will be subjected to spectral analysis. Power spectra of the monopolar and bipolar LFP signals will be computed using a multi-taper method, due to its low variance (Thomson 1982). Following computation of the power spectra in each 30s time segment, the power in the **θ**- (3-7 Hz), **α**- (7-13 Hz), **β**- (13-32 Hz), **γ**- (48-100 Hz) and upper gamma (200-400Hz) bands will be computed. This will provide a feature matrix representing the sub-band power levels at different depths during resting state and changes during movement-related segments for each monopolar and bipolar contact.

We will explore the dynamic LFP spectrum arising from each depth individually and investigate whether the depths related to increased **β**- (13-32 Hz) band power and **other frequencies** can be a predictor for the borders of the STN and optimal contacts used for DBS.

We expect that abnormal brain activity will be characterized by a preferred correlation process, reflective of the structure of the local neural elements. Abnormalities in local neural elements or circuits may produce time series with distinct autocorrelation patterns, which can then be captured by autoregressive (AR) model parameters. In brief, the AR model represents the current observation by a linear combination of the past samples and a white-noise input (Hayes 2006). The data in each epoch are assumed to be stationary, as they originate from the same depth. Each epoch is analyzed with an AR model of order ***p***. The model is,

$$x_t = a_1 x_{t-1} + ... + a_p x_{t-p} + e_t \ , \qquad (1)$$

where *x* is the output sequence, LFP data, $a_{1,..p}$ are the model parameters representing the weights of past samples, and e_t is the white noise.

This method provides a great advantage over other techniques in describing the entire length of the data in each segment by a few “subject specific” model parameters, consequently resulting in a significant

reduction in the dimensionality of the data analysis. At each contact, the model parameters will be estimated by using Burg's Algorithm. The optimal model order will be selected based on the evaluation of three different criteria—i.e., Akaike Information Criterion (AIC), final prediction error (FPE), and minimum description length (MDL), as described previously (Hayes 2006).

Once the AR model parameters have been estimated from the LFP data, these model parameters will be used along with subband powers as characteristic features for the prediction of STN location and stimulation settings. In addition, we will investigate whether the model parameters of different DBS contacts identified during rest and movement correlate with stimulation settings. We will explore different regression and classification techniques such as linear regression, linear discriminant analysis (LDA) and support vector machine (SVM) to estimate the predictive capability of the features extracted from LFP data. The estimation of the generalization capability of the developed models will be assessed by implementing a cross validation procedure with independent learning and testing sets. This will help to clarify the extent to which the stimulation correlates with actual LFP model parameters.

7.1.1.2 Sample Size Determination

Performance of a power calculation is not relevant to the type of study proposed. Our previous studies demonstrate heterogeneity in the LFP patterns of PD subjects. The reasons for these differences are not well understood. Accordingly, we have designed this project as a pilot project to demonstrate the feasibility of the approach to analyzing spatiospectral LFP patterns using a segmented electrode and exploring the relationships to clinical outcomes. A sample size of 8 was chosen to capture enough heterogeneity in order to develop a more detailed investigative protocol in the future with well-defined sample sizes based on the present observations.

7.1.1.3 Analysis Populations

In this study we will explore the predictive capacity of LFPs recorded from STN. In total, 8 patients undergoing bilateral STN DBS will be enrolled for this investigation over a 1-year period. The current surgical case load at BCM supports this level of enrollment.

7.1.1.4 Missing Data

No missing imputations will be performed.

7.1.2 Secondary [Safety/Effectiveness] Endpoint Hypothesis(es)

Compare the therapeutic window for stimulation delivered through directional and conventional leads and determine if the spatiospectral LFP patterns correlate with the presence of stimulation side effects.

7.2 Justification of Clinical Investigation Design

This is a prospective, feasibility study to explore the predictive capacity of LFPs recorded from STN. The outcomes of this pilot project will establish the scientific basis for whether LFPs recorded from a segmented electrode can be used for clinical decision making and to fine tune stimulation parameters.

7.3 Multiplicity

All statistical tests will be conducted using a Type I error of 0.05, unless stated otherwise. Family-wise error will be adjusted accordingly.

7.4 Overall Sample Size

A sample size of 8 was chosen to capture enough heterogeneity in order to develop a more detailed investigative protocol in the future with well-defined sample sizes based on the present observations.

7.5 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

8 Risks and Benefits

The risks associated with the medical device can be found in the Instructions for Use. The study does not require any additional procedures or assessments over the standard of care. There are no additional risks introduced to study subjects.

8.1 Risks Associated with the Device Under Investigation

8.1.1 Anticipated 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

8.1.2 Risks Associated with Clinical Investigation Assessments

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

8.2 Risk Control Measures

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

8.3 Possible interactions with concomitant treatments

There are no possible interactions with concomitant treatments.

8.4 Anticipated Benefits

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

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

8.5 Risk-to-Benefit Rationale

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

8.6 History of Device Modifications or Recall

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

9 Requirements for Investigator Records and Reports

9.1 Deviations from CIP

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator should not deviate from the CIP.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects; such non-compliance exposes subjects to unreasonable risks. Examples: failure to adhere to the inclusion/exclusion criteria, failure to perform safety assessments intended to detect adverse events. Investigators should seek to minimize such risks by adhering to the CIP.

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CIP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF. The site will submit the CRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

9.2 Safety Reporting

Safety surveillance within this study and the safety reporting performed both by the investigator and Sponsor starts as soon as the procedure begins. This is defined as from the time the [dilator/device delivery system has been introduced into the body].

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 clinical investigation or the subject withdrawal from the clinical investigation.

All adverse event data including deaths and device deficiency data (if applicable) will be collected throughout the clinical investigation and will be reported to the Sponsor on a CRF.

Adverse events will be monitored until they are adequately resolved or the subject has ended his/her participation in the trial, whichever comes first. The status of the subject's condition should be documented at each visit.

9.2.1 Subject Death

Subject deaths will be documented and reported to the Sponsor as soon as possible (but no later than 3 business days) after becoming aware of the event via the applicable CRF.

9.2.2 Complaints

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 involves an AE, the investigator must complete an AE CRF, including the information on the complaint and submit to Abbott as soon as possible.

Should a subject death be caused by the Abbott device or the device contributed to the death, the investigator should complete a Form 3500A (MedWatch) and submit to Abbott and the FDA within 10 days after becoming aware of the event.

9.3 Source records

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

9.4 Records Retention

The Sponsor and the Principal Investigators will maintain the clinical investigation documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational site or the Sponsor's facility, as appropriate.

These documents must be retained by the investigational site for a period of 2 years after the conclusion of the clinical investigation and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the investigator will notify the Sponsor.

10 Clinical Data Handling

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

10.1 Protection of Personally Identifiable Information

Abbott respects and protects personally identifiable information collected or maintained for this clinical investigation. 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 investigation. All data will be secured against unauthorized access.

10.2 Data Management Plan

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

Subject data will be captured in a validated electronic data capture (EDC) system hosted by the Sponsor.

CRF received data for the clinical investigation will be entered by trained Abbott personnel. An electronic audit trail will be used to track any subsequent changes of the entered data.

10.3 Document and Data Control

10.3.1 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.

10.3.2 Recording Data

The CRFs will be signed and dated by the authorized site personnel. Any change or correction to data reported on a paper CRF will be dated, initialed and explained if necessary, and will not obscure the original entry.

11 Monitoring

It is the responsibility of the Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of site non-compliance. On-site monitoring may occur at the discretion of the Sponsor.

12 Compliance Statement

12.1 Statement of Compliance

This clinical investigation will be conducted in compliance with the most current regional and local laws and regulations. Principles of Good Clinical Practice will be followed as based on the most current version of the World Medical Association (WMA) Declaration of Helsinki.

The investigator will sign a Clinical Trial Agreement and agrees to be compliant with it. The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the clinical investigation. If additional requirements are imposed by the IRB/EC or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an IRB/EC or a relevant Regulatory Authority with respect to the clinical investigation, that information will be forwarded to the Sponsor.

12.2 Quality Assurance Audits and Regulatory Inspections

The investigator and/or delegate should contact the Sponsor immediately upon notification of a regulatory authority inspection at the site. A monitor or designee will assist the investigator and/or delegate in preparing for the audit. The Sponsor may perform quality assurance audits, as required.

The Principal Investigator or institution will provide direct access to source data during and after the clinical investigation 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 investigation.

12.3 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 monitor or designee 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 investigation, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation. In case of termination, the Sponsor will inform the responsible regulatory authority, as required, and ensure that the IRB/EC is notified, either by the Principal Investigator or by the Sponsor.

13 Suspension or Premature Termination of the Clinical Investigation

The Sponsor reserves the right to terminate the clinical investigation at any stage, with appropriate written notice to the investigators, IRB/ECs and relevant Regulatory authorities, if required.

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

If suspicion of an unacceptable risk to subjects arises during the clinical investigation or when so instructed by the IRB/EC or regulatory authority, the Sponsor may suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the IRB/EC or regulatory authority, where appropriate, will be obtained before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

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

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects

enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

14 Clinical Investigation Conclusion

The clinical investigation will be concluded when:

- The site is closed AND
- The final report has been provided to the investigator or the Sponsor has provided formal documentation of clinical investigation closure.

15 Publication Policy

Publications or presentations of clinical investigation methods or results will adhere to Abbott's publication policy, which is based on Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines. A copy of the policy will be provided upon request of the investigator.

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Appendix A: CIP Revisions

Procedure for CIP Amendments

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

The acknowledgement of the amended CIP by the Coordinating Investigator (if applicable) and the Principal Investigators will be collected on the signature pages.

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

Revision History

Amendment Number	Version	Date	Rationale	Details
Not Applicable	VA	ddMMMyyyy	First release of CIP	NA

Appendix B: Definitions

Non-study Specific Definitions

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 clinical investigation.

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

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 function OR
- 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.

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.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE)
As defined in 21 CFR §812.3, unanticipated adverse device effects (UADE) are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Anticipated Serious Adverse Device Effect (ASADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Device Deficiency (DD)
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.

Vulnerable Subject
Vulnerable subject is defined as individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.
EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention.

Appendix C: Bibliography

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Appendix E: Case Report Form

Case report forms will be provided under separate cover.

Appendix F: Informed Consent Form

The informed consent form will be provided under separate cover.