

**Early Adapter Part II Study
Clinical Investigation Plan**

MDT20041

Version 6.0

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Clinical Investigation Plan

Study Title	Japan Post Market Adaptive Deep Brain Stimulation (aDBS) Study (Early Adapter) Part II
Clinical Investigation Plan Identifier	MDT20041
Product Name	Medtronic Percept PC
Sponsor	Medtronic Japan Co., Ltd. 1-2- 70 Konan, Minato-ku, Tokyo, Japan
Document Version	6.0
Version Date	October 31 st , 2022
Responsible Investigator	Nobutaka Hattori Prof. Department of Neurology Juntendo Hospital Address: 3-1-3 Hongo, Bunkyo-ku, Tokyo, Japan
Collaborative Investigator	Yasushi Simo Prof. Department of Neurology Juntendo university Nerima Hospital Address: 3-1-10 Takanodai, Nerima-ku, Tokyo, Japan [REDACTED] Medtronic Japan Co., Ltd. OU Clinical 1-2-70 Konan, Minato-ku, Tokyo, Japan



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1. Glossary

Term	Definition
AT	As treated
aDBS	Adaptive Deep Brain Stimulation (aDBS). Stimulation amplitude is automatically adjusted in real-time in response to LFP signal of interest
aDBS Mode	An aDBS Mode is an amplitude increment / decrement stimulation algorithm. The two aDBS modes being evaluated in this study are Dual and Single Threshold Mode
aDBS Setup	The initial process of setting up a subject to an aDBS mode.
AE	Adverse Event
BrainSense™	The family of features in sensing that record and process local field potential (LFP) signals.
CC	Complete-Case
cDBS	Continuous Deep Brain Stimulation (cDBS)
CIP	Clinical Investigation Plan
cIDBS	Closed Loop Deep Brain Stimulation
CRF	Case Report Form
DBS	Deep Brain Stimulation
DD	Device Deficiency
EC	Ethics Committee
ECT	Electroconvulsive Therapy
EQ-5D-5L	European Quality of Life – 5 Dimensions – 5 Levels
GIC	Global Impression of Change
GPI	Globus Pallidus
ICF	Informed Consent Form
INS	Implantable Neurostimulator
JSON	JavaScript Object Notation, a data file format

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Term	Definition
jRCT	Japan Registry of Clinical Trials
LFP	Local Field Potential
MedDRA	Medical Dictionary for Regulatory Activities
MDS-UPDRS II, III and IV	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale – Part II, III and IV
MRgFUS	Magnetic resonance-guided focused ultrasound
PD	Parkinson's Disease
PDQ-39	The 39-item Parkinson's Disease Questionnaire
RDC	Remote Data Capture
SAE	Serious Adverse Event
SOI	Signal of interest, also referred to as a biomarker in literature. The signal of interest for this study is Beta local field potential
STN	Subthalamic Nucleus
TEED	Total Electrical Energy Delivered
TMS	Transcranial Magnetic Stimulation
UDysRS	Unified Dyskinesia Rating Scale
USAE	Unanticipated Serious Adverse Event

2. Synopsis

Title	Japan Post Market Adaptive Deep Brain Stimulation (aDBS) Study (Early Adapter) Part II
Clinical Study Type	Post-market Randomized, Single Blind, Crossover, Multicenter Study
Product Name	Medtronic Percept PC
Indication under investigation	Parkinson's disease (PD) with motor impairment of patients for whom the effect from medication is insufficient.
Investigation Purpose	The purpose of the study is to evaluate the efficacy of aDBS (preferred mode, single or dual threshold) vs standard continuous DBS (cDBS) in decreasing Total Electrical Energy Delivered (TEED).
Primary Objective	To demonstrate decreased Total Electrical Energy Delivered (TEED) during adaptive (aDBS) as compared to continuous DBS (cDBS).
Secondary Objective	To demonstrate maintenance within an optimal beta LFP threshold of beta LFP power during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower LFP threshold preset for each patient.
Study Design	<p>Prospective randomized, single-blind, crossover, multicenter study of aDBS in subjects with Parkinson's disease.</p> <p>The study is expected to be conducted at two sites located in Japan. It is estimated that 20-30 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled to obtain a study population of 20 subjects who complete the aDBS treatment phase. Participants must have either completed the Early Adapter I study, or they must have undergone a standard assessment demonstrating their tolerability of aDBS (preferred mode)</p> <p>Study visits and/or phases include:</p> <ul style="list-style-type: none">• Enrollment: Consent,• Baseline Visit: Screening, Baseline assessments• Randomization• aDBS treatment phase<ul style="list-style-type: none">• Period A initiation: EQ-5D/ PDQ-39/ MDS-UPDRS II ("best" and "worst" conditions)/ MDS-UPDRS III and IV/ UDysRS assessments; program initiation (cDBS or aDBS); Apple watch distribution and setup• Post period A: EQ-5D/PDQ-39/ MDS-UPDRS II ("best" and "worst" conditions)/MDS-UPDRS III and IV/ UDysRS

	<p>assessments; Percept and Apple Watch/ iPhone data upload. DBS program initiation (cDBS or aDBS) for Period B</p> <ul style="list-style-type: none"> • Post period B: EQ-5D/PDQ-39, MDS-UPDRS II ("best" and "worst" conditions)/ MDS-UPDRS III and IV/ UDysRS assessments; Percept and Apple Watch/ iPhone data upload • Follow-up Phase: 3 visits in aDBS for approximately 7 months : EQ-5D/PDQ-39, MDS-UPDRS II ("best" and "worst" conditions)/ MDS-UPDRS III and IV/ UDysRS assessments; Percept and Apple Watch data upload.
Sample Size	<p>The sample size was estimated using a one-sided test ($\alpha=0.025$) for paired T-Test means (PASS 2019) to compare the difference in aDBS TEED to cDBS TEED of 22 and a standard deviation of 28, a minimum of 20 subjects achieves at least 90% power for the detection of an effect size of 0.79. These subjects will roll over from the Early Adapter 1 study or will qualify on the basis of demonstrated aDBS acceptability.</p>
Inclusion/Exclusion Criteria	<p><u>Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Subject has Parkinson's disease with motor impairments. 2. Subject is implanted with Percept PC and Medtronic DBS leads and extensions bilaterally in the same target (physician confirmed), STN or GPi. 3. Subject has completed Early Adapter 1 study <u>OR</u> if the subject has not completed Early Adapter 1, she/he has documented evidence that aDBS is well tolerated in at least one mode (single or dual threshold) (Note: Tolerance means that the investigator has determined that aDBS is suitable for PD treatment). For subject who only tolerated dual threshold mode, aDBS must be set up in both hemispheres.* 4. Subject has Beta band (8-30 Hz) amplitude $\geq 1.2 \mu Vp$ detected on either left and/or right DBS leads on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11; As assessed in screening from Early Adapter I study. For subjects who have not completed Early Adapter Part I, it can be assessed using the record of standard test of eligibility for aDBS at the site. 5. The subject responds to DBS Therapy. 6. The subject's cDBS parameters and PD medications are stable and expected to remain stable from enrollment through the end of the aDBS treatment phase. (Note: Stability is defined as no major changes in cDBS parameter and medication for the last 30 days prior to aDBS setup or as defined by the physician.)

7. Subject is configured to monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side
8. Subject is willing and able to attend all study-required visits and complete the study procedures.
9. Subject has the ability to understand and provide written informed consent for participation in the study prior to the study-related procedures being conducted.
10. Subject is a male or non-pregnant female. If female of childbearing potential, and if sexually active, must be using, or agree to use, a medically acceptable method of birth control as confirmed by the investigator.
*If only one hemisphere has signal $\geq 1.2\mu\text{Vp}$ when setting up the dual threshold mode, sensing from the hemisphere with signal $\geq 1.2\mu\text{Vp}$ can be used to configure adaptive DBS in both hemispheres.

Exclusion Criteria

1. Subject and/or caregiver is unable to utilize the patient programmer.
2. Subject has more than one lead in each hemisphere of the brain.
3. Subject has cortical leads or additional unapproved hardware implanted in the brain.
4. Subject has more than one INS.
5. No tested mode of aDBS (single or dual threshold) is tolerated.
(Note: Tolerance is defined that investigator has determined that aDBS is suitable for PD treatment.)
6. At enrollment, the subject's INS has a predicted battery life of <1 year.
7. Subject has untreated severe depression which may preclude them from study participation.
8. Subject requires diathermy, transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), or Magnetic resonance-guided focused ultrasound (MRgFUS).
9. Subject has a metallic implant in the head, (e.g., aneurysm clip, cochlear implant).
10. Subject has, or plans to obtain, an implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemaker, defibrillator, spinal cord stimulator).
11. Subject has, or plans to obtain, an implanted medication pump for the treatment of Parkinson's disease (e.g., CADD-Legacy1400 pump) and/or portable infusion pump.

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	<p>12. The subject has an abnormal neurological examination that would preclude him from study participation.</p> <p>13. Subject is breast feeding.</p> <p>14. Subject is under the age of 20 years.</p> <p>15. Subject is currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound the results of this study.</p> <p>16. Subjects with signal artifact on all 6 aDBS sense pathways (3 on each of both DBS leads) which preclude the clinician from setting thresholds*</p> <p>*As assessed in aDBS setup from Early Adapter Part I and aDBS data collection. For subjects who have not completed them, it is assessed at the baseline visit).</p>
Study Procedures and Assessments	<p>Subjects will be considered enrolled at the time they sign the informed consent form. Scheduled visits will include the following:</p> <p>Enrollment, Baseline, Randomization and Period A initiation (Visit 1), Post Period A (Visit 2) and Post Period B (Visit 3) Follow-up Visit 4, Follow-up Visit 5, and Follow-up Visit 6</p> <p>The following assessments/data will be collected during the study:</p> <ul style="list-style-type: none"> • Concomitant medications (non-PD) • PD Medications at time of visit and/or day prior • PDQ-39 • EQ-5D-5L • MDS-UPDRS II ("best" and "worst" conditions) • MDS-UPDRS III and -IV • UDysRS • DBS Global Impression of Change score (DBS GIC) • Patient preference questionnaire • Patient satisfaction questionnaire • Apple Watch/iPhone data** • Device data, including BrainSense data • Event markers • Adverse Events and Device Deficiencies • Pre-op/post-op imaging data (MRI and/ or CT) of the implant <p>** In principle, the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute.</p>
Safety Assessments	To assess safety in following items:

	<ul style="list-style-type: none">• Stimulation-related adverse events during the aDBS treatment phase.• Serious adverse events which occur through the study after consent and for which the relationship with Percept PC cannot be ruled out: for all subjects• Any-cause death throughout the study: for all subjects.• Device (Percept PC) deficiencies that potentially involves a serious adverse event throughout the study: for all subjects
Statistics	<p>Primary and secondary objectives will be analyzed using the Complete Case Analysis Set that will include all subjects who initiate the aDBS treatment phase and have complete data for the respective analysis. Safety analyses will be evaluated using the As-Treated (AT) Analysis Set. AT includes all subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) at enrollment and/or the aDBS treatment phase and uses the observed treatment used for each subject in each phase. The change in TEED will be used to evaluate the primary objective. A paired t-test will be used to compare the difference in TEED for aDBS (Single or Dual mode) to cDBS. Normality of the outcome will be assessed with the Shapiro-Wilk test. If large violations to the normality assumption are observed ($p < 0.05$), the primary analysis will use a Wilcoxon signed-rank test to assess statistical significance.</p> <p>The secondary endpoint of mean percent time in Beta window inside the predefined window will be assessed based on data collected from the Percept device using Brain Sense Timeline View function and will be analyzed using a paired t-test or nonparametric Wilcoxon Rank-Sum of % of time in the window for the preferred aDBS mode vs cDBS.</p> <p>The Gatekeeping procedures will be applied for the multiple testing procedures. After the primary study objective is met ($\alpha = 0.05$ two-sided, gatekeeper), the secondary study objective will be carried out at $\alpha = 0.05$ two-sided. No multiplicity adjustment will be performed for evaluations of the additional study objectives. No imputation will be used.</p>

3. Introduction

3.1 Background

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease associated with both motor and non-motor symptoms. It begins in 2-3 percent of people aged 65 or older but can begin as early as the third or fourth decade.¹ PD is caused by a loss of dopamine-producing cells in the substantia nigra

and is associated with pathological beta (approximately 13-35 Hz) bursts and excessive synchronization within the cortico-basal ganglia network of the brain.^{1,2,3} This disruption in brain activity is associated with the characteristic motor symptoms of the disease: resting tremor, rigidity, bradykinesia, and postural instability.⁴⁻⁷

In the initial stages of PD, motor symptoms are often well controlled using dopaminergic drugs. However, chronic use of these levodopa medications over a 5-10 year period is associated with symptom fluctuations, dyskinesia and other motor complications in up to 80% of PD patients.⁴ These complications may be equal to or worse in severity than the motor impairment caused by the disease itself.⁸ Deep Brain Stimulation (DBS) Therapy may be used to treat some of the motor complications of PD that are not adequately controlled with medication. DBS is a surgical intervention that involves the placement of electrodes in targeted areas of the brain. These electrodes are arranged on a lead and are connected to an implanted neurostimulator that delivers mild electrical pulses to targeted brain areas. Once patients are implanted with the DBS device, clinicians may adjust the electrical stimulation parameters to obtain maximal symptom relief and minimize stimulation-induced adverse effects. The use of DBS in the subthalamic nucleus (STN) and globus pallidus interna (GPi) has been shown to improve symptoms of PD.^{4,9,10,11,12,13,14,15,16,17} Several multicenter, randomized controlled trials conducted in the United States, Europe, and in several other geographies worldwide provide evidence of its effectiveness.^{18,19,20,21,22,23,24} Deep Brain Stimulation Therapy is currently delivered in a continuous fashion (cDBS) where stimulation settings are constant over time and do not adjust to fluctuations in symptoms typically experienced by Parkinson's disease patients during medication On and Off states. During On-medication states, the addition of stimulation using cDBS is thought to adversely affect dyskinesias and other side effects experienced by the patient.²⁵ To make DBS more responsive to an individual patient's clinical state, investigators have explored the use of adaptive DBS (aDBS) therapy.

aDBS Therapy, also known as closed-loop DBS (clDBS), adjusts stimulation in a variable fashion. It relies on a biomarker, or signal of interest (SOI), to adjust stimulation. The SOI must correlate to a patient's clinical state (i.e. severity of disease symptoms), dynamically reflect changes in disease symptoms, be persistent over time, be discernible from background artifacts and be measurable with minimal additional intervention.^{26,27,28,29} Perhaps the most studied SOIs within this context are local field potentials (LFPs), which represent the transient oscillatory activity of various neuronal populations in the brain.

During the last decade, researchers have worked to characterize LFP signals in the brain. LFPs represent the summed pre- and post-synaptic neuronal activity in the area of the brain where the LFPs are being recorded. Researchers have shown the presence of excessive LFP beta oscillations in the range of approximately 13-35 Hz and over-synchronization in the cortico-basal ganglia network in the brains of PD patients.^{4,30,31,32,33} In a review of 20 publications between 2001 and 2011, researchers reported measurable beta peaks in the Off-medication state in a mean of 95% of PD patients/nuclei.²⁹ These beta

LFP signals are persistent over time,^{34,35,36,37,38,39} can be measured using the currently approved Medtronic DBS leads,^{34,35,36,38,40} can correlate with severity of bradykinesia and rigidity in PD patients and are attenuated by both levodopa (i.e., in the ON-medication state) and DBS stimulation.^{7,28,31,32,41,42,43} The degree to which these LFP signals are attenuated correlates with the degree of improvement in symptoms of bradykinesia and rigidity.^{7,28,31,32,42,43,44}

In recent years, research has been conducted to test the feasibility of using aDBS Therapy where the stimulation adjusts automatically based on LFPs in the basal ganglia. Based on evidence that beta LFPs decrease in response to increasing stimulation, two slightly different aDBS control mechanisms have been utilized in these studies. The first is a scalar approach (i.e., dual threshold aDBS mode) whereby stimulation amplitude incrementally adjusted between upper and lower, clinician-defined therapeutic limits to maintain beta LFP within a defined range.^{45,46,47} The second is a binary approach (i.e., single threshold aDBS mode), whereby stimulation switches on when the beta LFP exceeds a preset threshold and switches off when the LFP falls below the preset threshold.^{25,48,49,50} Clinical studies using both single and dual threshold aDBS control mechanisms support the technical feasibility of using beta LFP signals as a signal of interest for aDBS.^{45,46,47,48,49,50,51,52,53,54}

Evidence from single center feasibility studies has demonstrated that aDBS is at least as efficacious as cDBS based on UPDRS III motor scores and could potentially be up to 27% more effective.^{47,48,49} aDBS may also reduce stimulation-induced adverse effects such as dyskinesia and speech impairment. In multiple studies, PD patients receiving aDBS showed less dyskinetic effects compared to cDBS, potentially by reducing the sum effect of stimulation and medication.^{25,52,54} Regarding speech, one study of 10 subjects showed a clinically meaningful improvement in speech intelligibility with aDBS over cDBS.⁵⁰ Overall aDBS was well tolerated in freely moving PD subjects both On and Off medications for up to 8 hours.^{47,49,52,53,55} In addition, multiple studies showed a significant reduction in the power usage with aDBS compared to cDBS, averaging about 50% of the power demand of standard cDBS Therapy.^{45-49,52,54}

Although the subjects and conditions of the individual studies assessing aDBS vary, these studies have consistently shown the feasibility of using aDBS controlled by STN beta LFP feedback and its potential to effectively reduce PD symptoms while reducing side effects and increasing battery longevity.

The DBS device used in this study is the only device that has an aDBS control mechanism (Generic name: DBS system, Trade name in Japan: Medtronic Percept PC) and is approved and commercially available in Japan. This study is expected to establish a better treatment method and improve patient QOL by evaluating the usefulness of aDBS in comparison with the conventional method of continuous stimulation cDBS.

4. Objectives and Endpoints

4.1 Purpose

The purpose of the study is to evaluate the efficacy of aDBS (preferred mode, single or dual threshold) vs standard continuous DBS (cDBS) in decreasing Total Electrical Energy Delivered (TEED).

4.1.1. Primary Objective

To demonstrate decreased Total Electrical Energy Delivered (TEED) during adaptive (aDBS) as compared to continuous DBS (cDBS).

4.1.2. Secondary Objective

To demonstrate maintenance within an optimal beta LFP threshold during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower LFP threshold of beta LFP power preset for each patient.

4.1.3. Safety Assessments

To assess safety in the following items:

- Stimulation-related adverse events during the aDBS treatment phase
- Serious adverse events which occur through the study after consent and for which the relationship with Percept PC cannot be ruled out: for all subjects
- Any-cause of death throughout the study: for all subjects.
- Device (Percept PC) deficiencies that potentially involve a serious adverse event throughout the study: for all subjects

4.1.4. Additional Objectives

To characterize clinical outcomes of aDBS (preferred mode) vs. cDBS, and by aDBS mode in the following items:

- EQ-5D-5L
- Parkinson's Disease Questionnaire (PDQ)-39
- Unified Dyskinesia Rating Scale (UDysRS)
- Movement Disorder Society-Sponsored Revision of Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II ("best" and "worst" conditions)*
- MDS-UPDRS III and IV

- LFP dynamics based on out of clinic patient event markers and PD Medication cycle
- Movement and sleep data collected from Apple Watch (will be correlated with Percept Device data and clinical measures)
- To assess a patient-specific anatomy using a visualization tool of lead location and simulated volume of neural activation based on Pre-op/post-op imaging data of Percept PC implant.
- Patient preference of aDBS (preferred mode) vs cDBS
- Patient satisfaction with aDBS (preferred mode)

* "Best conditions" is the time period when PD subjects are receiving relief from their Parkinson's disease symptoms, also known as "on" time or "on" period. "Worst conditions" is the time period when PD subjects are not receiving relief from their Parkinson's disease symptoms, also known as "off" time or "off" period.

Assess the average function of the subjects during the past week, including the assessment date, when they were in the "best conditions" and "worst conditions".

4.2 Endpoints

4.2.1. Primary Endpoint

Decreased total electrical energy delivered (TEED) during the aDBS treatment phase as compared with cDBS.

[Ground for the primary endpoint]

The total electrical energy delivered (TEED) reflects the power usage of the device and is an indicator of battery life. It was set to evaluate the usefulness of aDBS from the viewpoint of possible improvements in battery life.

4.2.2. Secondary Endpoint

Mean percent time within an optimal threshold of beta LFP power during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower beta LFP threshold preset for each patient.

5. Study Design

Prospective randomized, single-blind, crossover, multicenter study of aDBS in subjects with Parkinson's disease.

The study is expected to be conducted at two sites located in Japan. It is estimated that 20-30 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled to obtain a study population of 20 subjects who complete the aDBS treatment phase. Participants must have either completed the Early Adapter I study, or they must have undergone a standard assessment demonstrating tolerability of aDBS (preferred mode).

There is no set minimum or maximum number of subjects to be enrolled per study site.

5.1 Duration

The expected study duration is 1st October 2021 to 31st August 2024.

The expected enrollment period is 1st October 2021 to 31st December 2022.

The Participation of an individual subject will be about 12 months.

5.2 Rationale

The Early Adapter Part II study will utilize the Percept PC INS with the aDBS functionality that was developed using the clinical knowledge gained in numerous investigator-sponsored, single-center, feasibility studies and investigator experience with the Medtronic Activa PC+S INS, a first generation - sensing device. The aDBS control algorithm will rely on STN and GPi beta band (approximately 13-35 Hz) activity as the signal of interest.

The feasibility of using beta LFP has been demonstrated by multiple centers and across multiple research groups.^{25,45,46,47,48,49,50,51,52,53,54,55} The Early Adapter Part II Study will assess aDBS (preferred mode, single or dual threshold). Evidence generated by the Bronte-Stewart/Stanford group using a dual threshold algorithm and the Brown/Oxford group using a single threshold algorithm has demonstrated that aDBS is feasible. In addition, both dual and single threshold aDBS algorithms were well tolerated, were as effective or more effective than cDBS, may reduce DBS induced side effects and were associated with a significant reduction in DBS power usage compared to cDBS.^{25,45,46,47,48,49,50} Based on this evidence, this study will evaluate the efficacy of aDBS, which is equipped with a programming tool that is personalized and corresponds to each subject, in comparison to conventional cDBS. This study is designed as a crossover study to evaluate the study purpose, and randomized and single-blinded to minimize bias.

6. Product Description

[Generic name] DBS system

[Trade name in Japan] Medtronic Percept PC

[Manufacturer with marketing approval] Medtronic Japan Co., Ltd

[Form, Structure, and Principle]

The stimulator



Electrical Ratings

HCSVO, single unit

Material name

Case: Titanium alloy

Connector: Polysulfone, TiO₂, Silicone rubber

Accessories

Torque wrench, Connector Plug

Material name

Polyurethane

[Principles of Operation]

Providing electrical stimulation of the stimulator to the top of the leads implanted in the deep brain and reducing the symptoms of Tremor etc.

[Intended use] This device is intended for electrical stimulation to the deep brain and is used for reducing the following symptoms of patients for whom the effect from medication is insufficient:

- Tremor
- Parkinson's Disease with motor impairment
- Dystonia

[Method of Use]

Stimulator settings and functions are configured with clinician programmer.

[Device Deficiency/ Adverse Event] Refer to the latest package insert of Medtronic Percept PC.

Medtronic Percept PC has approved and commercially available in Japan. Refer to the latest package insert of Medtronic Percept PC for the detail information. .

6.1 General

Medtronic DBS Therapy uses programmable neurostimulators, leads and extensions to deliver electrical stimulation to the STN or GPi to manage some of the symptoms of PD.

The Percept PC system includes the Percept PC INS and external components that use telemetry to communicate with the INS for programming stimulation parameters. Figure 1 illustrates the full Percept PC system.

The devices that are considered for the Early Adapter Part II study system include the Percept PC INS, the Clinician Programmer and the Patient Programmer Application (PPA).

Incorporation of additional leads, or accessories into the study will be considered as they become commercially available if the addition does not affect the scientific soundness of the study.



Figure 1: Percept PC System

6.1.1. Medtronic DBS System

aDBS Feature

The intended purpose of the aDBS feature is to automatically adjust stimulation amplitude, within clinician-defined limits, based on changes in a patient's brain state measured using beta LFPs as a signal of interest. Under the assumption that correlations exist between brain state and clinical symptoms and side effects, the goal is to maintain the brain state such that certain clinical symptoms and side effects can be managed. The aDBS mode is set using a Clinician Programmer System. This study assesses a subject's preferred aDBS mode (i.e. Dual and Single Threshold modes).

aDBS Dual Threshold Mode

Dual threshold mode includes both an upper and lower control threshold on the LFP SOI and aDBS makes changes to the stimulation amplitude to attempt to maintain the LFP SOI between the two thresholds. In this scheme, when the LFP SOI is "high", then stimulation is increased, whereas when the LFP SOI is "low" stimulation is decreased to control the LFP SOI. When the patient tailored LFP Beta power SOI remains between the upper and lower thresholds, stimulation amplitude is held constant.

When the Beta power SOI exceeds the upper threshold, stimulation increments. When the Beta power SOI dips below the lower threshold, stimulation decrements. This aDBS mode is shown in Figure 2.

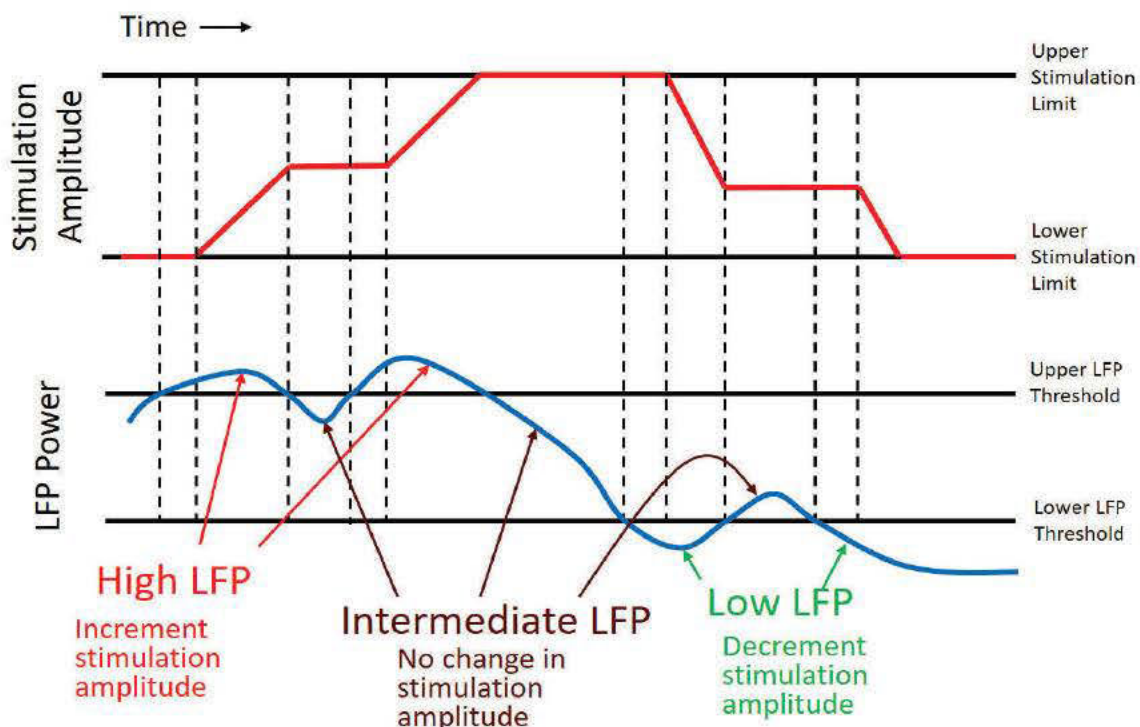


Figure 2: Dual Threshold aDBS Mode

aDBS Single Threshold Mode

Single threshold mode includes a single control threshold on the LFP SOI and aDBS makes changes to the stimulation amplitude based on the measured LFP and whether it is above or below the threshold. In this scheme, when the LFP SOI is above the threshold, then stimulation is incremented and when the LFP SOI is below the threshold, the stimulation is decremented. This mode has shorter default stimulation ramp up and ramp down durations than dual mode. This aDBS mode is illustrated in Figure 3.

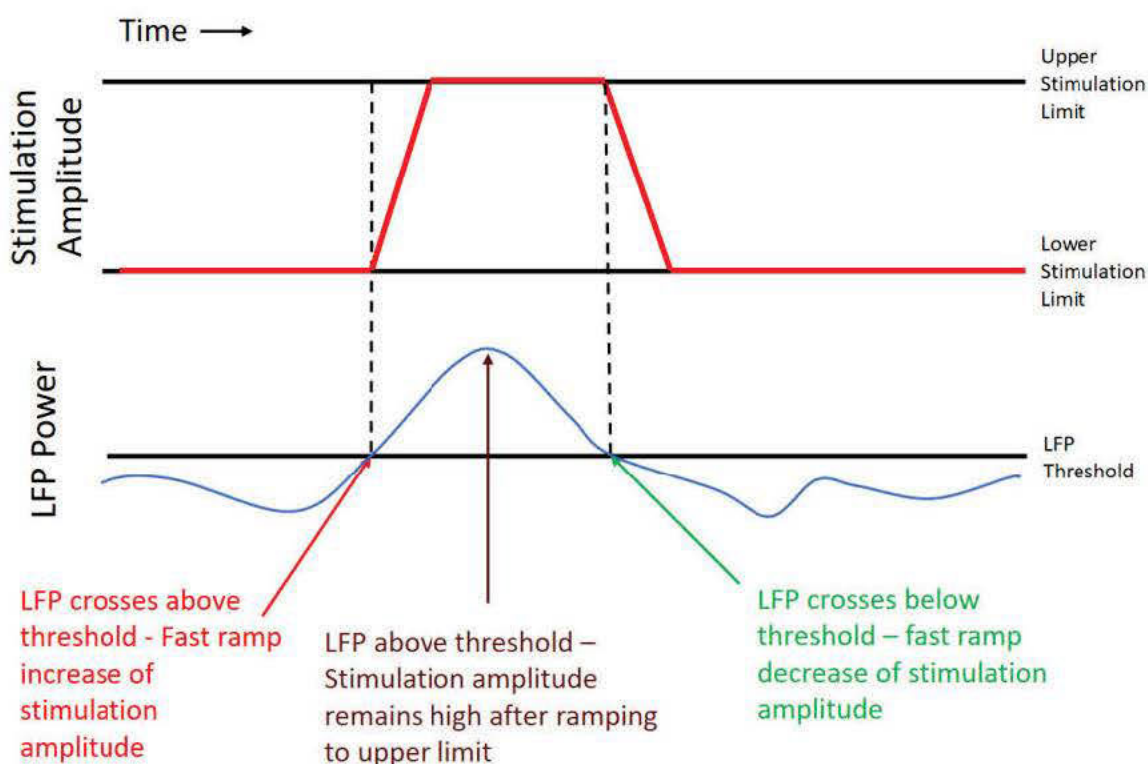


Figure 3: Single Threshold aDBS Mode

6.2 Equipment

6.2.1. Rental products

The Apple Watch will be used to provide a continuous, objective monitoring of key movement symptoms of Parkinson's disease (tremor), motor complications (dyskinesia), heart rate, steps and sleep time. The iPhone will be used to record PD Medication cycle. The Apple Watch/iPhone will use the Apple Movement Disorders App (Apple, Inc.) coupled with the STRIVE analysis platform (Rune Labs, Inc.). Functions of the watch will be controlled and synchronized through a provided iPhone (model to be

determined).

The Apple watch-based inertial sensing system can measure tremor and dyskinesia, enable out-of-clinic monitoring and aid medication titration in PD patients.

6.2.2. Rental products Receipt and Tracking

Apple Watch, iPhone and Wi-Fi router will be provided for the participants of the study. They will be provided to the sites by Medtronic and tracked using a product accountability log. Rental products Receipt and Tracking between the site and the subject is tracked using a lending log.

These products will be provided for study use and cannot be used for purposes other than study. In addition, they must be stored in a secured and locked location accessible only to those delegated individuals who are authorized by the PI to access them. At the end of the study participation, subjects return them to the site. The sites will return them to Medtronic at the end of the study. PI/ Sub investigator and site staff will manage these products with a duty of care. During the rental period, if it is necessary to repair the rental products due to defects in them or damage caused by normal use, Medtronic Japan Co., Ltd. can be contacted and repair them at the expense of Medtronic Japan Co., Ltd.

The following records will be maintained at minimum for accountability/ lending log;

Date of receipt, Date of return, quantities of received devices (Apple Watch, iPhone and Wi-Fi router), and quantities of devices returned.

6.3 Product Accountability

All products used in this study will be market released in Japan. Commercially available product supply will be managed in a manner consistent with other market-released products.

7. Study Site Requirements

7.1 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations (as required), informed consent, and on data collection and reporting tools under the direction of the PIs. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study. Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- Ethics Committee (EC) approval of the current version of the CIP and Informed Consent (IC)
- Fully executed Clinical Trial Agreement (CTA)

- Confirmation of conflict of interest
- Curriculum Vitae (CV) of PIs
- Documentation of delegated tasks
- Documentation of study training

Additional requirements imposed by local regulations (Ethical guidelines for human life science and medical research, etc.), the EC and RA shall be followed.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements (depending on their role) and must be delegated by the PI to perform study related activities.

7.2 Role of the Sponsor Representatives

Medtronic is responsible for preparing/modifying the CIP, creation of the study-related material, monitoring, audit, statistical analysis, data management writing papers, etc., as a sponsor.

Monitoring will be conducted under the responsibility of the PI according to Medtronic's monitoring manual.

Audits are planned for each fiscal year of Medtronic Japan Co., Ltd., Medtronic plc and its affiliates based on risks. At Medtronic Japan Co., Ltd., internal audits will be planned according to audit procedures of Medtronic Japan Co., Ltd. The work of the audit will be conducted by a member of Medtronic's internal audit department, which is independent of the study's implementation unit and which specializes in auditing. This department is completely independent from the department that conducts all clinical studies such as pre-market clinical trials, post-marketing surveillances, and clinical researches, and is in a third-party position.

8. Selection of Subjects

8.1 Study Population

The intended study population is subjects, who are attending or admitted to the Department of Neurology of study sites, with idiopathic Parkinson's disease implanted with a full Medtronic DBS system, including bilateral leads targeted to the internal globus pallidus (GPi) or the subthalamic nucleus (STN), extensions and a single Percept PC implantable neurostimulator. The subject and/or caregiver must be able to utilize the patient programmer.

Subject Enrollment

Subjects are enrolled into the study at the time they sign and date a study-specific subject Informed Consent (IC). Ensure that subjects meet all of the inclusion criteria and none of the exclusion criteria after enrollment.

8.2 Inclusion Criteria

To be eligible to participate in the study, a subject must meet all the following inclusion criteria:

Inclusion Criteria

1. Subject has Parkinson's disease with motor impairments.
2. Subject is implanted with Percept PC and Medtronic DBS leads and extensions bilaterally in the same target (physician confirmed), STN or GPi.
3. Subject has completed Early Adapter 1 study OR if the subject has not completed Early Adapter 1, she/he has documented evidence that aDBS is well tolerated in at least one mode (single or dual threshold) (Note: Tolerance means that the investigator has determined that aDBS is suitable for PD treatment). For subject who only tolerated dual threshold mode, aDBS must be set up in both hemispheres.※
4. Subject has Beta band (8-30 Hz) amplitude $\geq 1.2 \mu Vp$ detected on either left and/or right DBS leads on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11; As assessed in screening from Early Adapter I study. For subjects who have not completed Early Adapter Part I, it can be assessed using the record of standard test of eligibility for aDBS at the site.
5. The subject responds to DBS Therapy.
6. The subject's cDBS parameters and PD medications are stable and expected to remain stable from enrollment through the end of the aDBS treatment phase. (Note: Stability is defined as no major changes in cDBS parameter and medication for the last 30 days prior to aDBS setup or as defined by the physician.)
7. Subject is configured to monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side
8. Subject is willing and able to attend all study-required visits and complete the study procedures.
9. Subject has the ability to understand and provide written informed consent for participation in the study prior to the study-related procedures being conducted.

10. Subject is a male or non-pregnant female. If female of childbearing potential, and if sexually active, must be using, or agree to use, a medically acceptable method of birth control as confirmed by the investigator.

※If only one hemisphere has signal $\geq 1.2\mu\text{Vp}$ when setting up the dual threshold mode, sensing from the hemisphere with signal $\geq 1.2\mu\text{Vp}$ can be used to configure adaptive DBS in both hemispheres.

[Grounds for the criteria] 1-8 are the criteria to include applicable patients, 9 is to adhere to Helsinki Declaration, 10 is to secure patients' safety.

8.3 Exclusion Criteria

Exclusion Criteria

1. Subject and/or caregiver is unable to utilize the patient programmer.
2. Subject has more than one lead in each hemisphere of the brain.
3. Subject has cortical leads or additional unapproved hardware implanted in the brain.
4. Subject has more than one INS.
5. No tested mode of aDBS (single or dual threshold) is tolerated. (Note: Tolerance is defined that investigator has determined that aDBS is suitable for PD treatment.).
6. At enrollment, the subject's INS has a predicted battery life of <1 year.
7. Subject has untreated severe depression which may preclude them from study participation.
8. Subject requires diathermy, transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), or Magnetic resonance-guided focused ultrasound (MRgFUS).
9. Subject has a metallic implant in the head, (e.g., aneurysm clip, cochlear implant).
10. Subject has, or plans to obtain, an implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemaker, defibrillator, spinal cord stimulator).
11. Subject has, or plans to obtain, an implanted medication pump for the treatment of Parkinson's disease (e.g., CADD-Legacy1400 pump) and/or portable infusion pump.
12. The subject has an abnormal neurological examination that would preclude him from study participation.

13. Subject is breast feeding.
14. Subject is under the age of 20 years.
15. Subject is currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound the results of this study.
16. Subjects with signal artifact on all 6 aDBS sense pathways (3 on each of both DBS leads) which preclude the clinician from setting thresholds*

*As assessed in aDBS setup from Early Adapter Part I and aDBS data collection. For subjects who have not completed them, it is assessed at the baseline visit).

[Grounds for the criteria]

1-12 and 15 were defined the possibility of influencing the study outcomes, 13-14 are to secure patients' safety, 16 is to exclude subject for whom aDBS could not be set.

9. Study Procedures

9.1 Schedule of Events

The start of the study is defined as the date the first subject signs the informed consent. In addition, the completion of the study is defined as the date on which the summary of study results is submitted to EC and the Head of Institution.

Scheduled visits will include the following: Enrollment (Consent), Baseline, Randomization, aDBS Treatment phase [Period A initiation (Visit A), Post Period A (Visit 2), Post Period B (Visit 3)], Follow-up phase [Visit4, Visit5, Visit6]

Study Schematic is illustrated in Figure 4.

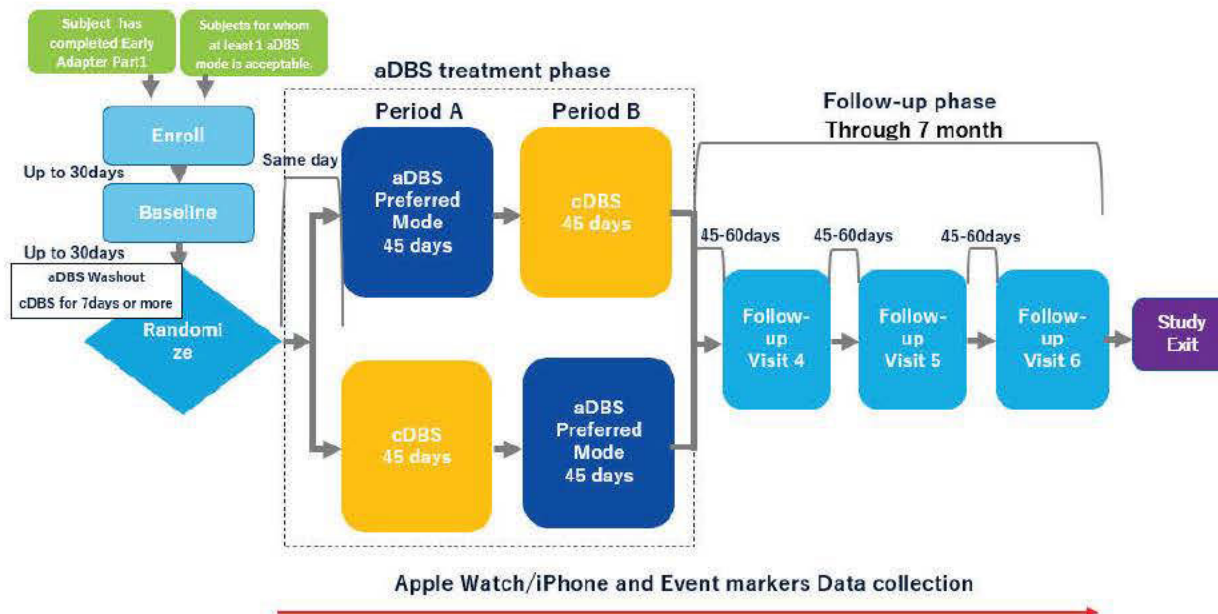


Figure4: Study Schematic

9.2 Data Collection

Table 1 shows the data collection requirements and Scheduled Visit Windows

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Medtronic

Table 1: Data collection and study procedure requirements at subject visits

Visit	Enrollment	Baseline	Randomization	aDBS Treatment Phase					Follow-up phase			Exit
				Visit 1	Out of clinic	Visit 2	Out of clinic	Visit 3	Visit 4	Visit 5	Visit 6	
Visit ranges (From the previous visit)		Up to 30 days		Up to 30 days		45 days ⁴		45 days ⁴	45-60 days ⁴	45-60 days ⁴	45-60 days ⁴	
Informed Consent	X											
Demographics		X ¹										
Medical & surgical history		X ¹										
PD history		X ¹										
Device Information		X ¹										
MRI/ CT image data		X ¹										
Signal Test/LFP threshold setting		X ¹										
aDBS washout (7 days or more)		X										
Randomization			X									
Concomitant medications (non-PD)		X		X		X		X	X	X	X	
PD medication		X		X		X		X	X	X	X	
Program initiation (cDBS or aDBS)				X		X						
PDQ-39				X		X		X	X	X	X	
EQ-5D-5L				X		X		X	X	X	X	
UDysRS				X		X		X	X	X	X	
MDS-UPDRS II ("best" conditions)				X		X		X	X	X	X	
MDS-UPDRS II ("worst" conditions)				X		X		X	X	X	X	
MDS-UPDRS III				X		X		X	X	X	X	

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Visit	Enrollment	Baseline	Randomization	aDBS Treatment Phase					Follow-up phase			Exit
				Visit 1	Out of clinic	Visit 2	Out of clinic	Visit 3	Visit 4	Visit 5	Visit 6	
Visit ranges (From the previous visit)		Up to 30 days		Up to 30 days		45 days ⁴		45 days ⁴	45-60 days ⁴	45-60 days ⁴	45-60 days ⁴	
MDS-UPDRS IV				X		X		X	X	X	X	
DBS GIC						X		X				
Preference questionnaire		X ¹						X ⁵				
Satisfaction questionnaire								X ⁶			X	
Apple Watch/iPhone distribution and programming				X								
Apple Watch/iPhone data collection**				X	X ²	X	X ²	X	X	X	X	
Device data		X ³		X		X		X	X	X	X	
Event markers (Option)					X		X		X	X	X	
Adverse Events	As they occur											
Device Deficiencies	As they occur											
Protocol Deviations	As they occur											
Reason for exit												X

¹ Not required if data collected prior to Early Adapter Part II

² PD Medication cycle, every 14 days during 45 days of Period A and B; Calendar reminders set on Apple Watch, with instructions

³ If Signal test was implemented

⁴ Visit ranges ± 7 days

⁵ Perform before unblinding subjects

⁶ Perform after unblinding subjects

** In principle, the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute.

Scheduled Visit Windows

Data analyses include all visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original schedule maintained for subsequent visits.

9.3 Prior and Concomitant Medications/Therapies

Subjects' Parkinson's disease medication should be stable at the time of enrollment in the study through the end of the aDBS Treatment Phase. During this time, the PI/ Sub investigator should make only clinically necessary changes to PD medication.

Parkinson's disease medications will be withheld for at least 12 hours prior to the Signal Test to assess Beta band (8-30 Hz) amplitude $\geq 1.2 \mu\text{Vp}$ or prior to setting the LFP threshold. If the LFP signals of the patient are smaller than $1.2\mu\text{Vp}$, then consider taking the patient off medications for 24 hours and bring him in again for the signal Test after medication has been withhold for 24 hours.

All Parkinson's disease medications and all concomitant medications, except for over the counter medications and herbal supplements, will be collected throughout the study.

9.4 Subject Consent

Prior to enrolling subjects, PI must create the site IC using the IC approved by the EC. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the EC. Any adaptation of the IC must be reviewed and approved by Medtronic and the EC if the IC is updated during the study.

The PI/ Sub investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. The IC process must be conducted by the PI/ Sub investigator, and the IC Form must be given to the subject in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the PI/ Sub investigator. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable. Since this study is intended for those who are 20 years of age or older and who can provide informed consent for participation in this study, consent from a legally authorized representative and informed assent does not apply for this study.

The subject must have ample time and opportunity to read and understand the IC form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject. Response to consultation made by subjects or their individuals concerned will be performed by the sub investigators at each study site. Details of contact is shown in the study-specific subject IC.

When the subject decides to participate in the study, the IC must be signed and personally dated by the subject and PI/ Sub investigators, as required by the IC, and ensured by the PI/ Sub investigators.

A copy of the IC signed and dated as required by law, must be provided to the subject.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

The original signed IC must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC must be available for monitoring and auditing.

1. Both the informed consent discussion and the written informed consent form to be provided to subjects should include explanations of the following Introduction
2. Your Illness
3. Device Description
4. Study Purpose and Significance
5. Planned Period of Participation and Planned Number of Participants
6. Study sites in Japan
7. Study Procedures
8. Potential inconveniences of this PMR Study
9. Possible Benefits of this PMR Study
10. Other Treatment Methods
11. Your Responsibilities

12. Cost Burden
13. Compensation for Health Injuries
14. Freedom to Discontinue Participation or Withdraw Consent
15. Arrangements after the PMR Study
16. Protection of Personal Information and Privacy
17. Possible Use of Data for Future Research
18. Means for Storage and Disposal of Specimens and Information
19. Publication of Study-related Data
20. Intellectual Property Rights
21. Research and Involvement with Corporations and Study sites
22. Access to Study-related Materials
23. Handling of study Results
24. Contact Information and Consultation Points

9.5 Enrollment

Subjects who have a complete Medtronic DBS system, including Percept PC, leads and extensions and who have either completed the Early Adapter Part I study, or who have tolerability of aDBS may be approached to participate in the study.

A subject is considered enrolled when the consent process has been fully executed.

The study-specific IC will be signed and dated prior to completion of any study-related procedures.

Subjects may choose to participate in an optional data collection of Events with LFP capture (Event markers). This will be clarified in the informed consent of the patients.

Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit.

9.6 Baseline

The baseline visit must occur within 30days after subject enrollment.

The PI/ Sub investigator will screen potential subjects by reviewing the study's inclusion/exclusion

criteria.

Enrolled subjects who do not meet all inclusion criteria or who meet any exclusion criteria will be discontinued from the study. No further study-related procedures will be completed, and subjects will be followed according to the site's standard procedures.

The PI/ Sub investigator will ensure the INS device time matches that of the clinician programmer tablet (network enabled). If the INS time does not match the network time, the INS time should be updated.

The following data will be collected at Baseline:

- Demographics (age, sex)*
- Medical & surgical history*
- PD history*
- Signal test (If implemented)
- Patient preference questionnaire. *
- Concomitant medications (non-PD)
- PD medication (When performing a signal test with Off PD medication, PD medication and does given at visit. Time of last dose of PD medications taken prior to the visit)
- Device identification information, including historical DBS implant information*
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report (If Signal test was implemented)
- Pre-op/post-op Magnetic Resonance Image (MRI) images and Computed Tomography (CT) images of Percept PC implant *
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*It is stated in the IC and consent is obtained from the subjects that these data collected prior to Early Adapter Part II are used for this study.

If both aDBS modes (single and dual threshold) are acceptable, a preference questionnaire is used to determine the preferred aDBS mode (single or dual threshold) for the subject. If the subject answers "Do not know" or "No preference" to the question "Which adaptive DBS mode do you prefer?", the PI/

Sub investigator determines the aDBS (preferred mode) which is suitable for the treatment of the patient.

The PI/ Sub investigator selects dual threshold mode from the BrainSense™ setup to set the LFP threshold if the subject's LFP threshold has not been set. The subjects who are on aDBS mode will leave the visit on cDBS settings (including BrainSense settings) in order to wash out aDBS for 7 days or more.

For the subjects with cDBS for 7 days or more, baseline can be a stand-alone visit or can occur on the same day as the randomization/Period A initiation visit.

The PI/ Sub investigator explains to subjects that the cDBS mode cannot be changed except in an emergency. If it is necessary to adjust the stimulation the subjects need to return to the site for adjustments. Visits for adjustments are recorded as unscheduled visits.

9.7 Randomization and Treatment Assignment

7 days or more after cDBS has been set and within 30 days after the baseline visit.

Subjects will be randomly assigned during a randomization to a subjects' preferred aDBS mode (single or dual threshold) or cDBS (BrainSense setting is ON). The randomization method is Permuted Block Randomization. The site personnel will obtain the randomization assignment via Remote Data Capture (RDC). The randomization assignment can be obtained upon completion of the Informed Consent, Inclusion/Exclusion Criteria and randomization CRFs.

Crossover is performed after 45 (± 7) days when a preferred aDBS mode (single or dual threshold) or cDBS is assigned to a subject. A subject will not have knowledge of the DBS mode assigned for the duration of the aDBS treatment phase.

The PI/Sub investigator explains to the subjects that the assigned DBS mode cannot be changed except in an emergency. If it is necessary to adjust the stimulation mode the patient needs to return to the study site to make adjustments. Visits for adjustments are recorded as unscheduled visits. All adjustments must be completed at least 14 days prior to the next visit. Any adjustments should be recorded as unscheduled visits. Any adjustments during the 14 days prior to the next visit will be considered as a protocol deviation.

In order to blind the subject to the aDBS mode assigned, PI/Sub investigator will set the group name of the preferred aDBS mode to "DBS1," the group name of cDBS to "DBS2" and the group name of non-adjusted or the non-preferred aDBS mode to "DBS3" on the Clinician Programmer. If there is another mode that has already been set, set the group name to "DBS4". These group names will be displayed on the Patient Programmer.

If blinding is broken during the aDBS treatment phase, record the reason for the blind breaking in the medical records of the subject and report it as a deviation.

9.8 aDBS Treatment Phase

This phase consists of three treatment periods [Period A initiation (Visit 1), Post Period A (Visit 2) and Post Period B (Visit 3)].

For subjects implanted a directional lead with separate electrodes (e.g., SenSight), set the output of each separate electrodes uniformly (use it as a ring-shaped electrode).

9.8.1. Period A initiation /Visit1

Same as Randomization day.

The PI/ Sub investigator should confirm the subject is in cDBS.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- PDQ-39 (subject's assessment of cDBS or aDBS washout period)
- EQ-5D-5L
- MDS-UPDRS II ("best" conditions)
- MDS-UPDRS II ("worst" conditions)
- MDS-UPDRS III (On stim (cDBS)/On med) – trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of cDBS or aDBS washout period)
- Upload data collected from Apple Watch, including movement and sleep data (Operation confirmation)
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

At the end of the visit, the PI/Sub investigator should program the subject to the assigned DBS mode for Period A. Start the program for Period A, and return the subject home.

Subjects will participate in a data collection of movement, sleep data and dosing cycle of PD medications with Apple Watch and iPhone. The subject will be given an Apple Watch and linked iPhone and instructed on its use. Upon receipt, the subjects should put on and activate the Apple Watch. Data collection will start immediately and will continue as long as the subject is wearing the watch and the watch is charged. After the recording, the subject will upload the data collected from Apple Watch via iPhone to the database specified by Rune Labs, Inc. Subjects will also record their PD medications in an iPhone application (STRIVE App, Rune Labs) every 14 days during Period A and Period B in aDBS treatment phase. An Apple Watch calendar will be set up to get notifications from Apple Watch for medication log. Subjects will receive further guidance on the daily charging schedule of the Apple Watch and data upload through the iPhone application (STRIVE App, Rune Labs, Inc.). Detailed procedures for the Apple Watch/iPhone data collection are outlined in the Rune Labs Study Manual. In principle, the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute by reporting in CRFs.

The PI/Sub investigator will set up a maximum of 4 event types, selected from the following options: dyskinesia, tremor, rigidity, freezing, sleep disturbance, took PD medication to collect Events with LFP capture (Event markers). PI/Sub investigator should instruct the subject on how to record each event type utilizing the Patient Programmer System.

9.8.2. Post Period A /Visit2

45(\pm 7) days after Period A/Visit1

The PI/ Sub investigator should confirm the subject is in the assigned mode for this visit. If the subject is not in the assigned mode, a deviation CRF will be completed and the reason for the mode change will be collected. If applicable the subject will start the visit over again after 45(\pm 7) days, where possible, i.e. if the subject tolerates well the assigned mode the assigned mode is setup, and if the subject was switched to another mode by accident.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- PDQ-39 (subject's assessment of prior 30-day period on the assigned mode in Period A)
- EQ-5D-5L

- MDS-UPDRS II ("best" conditions)
- MDS-UPDRS II ("worst" conditions)
- MDS-UPDRS III (On stim/On med) – trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of prior 30-day period on the assigned mode in Period A)
- DBS Global Impression of Change score (DBS GIC)
- Upload data collected from Apple Watch/iPhone, including movement and sleep data *,**
- Event markers (optional)*
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*: Confirm if it has been done

** : In principle, the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute.

At the end of the Post period A visit, the PI/Sub investigator should program the subject to the assigned DBS mode for Period B. Start the program for Period B, and return the subject home .

9.8.3. Post Period B/Visit3

45(±7) days after Post Period A/Visit2

The PI/ Sub investigator should confirm the subject is in the assigned mode for this visit. If the subject is not in the assigned mode, a deviation CRF will be completed and the reason for the mode change will be collected. If applicable the subject will start the visit over again after 45(±7) days, where possible, i.e. if the subject tolerates well the assigned mode and the assigned mode is setup if the subject was switched to another mode by accident.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the

JSON session data report

- PDQ-39 (subject's assessment of prior 30-day period on the assigned mode in Period B)
- EQ-5D-5L
- MDS-UPDRS II ("best" conditions)
- MDS-UPDRS II ("worst" conditions)
- MDS-UPDRS III (On stim/On med) – trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of prior 30-day period on the assigned mode in Period B)
- DBS Global Impression of Change score (DBS GIC)
- Patient preference questionnaire: Perform the Patient preference questionnaire of the modes assigned to period A and period B before unblinding subjects
- Patient satisfaction questionnaire: Perform the Patient satisfaction questionnaire on aDBS after unblinding subjects
- Upload data collected from Apple Watch/iPhone, including movement and sleep data *,**
- Event markers (optional)*
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*: Confirm if it has been done

** : In principle, the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute.

Following the end of Post period B visit, the PI/ Sub investigator breaks the blinding of a subject. For the next follow-up visit, the PI/ Sub investigator should program the subject to preferred DBS mode (aDBS or cDBS), taking into account the study subject's medical condition.

If the preferred mode is cDBS, the subject will be exited from the study following the process in section 9.15. No further study-related procedures will be completed, and subjects will be followed according to the site's standard procedures.

9.9 Follow-up Phase

Once subjects complete the aDBS treatment Phase, they enter a Follow-up Phase.

9.9.1. Visit4

45-60 (± 7) days after Post Period B /Visit3

The subject will arrive for the visit on subject's preferred aDBS mode.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- PDQ-39 (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- EQ-5D-5L
- MDS-UPDRS II ("best" conditions)
- MDS-UPDRS II ("worst" conditions)
- MDS-UPDRS III (On stim)/On med) - trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- Upload data collected from Apple Watch, including movement and sleep data*
- Event markers (optional)*
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*: Confirm if it has been done

For the next follow-up visit, the PI/ Sub investigator should program the subject to preferred DBS mode (aDBS or cDBS), taking into account the study subject's medical condition.

If the preferred mode is cDBS, the subject will be exited from the study following the process in section 9.15. No further study-related procedures will be completed, and subjects will be followed according to the site's standard procedures.

9.9.2. Visit5

45-60 (± 7) days after visit4

The subjects will arrive for the visit on subject's preferred aDBS mode.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- PDQ-39 (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- EQ-5D-5L
- MDS-UPDRS II ("best" conditions)
- MDS-UPDRS II ("worst" conditions)
- MDS-UPDRS III (On stim/On med) - trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- Upload data collected from Apple Watch including movement and sleep data *
- Event markers (optional)*
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*: Confirm if it has been done

For the next follow-up visit, the PI/ Sub investigator should program the subjects to preferred DBS mode (aDBS or cDBS), taking into account the study subject's medical condition.

If the preferred mode is cDBS , the subject will be exited from the study following the process in section 9.15. No further study-related procedures will be completed, and subjects will be followed according to the site's standard procedures.

9.9.3. Visit6

45-60 (± 7) days after visit5

The subjects will arrive for the visit on subject's preferred aDBS mode.

The following data will be collected:

- Concomitant medications (non-PD)
- PD medications
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- PDQ-39 (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- EQ-5D-5L
- MDS-UPDRSII ("best" and "worst" conditions)
- MDS-UPDRS III (On stim/On med) - trained rater
- MDS-UPDRS IV – trained rater
- UDysRS (subject's assessment of prior 30-day period on subject's preferred aDBS mode)
- Patient satisfaction questionnaire
- Upload data collected from Apple Watch including movement and sleep data.*
- Event markers (optional)*
- AE and device deficiency assessment (As they occur)
- Protocol Deviations (As they occur)

*: Confirm if it has been done

At the completion of this visit, they will be exited from the study following the process in section 9.15.

9.10 Unscheduled Visits

Any time the subject is seen for DBS programming adjustment or for an Adverse Event, the following data will be collected:

- Reason for the visit
- Concomitant medications (non-PD)
- PD medication: if applicable, PD medication and dose given at visit. Time of last dose of PD medications taken prior to the visit
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report
- Upload data collected from Apple Watch, including movement and sleep data*
- Event markers (optional) *
- Adverse Event and device deficiency assessment (As they occur)

*: Confirm if it has been done

9.11 System Modification

System modifications made to the DBS System will be completed according to the site's standard procedures. If the system modification occurs, the subject should be exited as needed, prior to receiving the system modification and considered for re-enrollment if possible. . Any visits for DBS setup due to a system modification will be recorded as unscheduled visits. If DBS cannot be acceptably set up, the subject will be exited from the study following the process in section 9.15.

Data collection:

- Device information (if applicable)
- Concomitant medications (non-PD)
- PD medication at visit: if applicable, PD medication and dose given at visit. Time of last dose of PD medications taken prior to the visit
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report

- Adverse Event and Device deficiency assessment (As they occur)

9.12 Assessment of Safety

AE information is collected in this study. See Section 11 for further information on the collection of AEs and safety information.

9.13 Recording Data

The PI/ Sub investigator must ensure accuracy, completeness and timeliness of the data reported in the case report forms (CRFs) and in all other required reports. Source documentation is defined as the first-time data appear, and may include original documents, data, and records.

Subject questionnaires (e.g. DQ-39, EQ-5D-5L, MDS-UPDRS II ("best" and "worst" conditions), patient preference, patient satisfaction), physician assessments (e.g. GIC, MDS-UPDRS III and IV, UDysRS) and medication diary (When PD medication cycle data collected from an iPhone is missing, and the data recorded in a medication diary is used as the data) may be collected on paper forms, the paper forms of the questionnaires and/ or the medication diary will be retained at the site as the original source documentation.

Data reported on the CRFs, which are derived from the source documents, must be consistent with the source documents and discrepancies need to be justified with documented rationale, and approved by the PI or delegate. The PI/ Sub investigator must ensure the availability of source documents from which the information on the CRFs was derived. Where printouts of medical records are provided as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, and (2) the date the copy was made.

The source documents must be made available for monitoring or auditing.

See Section 14.3 for data management in this study.

Refer to the following appendices for the questionnaire. (EQ-5D-5L (Appendix A), PDQ-39 (Appendix B), UDysRS (Appendix C), MDS-UPDRS II, III, IV (Appendix D), DBS GIC (Appendix E), Patient preference questionnaire (Appendix F), Patient satisfaction questionnaire (Appendix G).

Refer to Appendix H for the case report form (Sample collection item list).

9.14 Deviation Handling

A study deviation is defined as an event within a study that was not conducted according to the clinical investigation plan, CTA, EC policies or applicable standards, laws and regulations.

The PI/ Sub investigator may not deviate from the CIP unless the deviation is necessary in an emergency

situation to protect the rights, safety and wellbeing of the subject. Or due to an unforeseen circumstance that is beyond the PI/ Sub investigator's control (e.g., subject failure to attend a scheduled follow up visit, inadvertent errors, equipment failure). All deviations must be documented on CRF whether an inadvertent occurrence or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one CRF.

Refer to section 14.9.1 for deviation reporting requirements .

Deviations include, but are not limited to, the following:

- Failure to obtain subject's informed consent prior to beginning study activities
- Subject does not meet inclusion/exclusion criteria, but continues with the scheduled visits and aDBS setup.
- Failure to report AEs or Device Deficiencies
- Failure to collect CIP-required assessments
- Subject missed visit or visit outside of window

Deviations will be reviewed by the PI on an ongoing basis. The PI will assess the significance of all deviations for the study and evaluate the need for any corrective and/or preventative actions (e.g. amend the CIP, conduct additional training, terminate the study).

9.15 Subject Exit, Withdrawal or Discontinuation

Subjects will discontinue the study following completion of all study visits.

If a subject discontinues from the study prior to normal completion, the CRFs for visits that have occurred up to the point of withdrawal as well as the study exit CRF must be completed.

9.15.1. Study Exit

A study exit CRF is required for all subjects. Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject death
- Subject's DBS Therapy System permanently explanted (i.e., neurostimulator, lead, extension)

- Subject did not meet inclusion/exclusion criteria
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- PI/ Sub investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

The PI/ Sub investigator will attempt to collect the following information prior to the subject's early discontinuation from the study:

- Adverse event and device deficiency assessment
- Programming session report, with device interrogation and BrainSense data included in the JSON session data report upload
- A brief description of why the subject discontinued (if applicable)

9.15.2. Study Completed

At the completion of Follow-up Phase Visit6, subjects will be exited from the study. Both the CRFs for Follow-up Phase Visit6 and a Study Exit CRF need to be completed. Suggested language:

9.15.3. Lost to Follow-up

A subject is considered to be lost to follow-up if at least two attempts to contact the subject are unsuccessful. The method of attempt (e.g., two letters, two phone record or two emails) must be documented in the subject's medical record.

9.15.4. Study Exit Criteria in Individual Subject

9.15.4.1 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject revokes consent, the study site is required to document the reason for exit on the Exit CRF.

If possible, the following data should be collected prior to subject withdrawal:

- Adverse event and device deficiency assessment
- Final device interrogation and data upload
- Export JSON Session Data
- A brief description of why the subject discontinued (if applicable)

9.15.4.2 Investigator Withdraws Subject

- After enrollment if the subject doesn't meet the inclusion or exclusion criteria
- When the PI/ Sub-investigator decides to discontinue or the subject wishes to discontinue due to the adverse event
- When it becomes difficult to continue the study due to worsening of the underlying disease
- When the subject has difficulties in continuous visits due to moving, changing hospitals, busy schedules, etc
- If the subject becomes pregnant or is suspected of becoming pregnant
- When the PI/ Sub-investigator determines the necessity of discontinuing from the study

It is recommended that PI/ Sub investigators discuss any withdrawals with the study team prior to withdrawing subjects.

If a withdrawal by the PI/ Sub investigator is necessary, the following data should be collected prior to subject withdrawal if possible:

- Adverse event and device deficiency assessment
- Final device interrogation and data upload
- Export JSON Session Data
- A brief description of why the subject discontinued (if applicable)

10. Risks and Benefits

10.1 Potential Risks

10.1.1. Potential DBS risks

Deep Brain Stimulation Therapy is a reversible procedure (i.e., the stimulation can be turned off or the device can be removed most cases) that is able to adjust the stimulation to minimize or reverse complications and maximize therapeutic effects.

The risks, precautions, warnings, cautions, and contraindications associated with the Medtronic DBS Therapy and each system component are included in the package inserts.

10.1.2. Pregnancy

The safety of neurostimulation systems is unknown for pregnancy, unborn fetus, or delivery. Because the risks to the subject and/or unborn child while receiving neurostimulation are unknown, female subjects of childbearing potential must confirm a non-pregnant at screening visit and agree to use a medically acceptable method of birth control if female of childbearing potential, and if sexually active. Should a pregnancy occur during the study, the subjects are instructed to notify their PI/ Sub investigator immediately and the PI/ Sub investigator will notify Medtronic in a timely manner. Careful considerations of the risks and benefits of continuation in the study will be weighed by the subject and their PI/ Sub investigator.

10.1.3. Potential aDBS risks

The primary function of the aDBS is to adjust stimulation amplitude within clinician-defined stimulation limits. The risks of adaptive DBS are no different than the risks of commercially available cDBS risks, which are not increased due to participation in the study.

10.1.4. Potential Study Procedures Risks

Randomization, single-blind and crossover will be conducted in the study. Potential risks related to study procedures include:

- The safety of DBS is unknown for pregnancy, unborn fetus, or delivery. If a subject is or a subject becomes pregnant, there may be risks to the subject or the subject's unborn child that are not yet known.
- As a result of the mode change (aDBS and cDBS) subjects may experience differences in therapeutic effects and changes in condition between aDBS and cDBS
- Subjects may experience skin irritation from the Apple watch. Should irritation occur, the subject should remove the watch
- There may be risks or side effects which are unknown at this time.

10.1.5. Potential Study Procedure Inconveniences

Potential study procedure inconveniences include:

- The patient's assessments, such as QOL questionnaire, subjects are required to complete for the study may be burdensome.
- The patient's assessments that are required for the study may request information of a personal

nature

- The patients feel a burden on the operation of Apple Watch / iPhone required in this study.

10.2 Risk Minimization

The PI provides study personnel with CIP training to minimize the potential risks associated with this study.

The PI/ Sub investigator will carefully observe the subjects and be actively involved in the follow-up of the subjects.

When aDBS causes an uncomfortable stimulus to the subject, the subject can switch from aDBS to cDBS as needed.

10.3 Potential Benefits

All of the medical devices used in this study are approved for indication and covered by insurance for the subjects of this study, and the treatment methods of any group are treatment methods that can be performed as everyday insurance medical treatment. In addition, since all medical expenses including drug costs during the study period of the subject are paid by the patient's insurance and the patient's own expense, the special medical and economic aspects obtained by the subject participating in the study that there is no benefit. The information obtained from this clinical study may be useful to other patients in the future.

10.4 Risk-Benefit Rationale

The benefit of the study lies in the knowledge to be gained from the results and the potential to improve future DBS therapies. Deep Brain Stimulation Therapy including adaptive therapy for PD with Percept PC system has obtained regulatory approval and is covered by insurance, and both treatment methods can be performed as daily insurance medical treatment. There is no direct benefit expected to arise from a subject's participation in this study, but there may be risks from the study procedure. Measures have been taken to minimize the risks and all the potential risks in this study have been controlled to a level as far as possible.

11. Adverse Event and Device Deficiencies

11.1 Adverse Events

All DBS System Components which are used for this study are approved with demonstrated evidence of safety and effectiveness for their intended use. Therefore, the following AEs will be collected for safety analyses in this study:

- Stimulation-related adverse events
- Serious adverse events for which the relationship with Percept PC cannot be ruled out
- Any-cause death
- An Unanticipated Serious Adverse Event (USAE) in which the relationship with the use of the study device cannot be ruled out completely.

AE definitions are provided in Table 2. All reportable AE information for this study will be collected throughout the study duration, starting at the time of signing the IC.

11.2 Device Deficiency

The following Device Deficiency (DD) will be collected for safety analyses in this study

- Device (Percept PC) deficiencies that potentially could have led to a serious adverse event

DDs that did not lead to a serious adverse event but could have led to a serious adverse device effect include the following

- if either suitable action had not been taken
- if intervention had not been made
- if circumstances had been less fortunate

The DD definition is provided in Table 2. Reportable DD information will be collected throughout the study after signing the IC and reported to Medtronic on the DD eCRF. Note that DD that result in an AE to the subject should be captured as an AE only.

11.3 Correspondence to subjects

In the event of AE, the PI/ Sub investigator will take appropriate measures, such as treatment and discontinuation of use of the device, as necessary to ensure the safety of the subjects. If treatment is required, inform the subjects to that effect.

11.4 Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD CRF. All AEs must be followed until the AE has been resolved, is confirmed no further actions planned if unresolved, the subject dies or exits the study, or until study closure, whichever occurs first.

At the time of study exit, all collected AEs that are unresolved must be reviewed and an update to the original AE must be reported.

11.5 Definitions/Classifications

This study will be conducted following Japan Ethical guidelines for human life science and medical research and will collect the Adverse Events and Device Deficiencies specified in this protocol from the time of consent through study exit/discontinuation.

AEs and DDs which are collected in this study will be classified by Medtronic and/or the PI/ Sub investigator according to the standard definitions as outlined below.

Table 2: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	An unfavorable and unintended injury and illness or sign of such (including an abnormal laboratory finding) caused to research subjects, regardless of whether there is or is not any causal relation with the research implemented. (Ethical guidelines for human life science and medical research, Chapter 1, Part 2, (32)) (ISO 14155:2020 section 3.2 is equivalent to this AE definition)
Device Deficiency (DD)	Any influences of an undesirable condition for a medical device such as breakage and malfunction, etc. Which stage among design, manufacturing, marketing, distribution, and use caused the device deficiency is irrelevant. (Ministerial Notification on Reporting of Side Effect, etc. of Pharmaceutical Product, etc. dated October 2, 2014)

	(ISO 14155:2020 section 3.19 is equivalent to this DD definition)
Relatedness	
Relationship of Adverse Events	<p>The relationship of an adverse event will be classified as device-related, therapy/stimulation-related, procedure-related, related to the disease under study, and/or related to an underlying condition other than the disease under study based on the following definitions:</p> <ul style="list-style-type: none"> • Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the DBS system or any of the DBS system components • Procedure Related: An adverse event that occurs due to any procedure related to the surgical modification, or explant of the DBS system or any of the DBS system components. • Therapy/Stimulation Related: An adverse event related to therapy delivery by the DBS system (i.e. stimulation). Normally therapy related events resolve when the device is turned off or reprogrammed. • Related to the disease under study: An adverse event that is caused by Parkinson's disease • Related to an underlying condition other than the disease under study: An adverse event caused by a condition other than Parkinson's disease <p>Each of the relatedness classifications will be assessed for causality using four different levels of causality based on the following definitions:</p> <ul style="list-style-type: none"> • Not Related: relationship to the device or procedures can be excluded when: <ul style="list-style-type: none"> ▪ the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ the event has no temporal relationship with the use of the study device or the procedures; ▪ the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; ▪ the event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ the serious event can be attributed to another cause (e.g. an

	<p>underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);</p> <ul style="list-style-type: none">▪ the event does not depend on a false result given by the study device used for diagnosis, when applicable;▪ harms to the subject are not clearly due to use error;▪ in order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event <ul style="list-style-type: none">• Possible: the relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.• Probable: the relationship with the use of the study device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained• Causal relationship: the event is associated with the study device or with procedures beyond reasonable doubt when:<ul style="list-style-type: none">▪ the event is a known side effect of the product category the device belongs to or of similar devices and procedures;▪ the event has a temporal relationship with study device use/application or procedures;▪ the event involves a body-site or organ that<ul style="list-style-type: none">○ the study device or procedures are applied to;○ the study device or procedures have an effect on;○ the serious event follows a known response pattern to the medical device (if the response pattern is previously known);▪ the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);▪ other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;▪ harm to the subject is due to error in use;▪ the event depends on a false result given by the study device used for diagnosis, when applicable;▪ in order to establish the relatedness, not all the criteria listed above
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	<p>might be met at the same time, depending on the type of device/ procedures and the serious event.</p> <p>Events are considered “related” to the study medical device if their relationship to the device, procedure, or therapy is classified as “possible”, “probable”, or “causal”.</p>
Seriousness	
Serious Adverse Event (SAE)	<p>Of the above-defined AE, an event that:</p> <ol style="list-style-type: none"> 1) Results in death 2) Is life-threatening 3) Requires inpatient hospitalization or prolongation of existing hospitalization 4) Results in persistent or significant disability or incapacity, or 5) Is a congenital anomaly/birth defect to offspring. <p>(Ethical guidelines for human life science and medical research, Chapter 1, Part 2, (33)) (ISO 14155:2020, 3.45 is equivalent to this SAE definition)</p>
Unanticipated* Serious Adverse Event (USAE)	<p>Of the above-defined SAE, an event not consistent with the information in the research protocol, the document used for obtaining informed consent, or not consistent with the severity described in such, even if there is any description about the event.</p> <p>(Ethical guidelines for human life science and medical research, Chapter 1, Part 2, (34))</p>
Device Deficiency with SADE potential	<p>DDs that did not lead to a serious adverse event but could have led to a serious adverse device effect include the following</p> <ul style="list-style-type: none"> • if either suitable action had not been taken • if intervention had not been made, or • If circumstances had been less fortunate

* Anticipated AE/DD: Refer to the description regarding AE/DD in the package insert.

The following are not considered an AE for the study.

- Pregnancy
- Documented pre-existing conditions / planned treatment at the time of enrollment; unless the intensity, duration, or frequency of the condition is worsened from the time of enrollment
- Planned examination at the time of enrollment

- Programming adjustment or therapy suspension (could be an action taken as a result of an AE)
- Transient (acute) stimulation-induced effects that occur during programming sessions or while running aDBS that resolve with or without programming adjustments prior to the subject leaving a study follow-up visit and do not require further follow-up or medical care outside of the visit
- Neurostimulator replacement for battery depletion as disclosed in the product labeling (documented as a system modification)
- Worsening patient-questionnaire reported outcome scores (e.g. EQ-5D-5L, PDQ-39)
- Expected side-effects of Parkinson's disease medication

11.6 Reporting of Adverse Events and Device Deficiencies

In the event of SAE, the PI will take the necessary actions and report it to the EC and the head of the institution. Additionally, the PI will inform the other PIs. For those reporting processes, Standard Operating Procedures will be followed.

All reportable AEs and device deficiencies, which will be collected in this study per Section 11.1 and 11.2, will be recorded in the subject's medical record, the study CRF, and promptly reported to Medtronic or its designee. PI/ Sub investigators are required to keep records on all relevant observations.

Reportable adverse events and device deficiencies will include the following information, at a minimum:

- Date of event
- Diagnosis and description of the event
- Assessment of the seriousness and relationship to the product(s) under investigation, therapy, and procedure, the disease under study and an underlying condition other than the disease under study (AE only)
- Model and identifier (serial, lot number) for the involved device (if applicable)
- Treatment (AE only)
- Outcome and date of resolution (AE only)

It is the responsibility of the PI or designated Sub investigator, to identify the occurrence of reportable AEs and DDs and to ensure the required information is accurately documented on the CRF.

11.6.1. Adverse Event and Device Deficiency Classification

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. It is the responsibility of PI by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

AEs will be classified according to the Table 3:

Table 3: Event Classification Responsibilities

What is Classified	Who Classifies	Classifications
Relatedness*	PI/ Sub investigator Medtronic	Relationship to the: <ul style="list-style-type: none">• Procedure• Device• Therapy/Stimulation• Disease under study• An underlying condition other than the disease under study
Seriousness	PI/ Sub investigator	<ul style="list-style-type: none">• SAE• DD with SADE potential
	Medtronic	<ul style="list-style-type: none">• SAE• USAE• DD with SADE potential
Diagnosis	PI/ Sub investigator	Based on presenting signs and symptoms and other supporting data
	Medtronic	MedDRA term assigned based on the data provided by PI/ Sub investigator

*Adverse events that are classified as having a relationship of possible, probable or causal to the device, procedure or therapy/stimulation are considered to be related to the study device

11.7 Subject Death

The PI/ Sub investigator must notify Medtronic and the governing EC without unjustified delay after learning of a subject's death, regardless of whether the death is related to the device system or therapy. The PI/ Sub investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device, procedure or therapy.

Any subject death will be reported on the Adverse Event and Study Exit CRF accordingly. For the Adverse Event eCRF, the death should not be reported as a diagnosis of the event, rather as an outcome of the event which led to death.

If an autopsy is conducted, a copy of the de-identified report will be provided to Medtronic. Medtronic

requests that all device system components that were being used at the time of the death be returned to Medtronic for analysis.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death if a death certificate or summary report are unavailable. The PI/ Sub investigator creates summary of the death. Additionally, device disposition information should be updated, if available.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and procedure
- Device interrogation information/reports (if available)
- Device disposition information (if available)
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

11.8 Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and DDs and AEs related to any market released device during the study must be reported. The reporting of product complaints except for all reportable AE information for this study is not part of the study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the PI/ Sub investigator to report all product complaint(s) associated with a

medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. Medtronic will notify the Ras (e.g. CA) as applicable in accordance with the requirements upon learning of them and is not limited to AEs and DDs only.

12. Statistical Design and Methods

The study participants will be randomized to either sequence: the first treatment is aDBS and then cDBS, or the first treatment is cDBS then aDBS. According to the randomized sequence, the first treatment DBS mode is started in Period A and second DBS mode is started in Period B. Supporting analyses for the primary objective include verifying the lack of a period or carryover effect in randomized subjects.

The Early Adapter Part II study will be considered successful when the primary objective of the study is met. The main analysis of primary and secondary objectives will use the Complete Case set (CC) which include all subjects who initiate the aDBS treatment phase and have complete data for the respective analysis. The main analysis will include data from all sites. An assessment for poolability of the results across clinical sites will be conducted by descriptive analyses for individual sites for the primary and key secondary endpoint. Subject disposition will be reported in a CONSORT diagram to show the flow of participants through stages of the study.

12.1 General Aspects of Analysis

Data analysis will be performed by Medtronic-employed statisticians or designees. All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or any validated statistical software.

In the primary analysis report, continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For events that can occur more than once in a single subject, such as adverse events, the percentage will be based on subjects experiencing the event; both subject and event counts will be reported. P-values will be two-sided, with values less than 0.05 indicating statistical significance.

Since the impact of missing data is expected to be small no multiple imputation method for missing data is planned.

The Gatekeeping procedures will be applied for the multiple testing procedures. After the primary study objective is met ($\alpha=0.05$, two-sided gatekeeper), the secondary study objective will be carried out at $\alpha=0.05$ two-sided. No multiplicity adjustment will be performed for evaluations of the additional study objectives. No imputation will be used.

The analyses will use two population sets:

- The Complete Case set (CC) analysis includes all patients enrolled in the study those sign Patient Informed Consent, fulfill the inclusion and exclusion criteria and randomized who initiate the aDBS treatment phase and have complete data for the respective analysis. The CC set will be used for primary and secondary objectives.
- The As-Treated Set (AT) includes subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) at enrollment and/or the aDBS treatment phase and uses the observed treatment used for each subject in each phase. This set will be used for safety assessment.

12.2 Analysis Execution

Formal analysis for the Early Adapter II trial will occur when all active subjects have completed the aDBS treatment Phase of the study. Analysis will include both the primary and secondary objectives. Additional objectives will be addressed based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the study or have been exited. The inferential analysis for the primary and secondary objectives will not be updated for the final report.

Additional details of the analyses outlined in this section and additional exploratory analyses will be described in detail in the statistical analysis plan prior to the data freeze for the primary analysis report. All results will be reported in the final study report. Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan that will include the statistical rationale for divergence. If there are any changes from the original statistical analysis plan, revise the CIP or statistical analysis plan and describe the changes and their analysis results in the final study report.

12.3 Interim Analysis

No interim analyses are planned for this study.

12.4 Primary Objective

The primary objective is to demonstrate decreased Total Electrical Energy Delivered (TEED) during adaptive (aDBS) as compared to continuous DBS (cDBS). For this endpoint the CC cohort will be used.

The endpoint is the energy use as measured by TEED during the aDBS as compared with TEED during the cDBS during the aDBS treatment phase (from period A to period B). Denote the TEED on aDBS by $TEED_{aDBS}$ and the corresponding value for cDBS by $TEED_{cDBS}$. For each patient the difference between $TEED_{aDBS}$ and $TEED_{cDBS}$ will be calculated ($TEED_{aDBS} - TEED_{cDBS} = TEED_{DIFF}$). The hypothesis that $TEED_{DIFF} \neq 0$

will be tested by means of the Student's paired t-test and a p-value less than, or equal to, 0.025 will be regarded statistically significant. The formal hypothesis testing is:

$$H_0: \mu_{\text{TEEDaDBS}} - \mu_{\text{TEEDcDBS}} = 0$$

$$H_a: \mu_{\text{TEEDaDBS}} - \mu_{\text{TEEDcDBS}} \neq 0$$

Where the difference ($\mu_{\text{TEEDaDBS}} - \mu_{\text{TEEDcDBS}}$) is the electrical energy saving.

TEED is defined as the total energy delivered by an electrical system through the DBS leads over an arbitrary period of time. TEED is determined by the stimulation parameters (e.g., pulse width, frequency, amplitude) and the measured impedance.

The calculation of TEED when using constant voltage is:

$$\text{TEED} = (\text{Voltage}^2 * \text{Frequency} * \text{Pulse width}) / \text{Impedance}$$

The calculation of TEED when using constant current is:

$$\text{TEED} = \text{Current}^2 * \text{Frequency} * \text{Pulse width} * \text{Impedance}$$

The previous formulas can be used without modification with legacy lead.

When the lead is a directional lead with separate electrodes and it is programmed in Directional Stim Mode or Ring Mode Stimulation, each contact is considered independent. For each segment that is activated, TEED will be calculated individually using the formulas above, and then summed to obtain the total TEED for the lead. Leads programmed with monopolar settings will use the electrode unipolar impedance between the case and the active electrode. If 2 cathodes are used (dual monopolar settings), TEED will be calculated for each contact separately, and total TEED will be determined for the lead as the sum of the two TEED. Leads programmed to bipolar will use the impedance between the active electrodes.

Directional Stim Mode may be programmed during the follow-up phase. The primary endpoint on the difference in TEED will be assessed by means paired t-test to compare the difference in TEED for aDBS (preferred mode, single or dual threshold) to cDBS. Normality of the outcome will be assessed with the Shapiro-Wilk test. If large violations to the normality assumption are observed ($p < 0.05$), the primary analysis will use a Wilcoxon signed-rank test to assess statistical significance.

To compute TEED using the formula above, the average current drain from the JSON session data will be computed using the average stimulation currents from the timeline feature in the 14 days prior to the visit. This will be computed as the average of the currents from the timeline feature using the epochs that align with the analysis set (e.g., As-Treated analysis set uses the actual aDBS mode as reported from the device). The pulse-width, frequency, and impedance will be determined from the JSON session data as per study procedure.

12.4.1. Supporting analyses

The analysis approach makes two main assumptions: no period effect and no carryover effect (including their interaction). These assumptions will be tested first. If the period and carryover effects is not significant (i.e. the p-value is greater than or equal to 0.10), then the data from the two periods can be combined and analyzed. Otherwise, the data only from period A can be used to estimate the treatment effect. Details on supporting analyses will be reported in the statistical analysis plan.

12.5 Secondary Objective

The following secondary objective has specific hypothesis to be tested. This key secondary objective will be tested under a Gatekeeping strategy for the multiple testing procedures. After the primary study objective is met (gatekeeper), this secondary study objective will be carried out at $\alpha=0.05$ and a p-value less than 0.05 two-sided will be considered met as long as the primary objectives above it have also been met.

12.5.1. Secondary Objective #1

The secondary objective is to demonstrate maintenance within an optimal beta LFP threshold of beta LFP power during aDBS mode compared to cDBS.

The formal hypothesis testing is:

$$H_0: \mu_{\text{LFPaDBS}} = \mu_{\text{LFPcDBS}}$$

$$H_a: \mu_{\text{LFPaDBS}} \neq \mu_{\text{LFPcDBS}}$$

The secondary endpoint is the mean percent time within an optimal beta LFP threshold of beta LFP power during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower LFP threshold preset for each patient.

The secondary endpoint will be assessed based on data collected from the Percept device using Brain Sense Timeline View function and will be analyzed using a Paired T-test or nonparametric Wilcoxon Rank-Sum Test according the LFP normal or non normal distribution between percent of time in the window for the preferred aDBS mode vs cDBS.

12.6 Safety Assessment

To assess safety in following items:

- Stimulation-related adverse events during the aDBS treatment phase.

- Serious adverse events which occur through the study after consent and for which the relationship with Percept PC cannot be ruled out.
- Any-cause death throughout the study.
- Device (Percept PC) deficiencies that potentially involve a serious adverse event throughout the study: for all subjects

Stimulation-related adverse events will be summarized during the aDBS treatment phase for all subjects, with listings individualized by aDBS mode and cDBS.

Serious adverse events, adverse events, and device deficiencies that occur from the consent through study exit/discontinuation will be summarized for all enrolled subjects. The denominator will include the appropriate number of subjects for each respective phase and period. Events will be summarized by number of events, number of subjects who experienced the event, and percentage of subjects who experienced the event.

12.7 Additional Objective(s)

The additional objectives will be summarized by descriptive statistics and reported separately for aDBS and cDBS and by aDBS (preferred mode, single or dual threshold). No multiplicity adjustment will be performed for evaluations of the additional study objectives and no imputation of missing data will be used. The Complete Case analysis set will be used for the additional objectives.

12.7.1. Additional Objective #1

To characterize EQ-5D-5L by aDBS and cDBS, and by aDBS preferred mode. The EQ-5D will assess generic health status by five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the visual analogue scale (VAS). This endpoint will be described by summary statistics. The EQ-5D dimensions will be summarized as categorical measures using frequency counts and percentages and the index value and visual analog scale (VAS) will be summarized as continuous measures and summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. The above summary statistics will be reported by aDBS and cDBS and within the aDBS by preferred mode single and dual threshold.

12.7.2. Additional Objective #2

To characterize Parkinson's Disease Questionnaire (PDQ)-39 Summary Index (SI) and subscores (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort) by aDBS and cDBS, and by aDBS preferred mode. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive

statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be reported by aDBS and cDBS and by preferred mode single and dual threshold.

12.7.3. Additional Objective #3

To characterize Unified Dyskinesia Rating Scale (UDysRS) by aDBS and cDBS, and by aDBS preferred mode. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be reported by aDBS and cDBS and by preferred mode single and dual threshold.

12.7.4. Additional Objective #4

To characterize Movement Disorder Society-Sponsored Revision of Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II, III and IV. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be reported by aDBS and cDBS and by preferred mode single and dual threshold.

12.7.5. Additional Objective #5

To characterize LFP dynamics based on out of clinic patient event markers and PD Medication cycle. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be reported by aDBS and cDBS and by preferred mode single and dual threshold.

12.7.6. Additional Objective #6

To characterize movement and sleep data collected from Apple Watch. Metrics recorded are: Accelerometer data, Gyro data, MDKit symptoms (dyskinesia, tremor, tremor by severity), Heart rate and additional measurements. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be reported by aDBS and cDBS and by preferred mode single and dual threshold. Apple Watch data will be correlated with Percept Device data and clinical measures as deemed appropriate by Rune Labs, Inc.

12.7.7. Additional Objective #7

To assess a patient-specific anatomy using a visualization tool of lead location and simulated volume of neural activation based on Pre-op/post-op imaging data of Percept PC implant. This endpoint will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages.

12.7.8. Additional Objective #8 and #9

To assess the Patient preference of aDBS (preferred mode) vs cDBS and the Patient satisfaction with aDBS (preferred mode) will be assessed by Medtronic-developed questionnaires. Both will be described by summary statistics. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages.

12.8 Target Sample Size and Justification

Target sample size: 20-30 subjects

[Rationale for the sample size]

Based on the registry data and the bench testing, a conservative estimate based on the first quartile of TEED data for initial devices in the registry, TEED is expected to decrease between 35 and 22 units for aDBS single threshold mode and aDBS dual threshold mode, respectively^{56,57}. Due to the expected 5% of single threshold with bilateral aDBS with an expected TEED difference of 35 units, 25% of subjects in single threshold but with unilateral aDBS with an expected TEED difference of 18 units and 70% in dual threshold with an expected TEED difference of 22 units, we assume a difference of 22 units defined as the weighted average of those differences. A SD of 28 results in a medium to large effect size of 0.79⁵⁸. Based on these assumptions, the sample size was estimated using a two-sided (alpha=0.05) paired T-Test means (PASS 2019) to compare the difference in aDBS TEED to cDBS TEED of 22 and a standard deviation of 28, a minimum of 20 subjects achieves at least 90% power for the detection of an effect size of 0.79.

it is estimated that between 20-30 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled to obtain a study population of 20 subjects who complete the aDBS treatment phase. .

12.9 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Single-blind of subjects during the aDBS treatment Phase
- Randomized crossover to evaluate the aDBS vs cDBS

It is possible that some subjects with the new directional lead (e.g., SenSight) could be enrolled to this study. The directional lead could slightly reduce the TEED and have longer β -LFP within the optimal beta LFP threshold. In order to minimize this potential bias for those with the directional lead, physicians will set the output of each separate electrodes uniformly using it as a ring-shaped electrode (section 9.8). This mode is comparable to the legacy lead. Furthermore, since the impact of the directional lead is equal for both modes aDBS and cDBS and considering that all subjects will undergo both modes there should not be bias on the estimation of the difference between the two modes. This limited source of bias could slightly impact the absolute estimates only but it is unlikely to create invalid data and are acceptable for the purposes of the study in measuring the difference between aDBS and cDBS mode. In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

13. Ethics

13.1 Statement(s) of Compliance

This study will be conducted in compliance with this clinical investigation plan (CIP), the ethical principles that originate from the Declaration of Helsinki (2013), Ethical guidelines for human life science and medical research(March 23, 2021), Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and applicable local regulatory / EC requirements and laws in Japan as appropriate.

The study will be publicly registered in jRCT prior to the first enrollment.

13.2 Fund and Conflicts of Interest

The PIs/ Sub investigators in this study belong to the endowed chair established by the donation from Medtronic Japan Co., Ltd. In addition, this study will be conducted based on collaboration with Medtronic Japan Co., Ltd., and will be funded by Medtronic Japan Co., Ltd. In addition, Apple Watch, iPhone and Wi-Fi router used in the study will be lent by Medtronic Japan Co., Ltd. Study personnel belonging to Medtronic are employees of Medtronic. However, the following will be implemented to ensure transparency so that the study results will not be distorted in favor of the sponsor. Therefore, the study results will not be distorted in favor of Medtronic Japan Co., Ltd.

- The PI/ Sub investigator in this study shall submit requirements to Juntendo University Hospital conflicts of interest management committee in accordance with "Juntendo University Hospital Medical Research Conflict Management Regulations" and "Standard Operating Procedures for conflicts of interest Related to Human Medical Research". These requirements shall be reviewed by the committee. In addition, the results of the review shall be disclosed to the subjects on the informed consent and take actions so as not to damage transparency and reliability of the study.
- When conducting the study, CTA will be executed in advance and the study will be conducted.

Investigators can publish the study results, but when the study results are published, the status of conflicts of interest of the investigators and the role of the study funding source will be disclosed to ensure transparency.

- It is stated in the CIP and ICF that Medtronic Japan Co., Ltd. will be funded for this study and Apple Watch, iPhone and Wi-Fi router will be lent by Medtronic Japan Co., Ltd
- It is stated in the CIP and ICF that the PIs/ Sub investigators in this study belong to the endowed chair established by the donation from Medtronic Japan Co.
- Medtronic study personnel who carry out monitoring, statistical analysis, data management, and audits are regularly educated about “The Fair Competition Code of the Medical Devices Industry in Japan” and Medtronic business operation rules (conflicts of interest, etc.). Medtronic manages conflicts of interest and disclose information, and conduct the study complying with laws and regulations.
- Statistical analysis and data management will be carried out by independent departments based on Medtronic's standard work procedure manuals.
- Monitoring will be adequately implemented in accordance with monitoring procedures under the supervision of the PI.
- At Medtronic Japan Co., Ltd., internal audits will be conducted according to audit procedures of Medtronic Japan Co., Ltd. and as detailed in section 14.2.

The Conflicts of interest declarers in this study is as per table 4.

Table 4: Listing of Conflicts of interest declarers

Study site	Department and Title	Study Role	Investigator
Juntendo University Hospital	Prof. Department of Neurology	Principal investigator	Nobutaka Hattori
Juntendo University Hospital	Associate Professor. Department of Neurology	Sub investigator	Genko Oyama
Juntendo University Hospital	Prof. Department of Research and Therapeutics for Movement Disorders	Sub investigator	Atsushi Umemura

Juntendo University Hospital	Associate Professor. Department of Research and Therapeutics for Movement Disorders	Sub investigator	Hirokazu Iwamuro
Juntendo University Nerima Hospital	Prof. Department of Neurology	Principal investigator	Yasushi Shimo
Juntendo University Nerima Hospital	Associate Professor. Department of Neurology	Sub investigator	Asuka Nakajima

14. Study Administration

14.1 Monitoring

Monitoring will be implemented in accordance with Medtronic Japan's monitoring procedures under the supervision of the PI.

Monitoring visits will be conducted to assess the PI's adherence to the CIP, regulatory compliance including EC approval and review of the study, maintenance of records and reports, review of source documents against subject CRFs, and the subject's adherence to the study. Findings from each monitoring visit will be provided to the PI at the site via a monitoring follow-up letter. Corrective action will be taken to resolve any issues of noncompliance. If the PI is not complying with the executed Investigator Agreement, the Clinical Investigation Plan, the applicable laws and regulations, or the requirements of the reviewing EC, prompt action will be taken to secure compliance.

Medtronic will conduct site monitoring visits to monitor compliance with the protocol, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

Contact information for the study monitoring is provided in Appendix I.

14.2 Audit

Since this study does not involve any invasiveness but involves intervention, audits are audit is not applicable. However, internal audits will be planned according to audit procedures of Medtronic Japan Co., Ltd to ensure quality control and objectivity in the study. The work of the audit will be conducted by a member of Medtronic's internal audit department, which is independent of the study's implementation unit and which specializes in auditing. This department is completely independent from

the department that conducts all clinical studies such as pre-market clinical trials, post-marketing surveillances, and clinical researches, and is in a third-party position. Audits of institutes will not be conducted unless ethical and scientific issues arise. When an audit is conducted at an institution, the person in charge of auditing at Medtronic Japan Co., Ltd. will report the result of the audit to the PI and the head of the institution. Contact information for the audit is provided in Appendix I.

14.3 Data Management

Data management will be provided by Medtronic. Medtronic personnel will perform routine edit and consistency checks for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data discrepancies; PI/ Sub investigators and site personnel will review data discrepancies and respond to the discrepancies in a timely manner. The resolved discrepancy will become a part of the CRF record for the subject.

The PI, or designated Sub investigator, is responsible for the accuracy, completeness and timeliness of the data submitted and must review all data for accuracy and provide his/her approval of the CRF and sign each form with an electronic signature. If an already signed CRF is required changes, the PI or authorized delegate Sub investigator will re-sign the CRF.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents.

The study will use the Oracle Clinical (OC) RDC system, Medtronic-owned database, which allows the study sites to enter study data over a secured internet connection. The system maintains an audit trail on entries, changes or corrections in CRFs. The PI will ensure that only appropriately delegated study personnel are given access to the RDC system; user IDs and passwords may not be shared.

The Oracle Clinical Remote Data Capture (RDC) system is a fully validated system and 21CFR§11 Part E compliant. The RDC system controls user access, ensures data integrity, and maintains an audit trail of entries, and changes, and corrections in the CRFs. User access will be granted to each individual based on his or her delegation of authority for the study and completion of the required training.

The Json files generated from the Percept PC including BrainSense data, will be uploaded to a secure Medtronic database. After that, it is also transferred to the database specified by Rune Labs, Inc.

Apple Watch/iPhone data will be uploaded directly to the database specified by Rune Labs, Inc. Rune Labs, Inc. will store the information collected by the Apple Watches in a database developed by Rune Labs, Inc. and perform analyses of the Apple Watch data using the STRIVE analysis platform. They will provide these data (analyses of movement (with tremor, bradykinesia, and dyskinesia scores) superimposed on the beta LFP measures and device data when collected) to Medtronic.

Pre-op/post-op Magnetic Resonance Image (MRI) images and Computed Tomography (CT) images after

implanting procedure of Percept PC will be uploaded to a secure Medtronic database. They are then sent to MR-X-Brain GmbH for storage in database.

[Contents that will be entered directly into the in CRF and should be considered as the source documents]

The randomization CRF is considered as source data.

14.4 Direct Access to Source Data/Documents

The PI and/or study personnel shall permit direct access to source data and documents during monitoring, audits and regulatory inspections.

14.5 Confidentiality

Subject confidentiality is assured through use of subject identification numbers, and the de-identifying of records.

Handling of personal data/ information

When handling specimens, etc. for the study, a subject identification number (ID) irrelevant to the personal information of the subject will be designated. A subject Identification log for individual subjects and their anonymized numbers should be created. The subject Identification log will be stored in a locked locker in the site, and be strictly managed by the personal information management. The subject Identification log is stored only at the study site, and Medtronic should not obtain it. When the site shall upload the collected data to the database of Medtronic or the database of Rune Labs, Inc., a subject ID will be used the data anonymized to give full consideration not to identify the individual subject. Only authorized persons can access these databases and RDC.

JSON Session data will be pseudonymized when exported from the clinician tablet programmer. The subject identification numbers will be used for the Apple Watch/iPhone data collection.

Information collected in this study will be provided to the study's funders, Medtronic Japan Co.,Ltd and Medtronic plc, an Irish corporation, and its affiliates. Study data may be made available to third parties, e.g., outsourced data analysis, or in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The data provided will be handled appropriately in compliance with the guidelines of the recipient. The identity of a subject will never be disclosed in the event that study data are published.

Future usage of subject data

Medtronic will store strictly the research-related data/information collected from the subjects after the

completion of this study, Medtronic may use this study data for regulatory authority submission and may publish the results in peer reviewed scientific journal(s) and present the data at an academic conference (s). Statistical analysis which is unplanned at this time may be performed with these data in the future. Pseudonymously processed information may also be used in newly planned study in the future.

14.6 Compensation Information

Compensation will not be applied because this study does not involve any invasiveness. The PI/ Sub investigator shall take suitable actions immediately when any AE is confirmed. The PI/ Sub investigator will provide appropriate medical care as usual for the health hazards that occur.

14.7 CIP Amendments

Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be revised according to the EC defined procedure. All amendments to the CIP shall be agreed upon between Medtronic and the PI. Approval by regulatory agencies and EC must be obtained prior to implementing a CIP revision at the study site.

14.8 Record Retention

The study involves the exchange of specimen and/or information with other study sites. The PI is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 5 years after the date the investigation is completed or terminated. The retention period may be longer if required by Medtronic or local or global regulatory requirements.

The PI will ensure that essential study documents are not destroyed until permission has been obtained from Medtronic. The PI should take measures to prevent accidental or premature destruction of documents. Medtronic will be notified prior to the transfer of study documentation.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

The study records should be retained according to Table 5. Also, if information etc. will be disposed after storage period, these will be disposed remaining de-identified not to leave it identifiable of specific individuals.

Table 5 Preparation and retention of the records regarding the provision of information

Record	Provider	Receiver
Name of study site (receiver): As described in Appendix I in CIP .	If defined in the CIP and the site's procedure, the reports relating to existing sample/data provision to the other study sites are archived for 3 years after the date of provision of information (alternatively, receiver could archive the documents).	Retain CIP at least 25 years
Name of PI of the study site (receiver): As described in Appendix I in CIP	If defined in the CIP and the site's procedure, the reports relating to existing sample/data provision to the other investigational centers are archived for 3 years after the date that study completion is announced (alternatively, receiver could archive the documents).	Retain CIP at least 25 years
Name of collaborative investigational site (provider): As described in Appendix I in CIP		Retain CIP at least 25 years
Name of PI of collaborative investigator site (provider): As described in Appendix D in CIP		Retain CIP at least 25 years
Information provided: As described in CRF	If defined in the CIP and the site's procedure, the reports relating to existing sample/data provision to the other investigational sites are archived for 3 years after the date of provision of information (alternatively, receiver could archive the documents).	Retain CIP at least 25 years
Procedure to receive information: gathered RDC		Retain CIP at least 25 years

Record	Provider	Receiver
, electronic media(CD-R/DVD-R), the Database specified by Medtronic and Database specified by Rune Labs, Inc.		
Name of subjects and delegated parties	ICFs are archived for 3 years after the date of provision of information	25-year retention of the information obtained in RDC in the condition that individuals are unspecifiable after the date that the study completion is announced
Information on consent obtainment from subjects and delegated parties	ICFs are archived for 3 years after the date of provision of information	25-year retention of the information including informed consent process obtained in RDC in the condition that individuals are unspecifiable after the date that the study completion is announced
Address of collaborative investigational site (provider):		Retain CIP at least 25 years
Name of head of the collaborative investigational site		Retain clinical agreements at least 25 years

14.8.1 Investigator Records

The PI and the study site is responsible for the preparation and retention of the records listed below.

The following records must be retained, if applicable. The records below, except case record and CRFs must be stored in the study site file.

The CRF must be stored electronically in an electronic data capture system and the PI or designated investigator shall electronically sign during the course of the study.

- Correspondence with an EC , the sponsor, a monitor or regulatory body (e.g., CA, Notified Body) including required reports
- Apple Watch, iPhone and Wi-Fi router receipt/use records (Accountability log/ Lending log)
- Records of each subject's case history and device information. Case histories include the CRFs and supporting data (source documentation), such as:

- o Signed by the subject, PI/ Sub investigator, and as required, authorized designee and dated IC
 - o All signed and dated case report forms submitted by PI/ Sub investigator
 - o Observations of AEs/DDs
 - o Collected paper forms of subject questionnaires (e.g. MDS-UPDRS II, ,PDQ-39, EQ-5D-5L, UDysRS, patient preference, patient satisfaction), physician assessments (e.g. DBS GIC, MDS-UPDRS III, IV, UDysRS)and medication diary (When PD medication cycle data collected from an iPhone is missing, and the data recorded in a medication diary is used as the data),
 - o Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurse's notes (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study)
- A subject Identification log for individual subjects and their anonymized numbers
 - Signed and dated CTA
 - Study members list of study site team
 - Documentation of delegated tasks
 - EC approval documentation.
 - All EC-approved versions of the CIP, IC
 - Signed financial disclosure forms for all PIs/ Sub investigators (if applicable)
 - Study personnel training records
 - Final Study Report including the statistical analysis

The Study Organization will be kept separately from the CIP. The sponsor will maintain updated the study organization according to the updated study members lists of study site teams.

14.8.2. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, FD (if applicable) and current CV of PI delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements
- All signed and dated case report forms submitted by PI/ Sub investigator, including reports of AEs, AEs and DDs
- Copies of all EC approval letters and relevant EC correspondence and roster
- Names of the sites in which the study will be conducted
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP and revisions
- Study training records for Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports in accordance with Table 5.

14.9 Reporting Requirements

14.9.1. Principal Investigator Reports

The PI is responsible for the preparation (review and signature) of all case report forms, AEs and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan.

The PI will report the matters to be reported in Table 6.

Table 6: Principal Investigator (study site) reports

Report	Submit to	Description/Constraints
Ethical and Scientific Concerns	The Head of Institution, and EC as necessary	<p>When an investigator, etc. becomes aware of any fact or obtains any information that ethical justification or scientific validity of the research he/she is engaged in is, or might be impaired, the investigator, etc. shall report promptly to the principal investigator.</p> <p>When an investigator, etc. becomes aware of any fact or obtains any information that appropriateness of implementing the research he/she is engaged in or reliability of results of the research is, or might be impaired, the investigator, etc. shall promptly report to the principal investigator or the Head of Institution.</p> <p>When a serious concern from the viewpoint of respecting human rights of a research subject, etc. or implementing a research (such as information/data breach related to the research, etc.), an investigator, etc. shall report promptly to the Head of Institution and the principal investigator.</p> <p>When a principal investigator has reported any fact or information that ethical justification or scientific validity of the research is, or might be impaired, and if the continuation of the research will be hindered, the principal investigator shall report to the Head of Institution without delay and as necessary, suspend or terminate the research or revise the research protocol.</p> <p>When the Head of Institution has been reported any fact or information that ethical justification or scientific validity of the research is, or might be impaired, as necessary, the Head of Institution shall submit the matter to the EC for deliberation and take appropriate countermeasures promptly such as suspension of the research and examination of the cause. In this case, before opinions are presented by the EC, the Head of Institution, as necessary, shall impose to the principal investigator to suspend the research or take necessary temporary measures. (Ethical Guidelines for human life science and medical research, Chapter 6, Part 11, 1, 2 (2) and 2 (7))</p>

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Report	Submit to	Description/Constraints
Study Deviations	The Head of Institution	<p>When an investigator, etc. becomes aware of any fact or obtains any information that appropriateness of implementing the research he/she is engaged in or reliability of results of the research is, or might be, impaired, the investigator, etc. shall report to the principal investigator or the Head of Institution promptly.</p> <p>When the principal investigator becomes aware of any fact or obtains any information that appropriateness of implementing the research, he/she is engaged in or reliability of results of the research is, or might be, impaired, the principal investigator shall report to the Head of Institution promptly and, as necessary, suspend or terminate the research or revise the research protocol. (Ethical Guidelines for human life science and medical research, Chapter 6, Part 11, 1 (2) and 2 (3))</p>
Significant Deviation	MHLW	<p>When the Head of Institution becomes aware that any research which the entity is implementing or implemented previously is not complying with these Guidelines, the said Head of Institution shall promptly submit the matter to the EC for deliberation and take relevant measures as well as, if such noncompliance is serious, shall report to the Minister of Health, Labour and Welfare concerning the status and results of such countermeasures and make the said status and results public. (Ethical guidelines for human life science and medical research(, Chapter 6, Part 11, 3 (1).)</p>
Progress Report	The Head of Institution and EC	<p>The principal investigator shall report to EC and the Head of Institution, with respect to the progress of the research and status of any adverse event which occurs in implementing of the research, in accordance with specifications prescribed in the research protocol. (Ethical guidelines for human life science and medical research(, Chapter 6, Part 11, 2 (5).)</p>

Report	Submit to	Description/Constraints
Termination and Completion Report	The Head of Institution and EC	When research is finished (including the case of discontinuance), the principal investigator of the research shall report to EC and the Head of Institution with summarized results of the research without delay in writing or by electromagnetic means. (Ethical guidelines for human life science and medical research(, Chapter 3, Part 6, 6 (1))
Final Publication	The Head of Institution	<p>When the principal investigator has finished research, the principal investigator shall, without delay, make public the results of the research, having</p> <p>taken necessary measures to protect human rights of the research subject, etc. and other individuals concerned and the rights and interests of the investigator, etc. and other entity concerned.</p> <p>In addition, if the research involves invasiveness (not including minor invasiveness) and intervention, the principal investigator shall, without delay, report to the Head of Institution, when the final publication of results of the research has made. (Ethical guidelines for human life science and medical research(Chapter 3, Part 6, 6 (2).)</p>

14.10 Publication and Use of Information

Study information will be registered on the public database (Japan Registry of Clinical Trials (jRCT), URL: <https://jrct.niph.go.jp/>) established by the Ministry of Health, Labor and Welfare. Information registered on JRCT will be updated as appropriate. The report of primary endpoint will be created within one year from the date when the primary endpoint data is collected and the CSR and the summary of CSR will be created within one year from the date when all data is collected. The study results will be posted on jRCT within one month from the date when the EC provided their opinions.

14.10.1. Handling of Study Results

This study compares the Total Electrical Energy Delivered (TEED) of aDBS and cDBS.

Regarding the results of individual subjects, the difference between TEED aDBS and TEED cDBS, the PI/Sub investigator will explain the results in response to requests from the research subjects.

The results from this study will be disclosed in jRCT, and the results will be explained by the PI/Sub investigator in response to requests from the subjects.

14.10.2. Publication Committee

Medtronic may form the Early Adapter Part II Publication Committee from PIs. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document if it applies.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

14.11 Suspension or Early Termination

14.11.1. Planned Study Closure

Study closure is defined as closure of a study that occurs when regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic, whichever occurs first. The study closure process is complete when the PI reports the outline of the results of this study and the completion to the Head of Institution and the EC based on the regulations of the site. Ongoing EC oversight is required until the overall study closure process is complete. Refer to section 9.15 for additional information regarding study exit procedures.

14.11.2. Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single study site.

14.11.2.1 Study-wide termination or suspension

Possible reasons for considering study-wide suspension or termination of the study include but are not limited to:

- AEs associated with the system or product under investigation which might endanger the safety

or welfare of the subject

- Observed/suspected performance different from the product's design intent
- Decision by Medtronic

14.11.2.2 Investigator/ study site termination or suspension

Possible reasons for PI or study site termination or suspension include but are not limited to:

- EC approval lapse/expiration
- Persistent noncompliance with the clinical investigation plan
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow up on data queries and monitoring observations in a timely manner, etc.)
- Loss of appropriately trained PI/ Sub investigator
- Insufficient or lack of PI oversight
- EC suspension of the study site
- Fraud or fraudulent misconduct is discovered
- PI request (e.g. no longer able to support the study)

In cases of study suspension/termination, standard medical care will continue to be provided to subjects enrolled in the study and EC requirements will be followed. Subjects will be notified by the PI/ Sub investigator of suspension/termination due to unacceptable risk or of termination due to any other cause. PI is required to notify the EC of study suspension/termination.

14.11.3. Procedures for Termination or Suspension

14.11.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will inform the PIs and provide a detailed written explanation of the termination or suspension. Medtronic will inform the regulatory authority where required
- The PI will promptly inform the head of institution

- The PI will promptly inform the EC
- Subject enrollment will stop until the suspension is lifted
- The PI will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

14.11.3.2 Investigator-initiated

- The PI will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The PI will promptly inform the head of institution
- The PI will promptly inform the EC
- The PI will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

14.11.3.3 EC-initiated

- The PI will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The PI will inform his/her institution
- The PI will promptly inform the subjects and/or the personal physician of the subjects with the rationale for the study termination or suspension

14.11.4. Provision of medical treatment to subject after study closure/termination

After the study is completed, the subject will continue to receive treatment with usual Insured Medical Treatment including selection of aDBS and cDBS modes.

14.12 Outsourcing partial work on the study

Vendor information in this study is provided in Appendix I. Medtronic, plc and its associates, work operations will be outsourced to Rune Labs (California, USA), Inc and MR-X-Brain GmbH (Germany). Audit for these companies will be conducted based on Medtronic, Inc's annual plan for audit. Also, work assessment will be conducted annually and improvements will be required. If non-compliance and/or deviation is identified, discussions will be held promptly, and appropriate improvement measures will be formulated.

For methods of oversight at each, the PI at site receives reports on work operations as needed and reviews its details.

14.13 Study Organization

Refer to the Appendix I for this Study Organization.

14.14 A system and consultation point where the subjects, etc. and other individuals concerned can consult on research

Consultations from subjects and related parties will be handled by PI/ Sub investigator or study personnel at each institution. Details such as contact information will be shown in the ICF.

14.15 Other

The following items in Ethical guidelines for human life science and medical research, Part 7, 1 do not apply to this study.

16) When obtaining informed consent from legally acceptable representative, etc., procedures pursuant to the provisions in Part 9 below (including matters related to the criteria to select legally acceptable representatives, etc. and to be informed and consented to pursuant to the provisions in Parts 8 and 9 below);

17) When obtaining informed assent, procedures pursuant to the provisions in Part 9 below (including information to be provided);

- 18) When the research is to be implemented pursuant to the provisions in Part 8.8 below, means to determine on conformity of all requirements set forth in the Section;
- 19) When the research involves any Financial expenditure on or remuneration for the research subject, etc., a statement to that effect and details of such
- 20) When the research involves invasiveness (not including minor invasiveness), means to respond in cases of serious adverse event;
- 21) When the research involves any invasiveness, whether or not compensation will be offered for research-related injury and detail of such compensation;

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16. Appendices

- **Appendix A: EQ-5D-5L**

EQ-5D-5L is provided separately.

- **Appendix B: PDQ-39**

PDQ-39 is provided separately.

- **Appendix C: UDysRS**

UDysRS is provided separately.

- **Appendix D: MDS-UPDRS II,III, IV**

MDS-UPDRS II,III, IV is provided separately.

- **Appendix E: DBS Global Impression of Change score (DBS GIC)**

DBS Global Impression of Change score is provided separately.

- **Appendix F: Patient preference questionnaire**

Patient preference questionnaire is provided separately.

- **Appendix G: Patient satisfaction questionnaire**

Patient satisfaction questionnaire is provided separately.

- **Appendix H: Case Report Form (Sample collection item list)**

CRF is provided separately.

- **Appendix I: Study Organization**

Study Organization is provided separately.

17. Version History

Version	Summary of changes	Final confirmer (creator / changer)
1.0	'Not Applicable, New Document'	
1.1	Corrected Japanese typographical error in Japanese CIP	
1.2	No change from the previous version (This version is for an internal process in the study sponsor)	
2.0	9.2 Added footnote 5 and 6 in Table 1. 9.3 Corrected description 9.8 Added setting conditions for directional lead with separate electrodes 9.8.3 Added the timing of patient questionnaires regarding mode preferences / satisfaction 9.9.1 Corrected description 9.9.2 Corrected description 9.10 Added details when collecting data for PD treatments 12.1 Corrected description 12.4 Added TEED calculation formula for directional lead 12.9 Added bias related to directional read 14.3 Changed device data upload location 14.9.1 Corrected description in Table 6	

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3.0	<p>2. Modified the description of the sample size and inclusion criteria</p> <p>5. Added explanation of study population to the English CIP according to the Japanese CIP</p> <p>8.2. Added requirement to the inclusion criteria #3, aDBS must be set up in both hemispheres for subject who is only tolerated dual threshold</p> <p>12.2 Unified "Ancillary objective" to "Additional objective" in the English CIP</p> <p>12.4 Added description CC cohort will be used for primary endpoint. Corrected TEED calculation formula for directional lead</p> <p>12.7 Unified "Ancillary objective" to "Additional objective" in the English CIP</p> <p>12.8. Clarified the description of rationale for the sample size</p> <p>14.8 Changed Record Retention</p>	
4.0	<p>5.1 Changed the expected enrollment period</p> <p>9.8 Added description the data collected from an iPhone will be used for Data of PD medication cycle, but if the data is missing, the data recorded in a medication diary etc. can substitute. Corrected description</p> <p>9.13 Added description that Medication diary may be collected on paper forms</p> <p>14.3 Added the database for the Json files and images upload</p> <p>14.8.1 Added a medication diary to documents stored in the study site file</p> <p>14.9.1 Corrected description in Japanese CIP</p>	
5.0	<p>9.7 Added description that BrainSense setting ON during cDBS</p> <p>14.3 Added MRI and CT images are also sent to and stored by MR-X-Brain GmbH, , Corrected description</p> <p>14.5 Changed from correspondence table to subject Identification log</p> <p>14.8 Corrected description in Table 5</p> <p>14.8.1 Changed from correspondence table to subject Identification log</p>	

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	14.12 Added the vendor to whom the work is outsourced	
6.0	14.5 Added description of compliance with recipient guidelines and pseudonymized information in Confidentiality 14.12 Added the name of the country of the contractor	