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Clinical Investigational Plan Cover Page

Adaptive **D**BS **A**lgorithm for **P**ersonalized **T**herapy in **P**arkinson's **D**isease (ADAPT-PD) Trial

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	**A**daptive **D**BS **A**lgorithm for **P**ersonalized **T**herapy in **P**arkinson's **D**isease (ADAPT-PD) Trial
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1. Glossary

Term/Acronym	Definition
µV/√Hz	Micro-volts per root-hertz (amplitude spectral density)
Acute stimulation-induced effects	Transient effects that occur during implantable neurostimulator programming sessions or while running adaptive Deep Brain Stimulation that resolve with, or without, stimulation adjustments prior to the subject leaving a clinic visit and do not require further follow-up or medical care outside of the visit.
aDBS	Adaptive Deep Brain Stimulation (aDBS). This is the general concept under study whereby 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 Modes
aDBS Setup	The initial process of setting up a subject to an aDBS mode.
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
Algorithm	A defined process or set of rules to be followed for decision-making, (i.e., to increase or decrease stimulation amplitude).
Alpha - Beta	Synchronized local field potential neural oscillatory activity within the 8-30 Hertz frequency range. This is the signal of interest for this study.
App	Application
BDI-II	Beck Depression Inventory©- II
Best condition	The time period when PD subjects are receiving relief from their Parkinson's disease symptoms, also known as "on" time or "on" period

Term/Acronym	Definition
BKS	Bradykinesia Score (from wearable)
BrainSense™ Technology	The family of features in the Percept PC system that make use of the system capability to capture and display local field potential (LFP) signals.
CA	Competent Authority
cDBS	Continuous Deep Brain Stimulation (cDBS) is the commercially available Deep Brain Stimulation Therapy.
CDU Application	Clinical Data Upload web-based application
CEC	Clinical Events Committee
CE Mark	A certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA).
CFR	Code of Federal Regulations (US)
CIP	Clinical Investigation Plan
clDBS	Closed Loop Deep Brain Stimulation
CPA	Clinician Programmer Application
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CSV	Comma Separated Values, a data file format
CTA	Clinical Trial Agreement
CTM	Clinician Telemetry Module
CV	Curriculum Vitae
DBS	Deep Brain Stimulation
DD	Device Deficiency
Directional Stimulation	3387 and 3389 leads are not capable of delivering directional stimulation

Term/Acronym	Definition
	For SenSight leads, the same amplitude is not used on all three electrodes at the same electrode level (e.g. 1a-1c, 2a-2c)
Directional Stimulation Cohort	Cohort comprised of study subjects with the SenSight™ system programed to directional stimulation
DKS	Dyskinesia Score (from wearable)
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
DTL	Delegated Task List
Dual Monopolar	A Deep Brain Stimulation configuration where two contacts of one (or more) electrodes are programmed as a cathode (-) and the implantable neurostimulator (case) is programmed as the anode (+).
eCRF	Electronic Case Report Form
EC	Ethics Committee
ECT	Electroconvulsive Therapy
EEA	European Economic Area
EQ-5D-5L	Five-dimensional five-level generic measure designed to measure, compare and value health status across disease areas; developed by the EuroQol Group.
Event markers	Used to capture and record patient triggered events and provide additional information for analysis around patients outside the clinic.
EU	European Union
EU MDR	European Union Medical Device Regulation
FAL	Foreseeable Adverse Events Listing
FD	Financial Disclosure

Term/Acronym	Definition
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDS	Fluctuation and Dyskinesia Score (from wearable)
FW	Firmware
GCP	Good Clinical Practice
GIC	Global Impression of Change
GKC	Global Kinetics Corporation
GPi	Globus Pallidus Internus
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
IB	Investigator's Brochure
IC	Informed Consent
IDE	Investigational Device Exemption
INS	Implantable Neurostimulator
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITA	Investigational Testing Authorization
JSON	JavaScript Object Notation, a data file format
LFP	Local Field Potential
MAR	Missing at Random
MCIC	Minimal Clinically Important Change
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale – The assessment has 4 parts, I-IV

Term/Acronym	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Monopolar	A Deep Brain Stimulation configuration where one contact of one or more electrodes is programmed as a cathode (-) and the implantable neurostimulator (case) is programmed as the anode (+).
NPU	Neuro Programmer Upload. The NPU database will store clinician programmer JSON session reports from the neurostimulator interrogations.
OC	Oracle Clinical
PHI	Protected Health Information
PD	Parkinson's Disease
PDQ-39	The 39-item Parkinson's Disease Questionnaire
PDQ-39 SI	PDQ-39 summary index
PDSS-2	Parkinson's Disease Sleep Scale 2
PKG®	Personal KinetiGraph®(US), Parkinson's Kinetigraph (EU)
PMA	Premarket Approval
PPA	Patient Programmer Application
Primary Cohort	Cohort comprised of study subjects implanted with legacy lead models 3387 or 3389, or with the SenSight™ Directional Lead programmed to ring mode stimulation
PRO	Patient Reported Outcome
PTM	Patient Telemetry Module
PW	Pulse Width
RA	Regulatory Authority
RDC	Remote Data Capture

Term/Acronym	Definition
RF	Radio Frequency
Ring Mode	For 3387 and 3389 leads, stimulation is always delivered in Ring Mode For SenSight leads, all segmented electrodes at the same electrode level (e.g. 1a-1c, 2a-2c) are activated at the same amplitude
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOI	Signal of interest, also referred to as a biomarker in literature. The signal of interest for this study is Alpha - Beta local field potential.
Stable (cDBS Programming)	The current cDBS settings are deemed by the physician to be acceptable and not likely to require substantial changes in the near term.
STN	Subthalamic Nucleus
SW	Software
TEED	Total Electrical Energy Delivered
TMS	Transcranial Magnetic Stimulation
Troublesome dyskinesia	Dyskinesia which interferes with function or causes meaningful discomfort.
TÜV	TÜV SÜD is the EU Notified Body
UADE	Unanticipated Adverse Device Effect
UAE	Unavoidable Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VHI	Voice Handicap Index
WHODrug	World Health Organization Drug
Worst condition	The time period when PD subjects are not receiving relief from their Parkinson's disease

Term/Acronym	Definition
	symptoms, also known as “off” time or “off” period.

2. Synopsis

Title	**A**daptive **D**BS **A**lgorithm for **P**ersonalized **T**herapy in **P**arkinson's **D**isease (ADAPT-PD) Trial
Clinical Study Type	Pivotal Trial
Product Name	Percept™ PC Neurostimulator and aDBS™ Therapy
Sponsor	Medtronic
Local Sponsor	Medtronic Neuromodulation, USA Medtronic International Trading Sàrl, Switzerland EU Legal Representative: Medtronic Bakken Research Center B.V., The Netherlands Medtronic Canada ULC, Canada
Indication under investigation	Parkinson's disease (PD) – Deep Brain Stimulation (DBS) implant to subthalamic nucleus (STN) or Globus Pallidus (GPi) target sites
Investigation Purpose	The purpose of the study is to demonstrate the safety and effectiveness of adaptive DBS (aDBS) for Parkinson's disease.
Product Status	Investigational aDBS firmware will be enabled on an already implanted, commercially available Model B35200 Percept PC implantable neurostimulator (INS). An investigational version of the DBS Clinician Programmer will enable the aDBS functionality on the INS. An investigational version of the DBS Patient Programmer will be available to study subjects.
Primary Objective(s)	To demonstrate that the proportion of aDBS subjects with "On" time without troublesome dyskinesia during the Evaluation Phase exceeds a performance goal of 50%.
Secondary Objective	To demonstrate decreased stimulation energy use during the aDBS Evaluation Phase as compared with continuous DBS (cDBS).
Safety Assessments	To characterize: • Stimulation-related adverse events during the aDBS Evaluation and the cDBS Baseline Phases. • Serious adverse events, adverse events and device deficiencies throughout the study.
Additional Objectives	To characterize aDBS during the Evaluation Phase as compared to cDBS (Primary Cohort): • Voice Handicap Index (VHI): "best" and "worst" conditions • Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III subscore (On stim/On med) of tremor, rigidity, and bradykinesia questions where a side can be determined: 3.3 b, c, d, e (rigidity), 3.4 a, b (finger taps/bradykinesia), 3.15 a, b (postural tremor of hands), 3.16 a, b (kinetic tremor of hands), and 3.17 a, b, c, d (rest tremor amplitude)

	• MDS-UPDRS III (On stim/On med) • MDS-UPDRS II: "best" and "worst" conditions • MDS-UPDRS III speech question (On stim/On med) q 3.1 • MDS-UPDRS IV • EQ-5D-5L • PDSS-2 • Data collected from wearable (for example: % of wear time tremor was detected, Dyskinesia Score [DKS], Bradykinesia Score [BKS], Fluctuation and Dyskinesia Score [FDS]) • 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 • PDQ-39 speech questions 34 and 35 • % of subjects with at least 25% increase in projected battery longevity as compared with cDBS • Parkinson's Disease Home Diary: "On" time without troublesome dyskinesia, "On" time without dyskinesia, "On" time with non-troublesome dyskinesia, "On" time with troublesome dyskinesia, "Off" time, and Asleep time. • Patient preference of aDBS vs cDBS (as assessed by a Medtronic-developed patient preference questionnaire) • Patient satisfaction with aDBS (as assessed by a Medtronic-developed patient satisfaction questionnaire) • Device data from JSON file, including BrainSense data Subgroup analyses (from the entire study population): • For those with dyskinesia at least 25% of time: Wearable data • For those with speech side effects: VHI • For those with mixed programming (aDBS and cDBS): MDS-UPDRS III by side • For those who use event markers in long-term follow-up: characterize subject population and satisfaction with use of event markers • For those who finished the aDBS Evaluation Phase: one aDBS mode will be selected per subject based on subject preference or programming availability at the end of the aDBS Evaluation Phase. The aDBS Evaluation Phase results may be characterized based on the selected mode.
Primary Endpoint	Proportion of aDBS subjects with "On" time without troublesome dyskinesia exceeding the threshold. The threshold will be determined using the following: on a per-patient basis, the hours of "On" time

	without troublesome dyskinesia for aDBS is no worse than 1 standard deviation less than cDBS. The standard deviation is calculated from the difference between aDBS and cDBS in the Full Analysis Set (FAS).
Secondary Endpoint	Decreased total electrical energy delivered (TEED) during the respective aDBS Evaluation Period as compared with cDBS during the cDBS Baseline Phase.
Safety Analyses	• Stimulation-related adverse events during the cDBS baseline and aDBS evaluation phases for all subjects, with tabulations individualized by aDBS mode and by target site and combined after statistical comparisons for poolability. • Serious adverse events, adverse events and device deficiencies throughout the study for all subjects.
Study Design	Prospective, single-blind, randomized crossover, multi-center study of aDBS in subjects with Parkinson's disease. The study is expected to be conducted at approximately 12 centers located in the US, Europe and Canada. It is estimated that approximately 70-100 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled to obtain 40 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS evaluation phase. Accounting for a 10% dropout during the aDBS Evaluation Phase, a minimum of 36 subjects (at least 8 per brain target) will complete the aDBS Evaluation phase. In addition, approximately 15 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS and SenSight system will be enrolled in the Directional Stimulation Cohort to obtain 9 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. Accounting for dropout during the aDBS Evaluation Phase, a minimum of 8 subjects will complete the aDBS Evaluation Phase. Study visits and/or phases include: • Enrollment Visit: Consent, Screening • cDBS Baseline Phase: Local Field Potential (LFP) Screening and Baseline cDBS visits • aDBS Setup and Adjustment Phase: aDBS Setup visit and additional optional visits during an aDBS Adjustment period • aDBS Evaluation Phase: One-month treatment periods in each acceptable aDBS mode with aDBS evaluation visits at the end of each period. Randomized crossover to the two investigational treatments in subjects for whom both aDBS modes were acceptable and a single treatment period in those subjects for whom only one aDBS mode was acceptable.

	• Long-Term Follow Up Phase: Four visits in preferred aDBS mode for approximately 10 months • Extended Access Phase: Additional visits in the preferred aDBS mode every 6 months through commercial approval of aDBS
Randomization	Randomization to a crossover sequence of aDBS single threshold and aDBS dual threshold modes
Sample Size	<u>Primary Cohort</u> It is estimated that approximately 70-100 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled in the study to obtain 40 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS evaluation phase. It is expected that approximately 50% of enrolled subjects will be exited from the study at LFP Screening due to insufficient Alpha - Beta band amplitude and/or artifact. Accounting for a 10% dropout during the aDBS Evaluation Phase, a minimum of 36 subjects (at least 8 per brain target) are expected to complete the aDBS Evaluation phase. Because the device implant will occur outside of the study and the study requires participants to be stable on cDBS, the standard deviation of the change from cDBS to aDBS in "On" time without troublesome dyskinesia will be used to establish a threshold for assessing the performance goal. The threshold will be set as 1 standard deviation. If the difference between aDBS and cDBS (aDBS-cDBS) for a subject is at least -1 standard deviation, the threshold will be met for the subject. Using this threshold, the proportion of subjects who exceed the threshold will be computed. The sample size was estimated using a binomial distribution for a one-sided test for a proportion to compare to a performance goal of 50%. Assuming the alternative hypothesis of 85% of subjects exceeding the threshold described above, a minimum of 36 subjects achieves at least 90% power to reject a performance goal of 50%. Sample size was computed in PASS 11. For the safety analysis, a minimum of 30 subjects followed for approximately 30 days with aDBS out-of-clinic in the subjects' real-world environments provides greater than 95% probability that all stimulation-related adverse events with a true adverse event rate of at least 10% would be reported at least once. <u>Directional Stimulation Cohort</u> In addition, approximately 15 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS and SenSight

	system will be enrolled in the Directional Stimulation Cohort to obtain 9 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. Accounting for dropout during the aDBS Evaluation Phase, a minimum of 8 subjects will complete the aDBS Evaluation Phase.
Inclusion/Exclusion Criteria	There are two sets of criteria for study participation prior to the investigational use of aDBS. 1. Subjects must meet all general inclusion/exclusion criteria (as assessed at the Enrollment Visit) 2. Subjects must meet the LFP screening inclusion criterion (as assessed at the LFP Screening Visit) General <u>Inclusion Criteria</u> <u>Primary Cohort:</u> 1. Subject has idiopathic Parkinson's disease 2. Subject is implanted with Percept PC (Model B35200) and Medtronic DBS leads (Model 3387, 3389, B33005 or B33015) and extensions (Model 37085, 37086 or B34000) bilaterally in the same target (physician confirmed), STN or GPi 3. In the opinion of the investigator, the subject responds to DBS Therapy. 4. Based on the opinion of the investigator, the subject's cDBS parameters and PD medications are stable and expected to remain stable from enrollment through the end of the aDBS Evaluation phase 5. Subject is configured to ring mode monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side. 6. Subject is willing and able to attend all study-required visits and complete the study procedures (e.g. 1-month recall questionnaires, MDS-UPDRS III) 7. Subject has the ability to understand and provide written informed consent for participation in the study prior to the study-related procedures being conducted 8. Subject is a male or non-pregnant female. If female of child-bearing potential, and if sexually active, must be using, or agree to use, a medically-acceptable method of birth control as confirmed by the investigator 9. For subjects with the SenSight system: Subject is configured to the following stimulation rates: 55, 85, 110, 125, 145, 164 or 180 Hz (as required for sensing/aDBS)

	Directional Stimulation Cohort: Subjects must meet the same inclusion criteria as the primary cohort except for revised #2 and #5. Revised Inclusion Criteria: 2. Subject is implanted with Percept PC (Model B35200) and Medtronic DBS leads (Model B33005 or B33015) and extensions (Model B34000) bilaterally in the same target (physician confirmed), STN or GPi 5. Subject is configured to directional monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) Exclusion Criteria (All Cohorts) 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. At enrollment, the subject's INS has a predicted battery life of <1 year 6. Subject has Beck Depression Inventory II (BDI-II) > 25 7. Subject requires diathermy, transcranial magnetic stimulation (TMS), or electroconvulsive therapy (ECT) 8. Subject has a metallic implant in the head, (eg, aneurysm clip, cochlear implant) 9. Subject has, or plans to obtain, an implanted electrical stimulation medical device anywhere in the body (eg, cardiac pacemaker, defibrillator, spinal cord stimulator) 10. Subject has, or plans to obtain, an implanted medication pump for the treatment of Parkinson's disease (eg, DUOPA™ infusion pump) and/or portable infusion pump 11. Based on the opinion of the investigator, the subject has an abnormal neurological examination that would preclude them from study participation 12. Subject is breast feeding 13. Subject is under the age of 18 years 14. 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 as determined by the Medtronic study team 15. Subject is unable to use or tolerate wearable 16. Subjects with signal artifact on all 6 aDBS sense pathways (3 each on both DBS leads) which preclude the clinician from setting thresholds LFP Screening <u>Inclusion Criteria (All Cohorts)</u> 1. Subject has Alpha - Beta band (8-30 Hz) amplitude ≥ 1.2 µVp 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
Study Procedures and Assessments	Subjects will be considered enrolled at the time they sign the informed consent form. Scheduled visits will include the following: Enrollment, LFP Screening, cDBS Baseline, aDBS Setup, Randomization, aDBS Evaluation Visit 1, aDBS Evaluation Visit 2, Long-term follow-up Visit 3, Long-term follow-up Visit 4, Long-term follow-up Visit 5, and Long-term follow-up Visit 6. Subjects participating in the extended access phase prior to commercial approval of aDBS, will have visits every 6 months. The following assessments / data will be collected during the study: • Concomitant medications • PDQ-39 • EQ-5D-5L • MDS-UPRDS Parts I-IV • Parkinson's Disease Home Diary • VHI • PDSS-2 • aDBS Global Impression of Change score • Patient preference questionnaire • Patient satisfaction questionnaire • Wearable data • Programming session data, including BrainSense data • Event markers (optional) • Adverse Events and Device Deficiencies
Statistics	Primary and secondary objectives will be analyzed using the FAS. The FAS includes all Primary Cohort subjects, using the intention-to-treat (ITT) principle, who initiate the aDBS Evaluation Phase using the randomized treatment assignment for each subject that was randomized and the programmable treatment assignment for those subjects that may only be configured to one aDBS mode (dual or

	single threshold). Safety analyses will be evaluated using the As-Treated (AT) Analysis Set. AT includes all Primary Cohort subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) during the cDBS Baseline Evaluation Phase and/or the aDBS Evaluation Phase, and Long-term Follow-up Phase and uses the observed treatment used for each subject in each phase. The Parkinson's Disease Home Diary from the two weeks prior to the Baseline visit (cDBS) and the aDBS Evaluation visits (aDBS) will be used to evaluate the primary objective. The observed proportion will be computed for each aDBS mode separately and compared to the performance goal using a binomial exact test. The secondary objective will evaluate the decrease in Total Electrical Energy Delivered (TEED) for each aDBS mode compared to cDBS using data from the 14-days prior to the Baseline visit (cDBS) or the respective aDBS Evaluation Visit (aDBS). Supporting analyses for the objectives in the Primary Cohort include: verifying the lack of a period or carryover effect, verifying poolability by assessing target site effects (STN/GPi) and center effects. In addition, summarized results from the Directional Stimulation Cohort will be provided as supporting analyses to the primary, secondary, and safety Primary Cohort results. Sensitivity analyses will be performed. The additional objectives will be evaluated from the Primary Cohort to compare each outcome for each aDBS mode during the aDBS Evaluation Phase compared to cDBS during the cDBS Baseline Phase. The familywise error rate will be controlled using one-sided tests with an overall alpha-level of 0.025 approach to multiple testing. Each primary hypothesis (one for each aDBS mode) will be assigned a Bonferroni corrected alpha (0.0125) for the respective primary hypothesis (see Section 13.4.1). The primary hypothesis will serve as a gatekeeper for the secondary hypothesis within each mode. Sample size in the Primary Cohort may be increased to a maximum of 55 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS evaluation phase to obtain at least 8 subjects per aDBS mode and 8 subjects per target site (STN/GPi).

	All attempts will be made to minimize missing data. If 5% of the data or fewer are missing for the analysis, no imputation will be used. Otherwise, if missing data are observed, multiple imputation will be used with the primary and secondary objectives. If an aDBS mode is not programmable to a patient, summary statistics will be computed to summarize the percent who were not programmed to a mode and no imputation will occur for that outcome for that aDBS mode. The Complete Case Analysis Set and the As-Treated Analysis Set will be used for sensitivity analysis to the primary and secondary objective analyses.

3. Introduction

3.1. Background

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease associated with both motor and non-motor symptoms. It affects 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.[4-5, 6,7]

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 is thought to contribute to 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 is 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.

3.2. Purpose

The purpose of the study is to demonstrate the safety and effectiveness of adaptive DBS (aDBS) for Parkinson's disease.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

To demonstrate that the proportion of aDBS subjects with "On" time without troublesome dyskinesia during the Evaluation Phase exceeds a performance goal of 50%.

4.1.2. Secondary Objective

To demonstrate decreased stimulation energy use during the aDBS Evaluation Phase as compared with cDBS.

4.1.3. Safety Assessments

To characterize:

- Stimulation-related adverse events (AEs) during the aDBS evaluation and the cDBS baseline phases.
- Serious adverse events (SAEs), adverse events and device deficiencies throughout the study.

4.1.4. Additional Objectives

To characterize aDBS as compared to cDBS (Primary Cohort):

- Voice Handicap Index (VHI): "best" and "worst" conditions
- MDS-UPDRS III subscore (On stim/On med) of tremor, rigidity, and bradykinesia questions where a side can be determined: 3.3 b, c, d, e (rigidity), 3.4 a, b (finger taps/bradykinesia), 3.15 a, b (postural tremor of hands), 3.16 a, b (kinetic tremor of hands), and 3.17 a, b, c, d (rest tremor amplitude)

- MDS-UPDRS III (On stim/On med)
- MDS-UPDRS II: “best” and “worst” conditions
- MDS-UPDRS III speech question (On stim/On med) q 3.1
- MDS-UPDRS IV
- EQ-5D-5L
- PDSS-2
- Data collected from wearable (for example: % of wear time tremor was detected, Dyskinesia Score [DKS], Bradykinesia Score [BKS], Fluctuation and Dyskinesia Score [FDS])
- PDQ-39 Summary Index (SI) and subscores: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort
- PDQ-39 speech questions 34 and 35
- % of subjects with at least 25% increase in projected battery longevity as compared with cDBS
- Parkinson’s Disease Home Diary: “On” time without troublesome dyskinesia, “On” time without dyskinesia, “On” time with non-troublesome dyskinesia, “On” time with troublesome dyskinesia, “Off” time, and Asleep time.
- Patient preference of aDBS vs cDBS (as assessed by a Medtronic-developed patient preference questionnaire)
- Patient satisfaction with aDBS (as assessed by a Medtronic-developed patient satisfaction questionnaire)
- Device data from JSON file including BrainSense data

Subgroup analyses (from the entire study population):

- For those with dyskinesias: at least 25% of time: Wearable data
- For those with speech side effects: VHI
- For those with mixed programming (one hemisphere with aDBS and one with cDBS): MDS-UPDRS III by side
- For those who use event markers in long-term follow-up: characterize subject population and satisfaction with use of event markers
- For those who finished the aDBS Evaluation Phase: one aDBS mode will be selected per subject based on subject preference or programming availability at the end of the aDBS Evaluation Phase. The aDBS Evaluation Phase results may be characterized based on the selected mode.

4.2. Endpoints

4.2.1. Primary Endpoint

Proportion of aDBS subjects with "On" time without troublesome dyskinesia exceeding the threshold. The threshold will be determined using the following: on a per-patient basis, the hours of "On" time without troublesome dyskinesia for aDBS is no worse than 1 standard deviation less than cDBS. The standard deviation is calculated from the difference between aDBS and cDBS in the Full Analysis Set (FAS).

A performance goal of 50% was chosen for this study in order to demonstrate that at least 50% of the subjects are able to achieve the threshold with 95% confidence, demonstrating some level of efficacy. The endpoint of the Parkinson's Disease (PD) Home Diary was chosen to determine the threshold of success as it is a measure of the subject response to DBS therapy over time, because the aDBS algorithm will adapt the therapy over time, and because the PD Home Diary has been used as an endpoint in previous DBS trials. A unit of one standard deviation was chosen as it is an acceptable amount of statistical variability in the PD Home Diary endpoint given the fluctuating nature of Parkinson's disease and the percentiles of a normal distribution.

4.2.2. Secondary Endpoint

Decreased total electrical energy delivered (TEED) for each aDBS mode during the respective aDBS Evaluation Period as compared with cDBS during the cDBS Baseline Phase.

5. Study Design

The ADAPT-PD trial is a prospective, multicenter, single-blind, randomized crossover clinical investigation and is designed to demonstrate the safety and effectiveness of adaptive DBS for Parkinson's disease. It is composed of a primary trial cohort (Primary cohort) with subjects programmed in ring mode and a cohort of subjects implanted with the SenSight system and programmed to directional stimulation (Directional Stimulation Cohort). For subjects with the 3387 and 3389 DBS leads, stimulation is always delivered in Ring mode. In subjects with the SenSight lead, ring mode is when all segmented electrodes at the same electrode level (e.g. 1a-1c, 2a-2c) are activated at the same amplitude. Directional stimulation, which can only be programmed in subjects with SenSight leads, is when the same amplitude is *not* used on all three electrodes at the same electrode level (e.g. 1a-1c, 2a-2c).

The study is expected to be conducted at approximately 12 centers located in the US, Europe and Canada. It is estimated that approximately 70-100 subjects implanted with a commercially available

Medtronic DBS system with Percept PC INS will be enrolled in the Primary Cohort to obtain 40 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. Accounting for a 10% dropout during the aDBS Evaluation Phase, a minimum of 36 subjects (at least 8 per brain target) will complete the aDBS Evaluation Phase. In addition, approximately 15 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS and SenSight system will be enrolled in the Directional Stimulation Cohort to obtain 9 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase and a minimum of 8 subjects who complete the aDBS Evaluation Phase.

There is no minimum number of subjects required to be enrolled at a center. For the Primary Cohort, each study center will stop enrollment after they have identified a maximum of 8 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase (~25% of the total planned number of subjects). For the Directional Stimulation Cohort, each study center will stop enrollment after they have identified a maximum of 5 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. The actual number of subjects at a study center may be slightly larger due to the number of subjects that are enrolled prior to cessation of enrollment. This restriction is intended to reduce the possibility that the results from one study center will be overly influential in the overall study results.

The study consists of four phases following enrollment:

- cDBS Baseline Phase (approximately 1 month): LFP Screening, Baseline cDBS and Off stimulation Assessments
- aDBS Setup and Adjustment Phase (up to 2 months): aDBS Setup visit and additional optional visits during an aDBS Adjustment period
- aDBS Evaluation Phase (approximately 2 months): One-month treatment periods in each acceptable aDBS mode with aDBS evaluation visits at the end of each period. Randomized crossover to the two investigational treatments in subjects for whom both aDBS modes were acceptable and a single treatment period in those subjects for whom only one aDBS mode was acceptable.
- Long-Term Follow Up Phase (approximately 10 months): Four scheduled visits in the preferred aDBS mode

Subject participation in an Extended Access Phase is optional and includes additional visits in the preferred aDBS mode every 6 months through commercial approval of aDBS.
The design of the Directional Stimulation Cohort is the same as the main ADAPT-PD trial. Subjects enrolled in the Directional Stimulation Cohort will follow the same visit schedule.

5.1. Duration

The study duration is expected to be approximately 5 years. It is estimated that approximately 16 months will be needed to enroll 70-100 subjects in order to obtain 40 subjects for whom at least 1 aDBS mode is acceptable and who will enter the aDBS Evaluation Phase of the Primary cohort and to enroll approximately 15 subjects in order to obtain 9 subjects for whom at least 1 aDBS mode is acceptable and a minimum of 8 who complete the aDBS Evaluations Phase in the Directional Stimulation Cohort.

Study participation for subjects who are enrolled, but do not meet the LFP screening criteria is estimated to be approximately 1 month. Subjects who do not meet the LFP screening criteria will be exited at the beginning of the cDBS Baseline phase.

Subjects who meet the LFP screening criteria will be followed for approximately an additional 4 months in the cDBS Baseline and aDBS Setup and Adjustment phases. Subjects who cannot be set up or acceptably configured on at least one aDBS mode will be exited prior to randomization.

Subjects who meet the LFP screening criteria and can be acceptably configured on at least one aDBS mode will enter the aDBS Evaluation Phase. If both aDBS modes were acceptable subjects will be randomized and followed for approximately 2 months. If only one aDBS mode was acceptable, they will complete a single one-month period in the aDBS Evaluation phase. This will be followed by approximately 10 months in the Long-term Follow-up phase for a total of approximately 1 year in aDBS.

Subjects will be allowed extended access to aDBS through commercial approval of aDBS in the geography in which the subject is enrolled. The subject will continue the study in their preferred aDBS mode until aDBS is commercially approved or closure of the study, whichever comes sooner.

The study may also be stopped on recommendation of the DMC. See Section 12.1.

5.2. Rationale

The ADAPT-PD study will utilize the commercially approved Model B35200 Percept PC INS that has investigational aDBS functionality enabled. This aDBS functionality 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 aDBS device. The aDBS control algorithm will rely on STN and GPi Alpha- - Beta band (approximately 8-30 Hz) activity as the signal of interest. The feasibility of using Alpha - 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 ADAPT-PD Study will assess both dual and single threshold aDBS modes (algorithms). 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 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 protocol will use a larger sample size across multiple centers under controlled conditions to further evaluate these results to support the use of aDBS as an additional programming tool to further personalize the already established and effective cDBS therapy.

6. Product Description

6.1. General

Medtronic DBS Therapy uses implantable, 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. Table 1 provides a listing of the Percept PC system components which will be used in the ADAPT-PD Trial. Figure 1 illustrates the full Percept PC system. The commercially available components are described below in Section6.1.1.

The devices that are considered investigational for the ADAPT-PD system include the Model B35200 Percept PC INS when aDBS firmware is enabled, the Model A610 Clinician Programmer Application Version 3.0 with aDBS software enabled and the Model A620 Version 2.0 Patient Programmer Application (PPA) with aDBS functionality. These components are described in Section 6.1.2. The devices will become investigational in the ADAPT-PD Trial when the aDBS firmware or software feature flags are enabled or when aDBS screens are displayed on the programmers. There is no physical difference between the commercially available components of the Percept PC system and the investigational components. Parts of the clinician programmer system and patient programmer system to be used in the ADAPT-PD Trial are completely unchanged from the commercially available versions but are packaged and used with devices that will be considered investigational once aDBS is enabled and will therefore also be considered investigational.

The combination of approved labeling, investigational labeling and the Clinical Investigation Plan contains adequate information for the purposes of the investigation. The investigational labeling will be provided to investigational sites, IRBs/ECs and Regulatory Authorities (as applicable) in the Investigator's Brochure (IB). Investigational labeling for the Patient Programmer System will be provided to patients after aDBS is set up.

Table 1: Medtronic DBS System Components

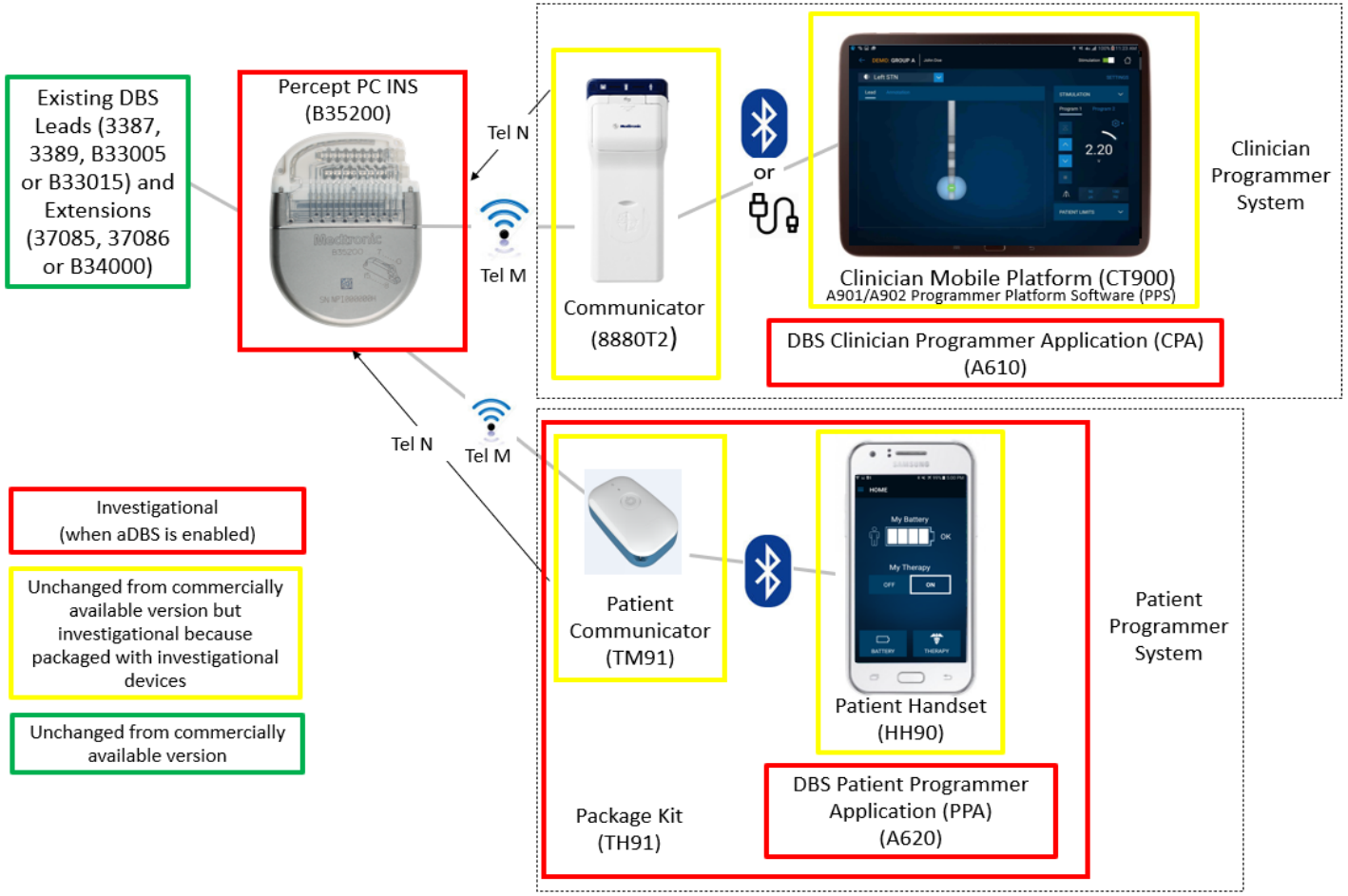
	Component	Model
Implantable	Neurostimulator	Model B35200 Percept PC INS with aDBS firmware (FW) enabled* • Product Firmware Version 7.5 • Device Firmware Version 7.5 • Core Firmware Version 7.5
External	Clinician Programmer System Components	• Model 8880T2 Version 1.107 Clinician Telemetry Module** • Model CT900 Clinician Programmer Tablet** ○ Model A610 Clinician Programmer Application Version 3.0 with aDBS software enabled** ○ Model A901 Version 1.0 Communication Manager** ○ Model A902 Version 1.0 Patient Data Services**
	Patient Programmer System Components	TH91 Package Kit 1. Model TM91 Version 2.1 Patient Telemetry Module** 2. Model HH90 Patient Programmer Phone** 3. Model A620 Version 2.0 Patient Programmer Application (PPA) with aDBS functionality*

*Components are physically the same as the commercially available product with investigational firmware or software feature flags enabled or investigational screens displayed. The software/firmware versions are the same as the commercially available product.

**Components are not modified from the commercially available version but will be considered investigational as they are packaged together with the Patient and Clinician Programmer Applications as a system.

The commercially approved (FDA approved, CE marked, and Health Canada licensed) devices will be used within the scope of their approved labeling for which FDA approval, CE mark, or Health Canada approval has been obtained.

Figure 1: Percept PC System



6.1.1. Medtronic Commercially Available DBS System Components

Model B35200 Percept PC INS

The model B35200 Percept PC Neurostimulator with BrainSense™ (Product Firmware Version 7.5, Device Firmware Version 7.5, Core Firmware Version 7.5) is commercially available for DBS Therapy and is part of an active implantable device system for deep brain stimulation and sensing. The DBS system delivers electrical stimulation to targeted regions of the brain, defined by anatomy and/or physiology, to suppress the symptoms associated with a neurologic disorder treatable by brain stimulation. The neurostimulator is a multiprogrammable device that delivers stimulation through 1 or 2 leads. The stimulation settings are stored in programs. Programmable parameters include amplitude, pulse width, rate, and cycling. Percept PC is able to deliver cDBS and also has the capability to sense and record bioelectric data through the DBS leads implanted in the brain.

Percept PC has embedded firmware which adjusts the stimulation output of the device to conform to clinician programmed parameters. The firmware stores data pertinent to device operation and sends the data via radio frequency (RF) telemetry when requested by one of the programmers (clinician programmer or patient programmer). The firmware limits stimulation outputs to within clinician-defined ranges and modes.

The commercially available Model B35200 Percept PC INS will be implanted prior to subject enrollment in the study. The commercially available Model B35200 Percept PC INS contains the aDBS FW, but the FW is not active.

DBS Leads (Includes models 3387, 3389, B33005 and B33015)

The Models 3387 and 3389 DBS Leads are composed of a polyurethane protective sheath with four platinum/iridium electrodes located at the distal end, which are used to deliver the electrical stimulation to the target site.
The Model 3387 DBS Lead features wide (1.5 mm) spacing between each of the four electrodes at the distal end. The Model 3389 DBS Lead features narrow (0.5 mm) spacing between each of the four electrodes at the distal end.

The Models B33005 and B33015 SenSight Leads are composed of a polyurethane protective sheath with eight platinum/iridium electrodes located at the distal end (in a 1-3-3-1 configuration with the second and the third electrodes separated into three separate electrodes spaced 120° from the center of each segment), which are used to deliver the electrical stimulation to the target site.

The Model B33015 SenSight Lead features wide (1.5 mm) spacing between each of the four electrode levels at the distal end. The Model B33005 SenSight Lead features narrow (0.5 mm) spacing between each of the four electrode levels at the distal end.

DBS Extension Kits (Includes models 37085, 37086, or B34000 in 40, 60, 95 cm lengths)

The Model 37085 and 37086 Extensions connect the neurostimulator to the lead, providing an electrical path that allows stimulation to be delivered to the target site. The Model 37085 and 37086 DBS Extensions are identical. The only difference is the Model 37085 DBS Extension Kit contains a tunneling tool and the Model 37086 DBS Extension Kit does not.

The Model B34000 SenSight Extension connects the neurostimulator to the lead, providing an electrical path that allows stimulation to be delivered to the target site.

Clinician Programmer System Components (Model A610 Clinician Programmer Application, Model CT900 Clinician Programmer Tablet, Model 8880T2 Clinician Telemetry Module, Model A901 Communication Manager and Model A902 Patient Data Services)

The Medtronic Model A610 DBS Version 3.0 () Clinician Programmer Application (CPA) is intended for use by clinicians in the programming of Medtronic neurostimulators (external and implantable) for deep brain stimulation (DBS).

The Model CT900 clinician programmer tablet, with Android®-based operating system, is intended for use by clinicians to use in conjunction with the CPA to program Medtronic neurostimulators.

The Model 8880T2 Communicator is intended for use by clinicians to use in conjunction with the clinician tablet and CPA for communication with Medtronic Neuromodulation therapy devices.

The Model A901 Version 1.0 Communication Manager Application is intended to manage the telemetry communications for the clinician tablet.

The Model A902 Version 1.0 Patient Data Service Application is intended for use by clinicians to access reports for all patients whose Medtronic devices have been programmed using the CPA on the clinician tablet. The Patient Data Service app can also be used to access reports for all patients whose Medtronic devices have been programmed using any clinician programmer application on the same clinician tablet. The Patient Data Service app can be used to adjust (or disable) the auto-delete feature, which automatically deletes patient data (after it has been compiled into reports) after a designated amount of time.

Patient Programmer System Components (TH91 package kit includes: Model A620 Patient Programmer Application, Model HH90 Patient Programmer Phone, Model TM91 PTM)

The Model HH90 Patient Programmer Handset has a screen like a smartphone and contains the Model A620 patient programming application.

The Model TM91 PTM allows the A620 Patient Programmer Application on the HH90 Patient Programmer Phone to connect with the subject's neurostimulator.

6.1.2. Medtronic Investigational DBS System Components

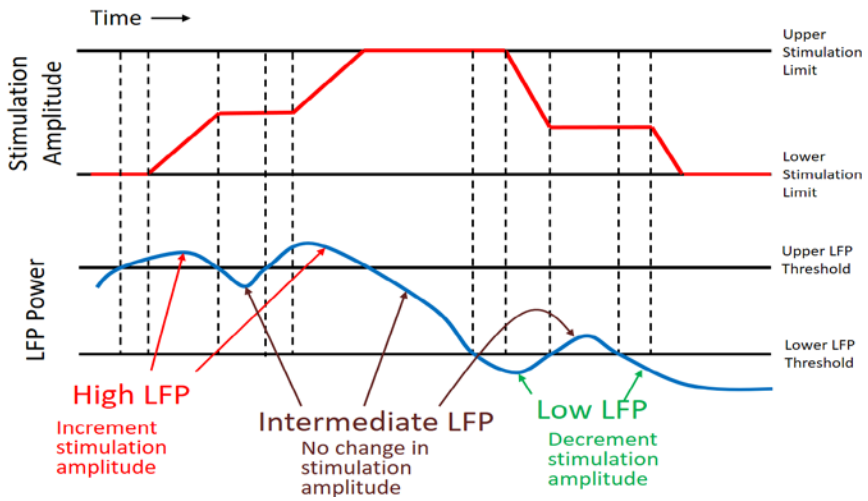
aDBS Feature

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 Alpha - 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 feature is investigational for this study and is enabled using a Clinician Programmer System with investigational aDBS software enabled. The ADAPT-PD Trial will study two aDBS modes, Dual and Single Threshold modes. Additional modes will be available on the clinician programmer as part of the aDBS feature but will not be used in the ADAPT-PD Trial.

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 Alpha - Beta power SOI remains between the upper and lower thresholds, stimulation amplitude is held constant. When the Alpha - Beta power SOI exceeds the upper threshold, stimulation increments. When the Alpha - Beta power SOI dips below the lower threshold, stimulation decrements. This aDBS mode is shown in Figure 2.

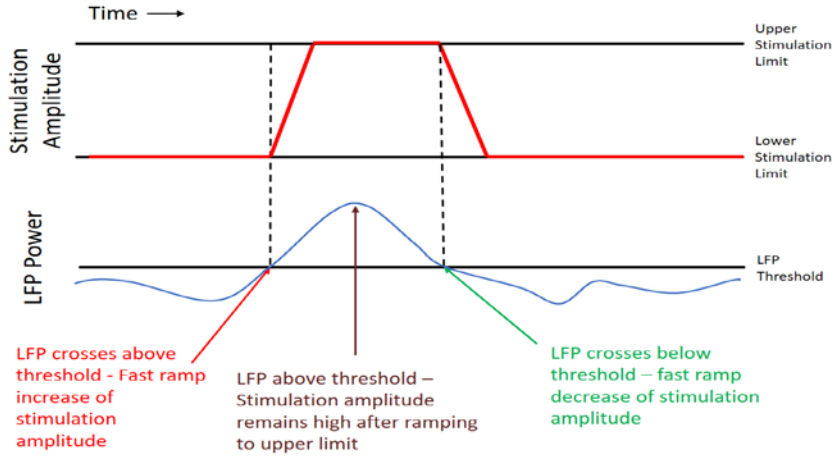
Figure 2: Dual Threshold aDBS Mode



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



Investigational Model B35200 Percept PC INS with aDBS Firmware Enabled

Although no physical changes are made to the Model B35200 Percept PC INS, it becomes investigational at the aDBS Setup visit when the investigational aDBS FW is enabled by software on an investigational version of the Clinician Programmer System. When the firmware is enabled, the device has the ability to adapt stimulation based on the sensed bioelectric data from the DBS leads implanted in the brain.

The estimated number of times the investigational aDBS firmware will be enabled on the commercially available Model B35200 Percept PC is 70. Once for each patient that enters the aDBS Setup and Adjustment phase.

Investigational Clinician Programmer System Components (Model 8880T2 Clinician Telemetry Module; Model CT900 Clinician Programmer Tablet, with Model A610 Clinician Programmer Application, Model A901 Communication Manager and Model A902 Patient Data Services installed)

The Medtronic Model A610 DBS Version 3.0 Clinician Programmer Application (CPA) utilized for the study will have investigational aDBS software enabled by Medtronic. The investigational aDBS feature allows the physician to program aDBS on the Percept PC INS, including selecting an LFP signal of interest (Alpha -Beta for this study), programming electrode configuration, capturing LFP thresholds, setting upper and lower stimulation limits, transition durations and suspend amplitude. The software version number (3.0) is the same for the commercial and investigational versions. A feature identifier will indicate if the aDBS feature is enabled or disabled (i.e. whether it can configure/modify aDBS).

The Model 8880T2 Communicator; the Model CT900 clinician programmer tablet, with Android®-based operating system with the Model A901 Version 1.0 Communication Manager Application and the Model A902 Version 1.0 Patient Data Service Application installed are unchanged from the commercially available versions.

Although only the CPA will be modified from the commercially available version by displaying investigational screens which allow programming of aDBS, all components will be considered investigational as they are packaged together as a system.

The estimated number of Investigational Clinician Programmer Systems to be used in the study is 24 clinician systems, two for each participating center. These systems will be provided to the participating centers exclusively for use in this study.

Investigational Patient Programmer System Components (TH91 package kit includes: Model TM91 PTM and Model HH90 Patient Programmer Phone with Model A620 Patient Programmer Application installed)

The patient programmer system components utilized in the study will be investigational marked versions of the commercially available product. When the patient programmer system is paired with a

Percept PC with investigational aDBS enabled, the Model A620 Version 2.0 Patient Programmer Application will display investigational screens which are not seen in the commercially available product. These screens allow the subject to pause and resume Adaptive Therapy. The software version number (2.0) is the same for the commercial and investigational versions. A feature identifier will indicate if the aDBS feature is enabled or disabled (i.e. whether it can configure/modify aDBS).

The Model HH90 Patient Programmer Handset and the Model TM91 PTM are unchanged from the commercially available versions. Although only the Patient Programmer Application will be modified from the commercially available version by displaying investigational screens, all three components will be considered investigational as they are packaged together as a system.

The estimated number of Investigational Patient Programmer Systems to be used in the study is 70 patient systems, one for each patient that enters the aDBS Setup and Adjustment phase. These systems will be provided to the participating centers for distribution to patients exclusively for use in this study.

6.2. Manufacturer

Medtronic, Inc., 710 Medtronic Parkway, Minneapolis, MN 55432, USA, is the legal manufacturer of the Percept PC System for the ADAPT-PD Trial. Detailed manufacturing information for the investigational products used in this study is listed in Table 2 below.

Table 2: Manufacturing Information for Investigational Products

Facility	Responsibility
Medtronic Puerto Rico Operations Co., Juncos Road 31, Km. 24, Hm 4 Ceiba Norte Industrial Park Juncos, Puerto Rico 00777 Establishment Registration: #3004209178	Manufacturer for: • Model B35200 Percept PC INS
Medtronic Rice Creek Facility Medtronic Neuromodulation 7000 Central Ave NE Minneapolis, MN 55432 Establishment Registration #2182207	Product specification developer for: • Model A610 Clinician Programmer Application • Model 8880T2 Communicator • Model A620 Patient Programmer Application • Model TM91 Communicator
	Application of investigational labeling for: • Study Patient Programmer System • Study Clinician Programmer System

Plexus Manufacturing Sdn. Bhd. Bayan Lepas Free Industrial Zone, Phase II Bayan Lepas, Penang, Malaysia 11900 Establishment Registration #3004593495	Contract Manufacturer for: • Model 8880T2 Communicator
Jabil Circuit (Shanghai), LTD. 600 Tian Lin Road Shanghai, China 200233 Establishment Registration #3005210579	Contract Manufacturer for: • Printing the labeling for A620 PPA • Placing A620 PPA labeling inside the TM91 box • Manufacture the TM91 Communicator product
Medtronic Sofamor Danek USA, Inc Memphis Manufacturing 438 Swinnea Road Memphis, TN 38118 Establishment Registration #3003120897	Kit Assembler for: • Placing the TM91 box and the HH90 Handset box into the TH91 box • Print the TH91 label and place on the box

6.3. Packaging

The following investigational components (physical components of the Clinician Programmer System and Patient Programmer System) and their immediate package will be affixed with a sticker which contains a statement according to local requirements:

- Clinician Programmer System
  - Model CT900 Clinician Programmer Tablet
  - Model 8880T2 Communicator (also referred to as the Clinician Telemetry Module (CTM))
- Patient Programmer System
  - Model HH90 Patient Programmer Handset
  - Model TM91 Communicator (also referred to as the Patient Telemetry Module (PTM))
  - Model TH91 Package Kit that contains the above parts

The Percept PC Model B35200 Neurostimulator will not be physically labeled as an investigational device as the device will have been implanted as part of a commercially available DBS System.

In the US, the Medtronic investigational DBS System components listed above or their immediate package will be labeled with the following information according to 21CFR§812.5:

- Name and place of business of the manufacturer, packer or distributor
- The quantity of the contents, if appropriate
- The statement “CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use”
- A description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions will be provided in labeling under a separate cover.

In the EU and the UK, labeling for the investigational devices listed above will follow the applicable ISO14155:2020 and EU MDR 2017/745 requirements. This shall include a statement indicating the device is "exclusively for clinical investigation," and follow applicable local labeling language requirements in accordance with national regulations.

In Canada, following Medical Devices Regulations / SOR98-282, the Medtronic investigational devices listed above will be labeled with the following information:

- The name of the manufacturer
- The name of the device
- The statements "Investigational Device" and "Instrument de recherche", or any other statement, in English and French, that conveys that meaning
- The statements "To Be Used by Qualified Investigators Only" and "Réservé uniquement à l'usage de chercheurs compétents", or any other statement, in English and French, that conveys that meaning

Labeling for the investigational devices will be provided under a separate cover and will also be labeled with a statement according to local requirements.

Products used in this study that are commercially available are packaged and labeled accordingly consistent with local regulations. Labeling and patient material are provided in local language for CE marked devices.

6.4. Intended Population

The intended study population is subjects with idiopathic Parkinson's disease implanted with a 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.

6.5. Equipment

The Global Kinetics Corporation (GKC) PKG® or Personal KinetiGraph®(US) /Parkinson's Kinetigraph (EU) system will be used to provide a continuous, objective monitoring of key movement symptoms of Parkinson's disease, including bradykinesia, dyskinesia and tremor. The PKG system consists of a wrist-worn movement recording device known as the PKG Watch, proprietary algorithms and a data-driven report known as the PKG. GKC will provide a processed data file to Medtronic for analysis. GKC will be responsible for maintenance and calibration of the PKG Watch.

In Canada, the PKG system is considered investigational and will be used in the study under an Investigational Testing Authorization (ITA). Investigational product requirements in Sections 6.8-6.11 also apply to the PKG system.

6.6. Product Use

Commercially available products for the study will be used consistently with the Medtronic DBS Therapy for PD indication and the associated product labeling.

The Medtronic investigational product will be described in the Investigator's Brochure (IB), provided under separate cover. The investigator agrees not to use the investigational devices on any person except subjects enrolled in this study.

6.7. Product Training Requirements

Selected investigators will have experience with commercially available Medtronic DBS Therapy products. Investigators and delegated site staff will receive training on the use of the investigational products prior to enrollment of the site's first subject.

6.8. Product Receipt and Tracking

In order to allow shipment of non-implantable investigational product (Clinician Programmer System and Patient Programmer System) to a study center and for a study center to enable aDBS FW on a commercially available Percept PC INS, Medtronic must declare in writing that the study center is activated and ready to enroll subjects. The investigational product must only be used for the purpose of the ADAPT-PD Trial and in compliance to the clinical investigation plan.

Upon receipt of non-implantable investigational product (Clinician and Patient Programmer Systems), the principal investigator or designated individual, will visually inspect and notify Medtronic of any noted issues or discrepancies.

The investigational products listed in Table 1 above will be tracked using a product accountability log, with the exception of the TH91 package kit (box). Refer to Section 6.11: Product Accountability. Detailed instructions on the maintenance of records related to investigational product receipt and tracking will be provided under a separate cover.

6.9. Product Storage

Investigational products must be stored in a secured and locked location accessible only to those delegated individuals who are authorized by the principal investigator to access them. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study center.

6.10. Product Return

Medtronic investigational products must be returned to Medtronic when they are no longer in use, regardless of the reason for explant or removal from use. The PKG System must be returned to GKC at the end of the study.

Prior to the explant of the Percept PC neurostimulator, a device interrogation should be completed, if possible, and the device data submitted. The aDBS feature should be disabled prior to explant. Once disabled the device is no longer investigational.

Medtronic also requests the return of explanted devices from non-clinical sources such as funeral homes and will assume responsibility for storage and disposal of the product once received, if possible.

For explanted devices, Return Product kits or envelopes are available to send neurostimulators to Medtronic. These kits are sized to accommodate the devices from a single subject and are designed to meet postal regulations for mailing biohazardous materials.

Commercially available DBS System components will be returned, when possible, to Medtronic for analysis if opened and not successfully implanted or upon explant or when no longer in use, regardless of the reason for explant or removal from use.

At the end of the study, all unused investigational products provided for the study will be returned to Medtronic.

6.11. Product Accountability

The study center is responsible for maintaining tracking of the investigational devices listed in Table 1. Medtronic will provide an electronic accountability log. Non-implantable investigational product accountability begins at the point of distribution from Medtronic. Accountability for the investigational Percept PC INS begins at the time aDBS FW is enabled on the INS and ends when aDBS FW is turned off at subject withdrawal.

Each product will be identified using serial, lot, or part number and installed software/firmware version(s). A product accountability log must be updated at each investigational center when non-implantable investigational components are received, opened but not used, distributed to a subject, explanted, disposed of, or returned to Medtronic or when aDBS FW is enabled or turned off on the Percept PC INS. Products that are unused, expired or malfunctioning will also be tracked. A Medtronic monitor, or trained Medtronic staff, will review the product accountability log during monitoring or study visits. The product accountability log will indicate dates and the quantity and description, including serial, lot, or part number, installed software/firmware version(s) and expiration date (if applicable for non-implantable products), subject ID (if applicable), reason(s) for and method of destruction/disposal

for explanted components not returned to Medtronic (if applicable), and name of the person responsible for return or destruction/disposal (if applicable) of all investigational DBS System components on hand at any time during the study.

Medtronic will perform periodic reconciliation of the investigational product to ensure traceability.

7. Study Site Requirements

7.1. Investigator/Investigation Site Selection

All investigators managing the subject's Parkinson's disease must be qualified practitioners and experienced in the diagnosis and treatment of subjects with PD. All investigators must be experienced and trained in the use of DBS.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of Deep Brain Stimulation
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
    - Has the required number of eligible subjects needed within the recruitment period
    - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

7.2. 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. 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:

- IRB/EC approval (and voting list, as required by local law) of the current version of the CIP and Informed Consent (IC)
- Regulatory Approval (RA) or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure (if applicable)
- Current Curriculum Vitae (CV) of investigators and key members of the investigation study site team
- Documentation of delegated tasks
- Documentation of study training

Additional requirements imposed by local regulations, the IRB/EC and RA shall be followed, if appropriate.

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 principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

7.3. Role of the Sponsor Representatives

Sponsor representatives who are qualified and designated on the sponsor technical support list may participate in the conduct of the study under the direct supervision of the investigator as described below. The investigator or authorized study center personnel designated on the delegation of authority form (eg, programmer, neurologist) must be present to collect data, record the study activities, and to be responsive to the subject's needs during an activity performed by a Medtronic representative.

In addition to performing monitoring and auditing activities, Medtronic personnel may:

- Provide technical support during study visits under the supervision of a study investigator. This support may include technical assistance for products, systems, and programming, and the training of study center personnel on the use of Medtronic equipment or CIP-related procedures and other study activities
- Take responsibility for product transfer, but will not have direct access to the locked device storage area
- Clarify and troubleshoot device behavior, operation, or diagnostic output as requested by the investigator or other health care professional
- Privately discuss any issues with programming or subject compliance with the Principal Investigator or site personnel
- Observe study-related procedures to provide information relevant to study-required data collection
- Review collected data and study documentation for completeness and accuracy

- Perform device interrogation while under the direction of the investigator or study center personnel with delegated responsibility for device programming
- Facilitate device data transfer to Medtronic

Medtronic personnel **may not:**

- Practice medicine provide medical diagnoses or make decisions related to subject treatment/care
- Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted
- Discuss a subject's condition or medical treatment with the subject or a member of the subject's family
- Provide the subject with any form/questionnaires related to the product(s) used in this study
- Create source documentation on data collection and reporting tools (unless tools are explicitly created to be completed by sponsor staff and the sponsor staff is on the Technical Support List)

8. Selection of Subjects

8.1. Study Population

The intended Primary Cohort study population is subjects 18 years of age or older 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. In addition, subjects must be responsive to DBS Therapy, and have a Alpha - Beta band (8-30 Hz) amplitude ≥1.2 µVp detected on left and/or right DBS leads on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11.

The Directional Stimulation Cohort population is the same with the exception that subjects must be implanted with the SenSight system and using directional stimulation.

8.2. Subject Enrollment

Subjects are enrolled into the study at the time they sign and date a study-specific subject Informed Consent (IC). The date the subject signed the IC must be documented in the subject's medical records.

There are two sets of criteria for study participation prior to the investigational use of aDBS.

- Subjects must meet all general inclusion/exclusion criteria (as assessed at the Enrollment Visit)
- Subjects must meet the LFP screening inclusion criterion (as assessed at the LFP Screening Visit)

8.3. Inclusion Criteria

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

General (Primary Cohort):

1. Subject has idiopathic Parkinson's disease
2. Subject is implanted with Percept PC (Model B35200) and Medtronic DBS leads (Model 3387, 3389, B33005 or B33015) and extensions (Model 37085, 37086 or B34000) bilaterally in the same target (physician confirmed), STN or GPi
3. In the opinion of the investigator, the subject responds to DBS Therapy.
4. Based on the opinion of the investigator, the subject's cDBS parameters and PD medications are stable and expected to remain stable from enrollment through the end of the aDBS Evaluation phase
5. Subject is configured to ring mode monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side.
6. Subject is willing and able to attend all study-required visits and complete the study procedures (e.g. 1-month recall questionnaires, MDS-UPDRS III)
7. Subject has the ability to understand and provide written informed consent for participation in the study prior to the study-related procedures being conducted
8. Subject is a male or non-pregnant female. If female of child-bearing potential, and if sexually active, must be using, or agree to use, a medically acceptable method of birth control as confirmed by the investigator
9. For subjects with the SenSight system: Subject is configured to the following stimulation rates: 55, 85, 110, 125, 145, 164 or 180 Hz (as required for sensing/aDBS)

General (Directional Stimulation Cohort):

Subjects must meet the same inclusion criteria as the primary cohort except for revised #2 and #5.

Revised inclusion criteria:

2. Subject is implanted with Percept PC (Model B35200) and Medtronic DBS leads (Model B33005 or B33015) and extensions (Model B34000) bilaterally in the same target (physician confirmed), STN or GPi
5. Subject is configured to directional monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10)

LFP Screening:

1. Subject has Alpha - Beta band (8-30 Hz) amplitude ≥ 1.2 µVp 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

8.4. Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in the study:

General (Primary Cohort):

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. At enrollment, the subject's INS has a predicted battery life of <1 year
6. Subject has Beck Depression Inventory II (BDI-II) > 25
7. Subject requires diathermy, transcranial magnetic stimulation (TMS), or electroconvulsive therapy (ECT)
8. Subject has a metallic implant in the head, (eg, aneurysm clip, cochlear implant)
9. Subject has, or plans to obtain, an implanted electrical stimulation medical device anywhere in the body (eg, cardiac pacemaker, defibrillator, spinal cord stimulator)
10. Subject has, or plans to obtain, an implanted medication pump for the treatment of Parkinson's disease (eg, DUOPA™ infusion pump) and/or portable infusion pump
11. Based on the opinion of the investigator, the subject has an abnormal neurological examination that would preclude them from study participation
12. Subject is breast feeding
13. Subject is under the age of 18 years
14. 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 as determined by the Medtronic study team
15. Subject is unable to use or tolerate wearable
16. Subjects with signal artifact on all 6 aDBS sense pathways (3 each on both DBS leads) which preclude the clinician from setting thresholds

General (Directional Stimulation Cohort):

General exclusion criteria for the Directional Stimulation Cohort are the same as for the Primary Cohort.

9. Study Procedures

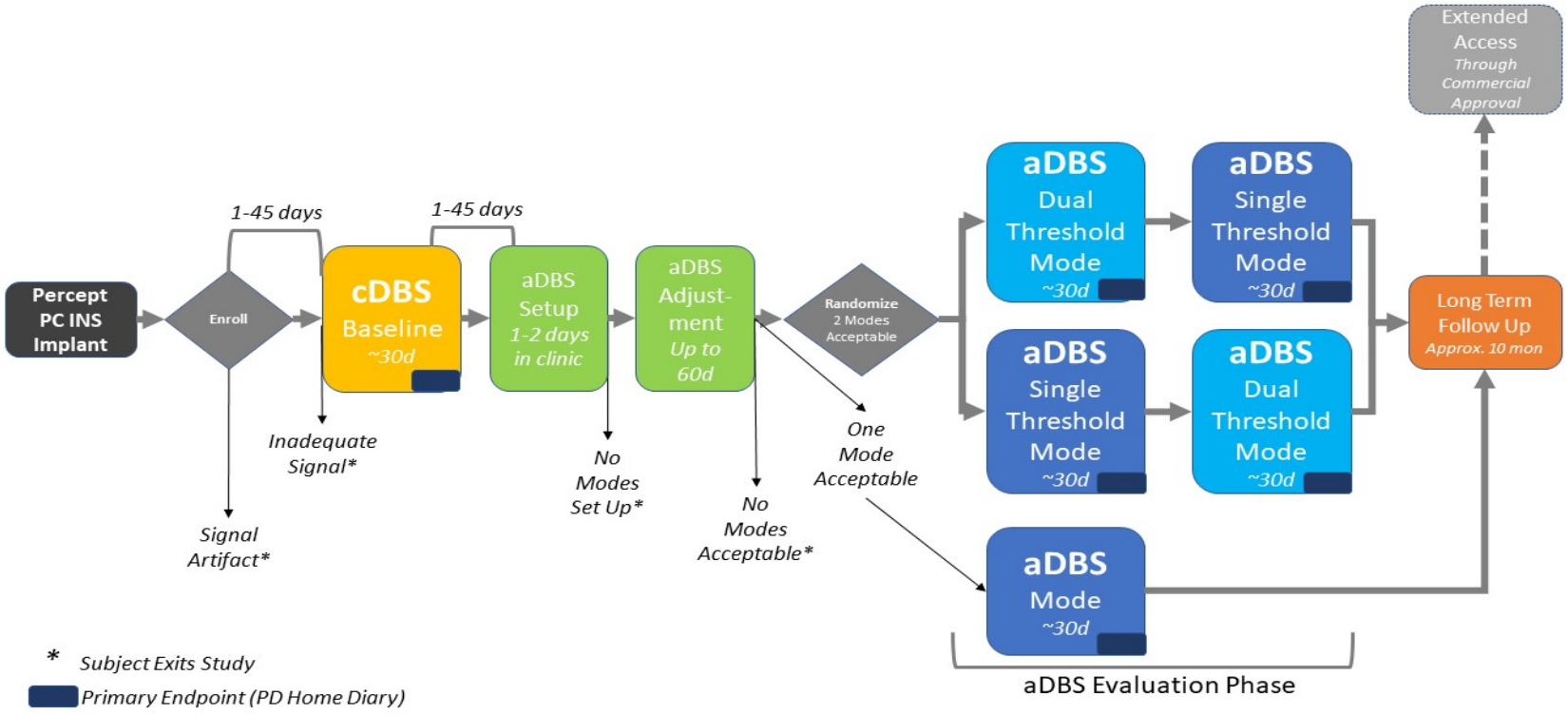
The study schedule, procedures, and methods of assessment are defined in detail to enable compliance with the required activities, and to ensure that the resulting data meet the criteria for evaluability Figure 4. Case report forms (CRFs) will be provided for use in collecting data for all subjects; the pertinent CRFs along with the applicable source documentation will be completed for each subject at the time of each

study visit. Subjects enrolled in the Directional Stimulation Cohort will follow the same study schedule, procedures and methods of assessment.

The start of the study is defined as the date the first subject signs the informed consent. The completion of the study is defined as the completion of the last required follow-up visit by the last subject.

9.1. Schedule of Events

Figure 4: Study Schematic



9.2. Data Collection

Data collection requirements are summarized in Table 3 below.

Table 3: Study Procedures and Data Collection by Visit

PHASE NAME		cDBS Baseline Phase		aDBS Setup and Adjustment Phase		aDBS Evaluation Phase		Long-term Follow-up Phase				Extended Access Phase			
VISIT NAME	Enrollment	LFP Screening	cDBS Baseline	aDBS Setup	Randomization	Visit 1	Visit 2*	Visit 3	Visit 4	Visit 5	Visit 6	Extended Access Visits	Subject Withdrawal / Discontinuation	Unsched. Visit	System Mod.
Informed Consent	X														
Demographics	X														
Medical & surgical history	X														
PD history	X														
C-SSRS (screening)	X														
BDI-II	X														
Pregnancy test	X														
Device information	X														X
Signal Test	X	X		X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PD medication at visit				X											
PD medication prior to visit		X		X											
PDQ-39			X			X	X	X	X	X	X	X			
EQ-5D-5L			X			X	X	X	X	X	X	X			
MDS-UPDRS IA			X			X	X								
MDS-UPDRS Patient Questionnaire (Part IB & II) *Worst condition*			X			X	X								

PHASE NAME		cDBS Baseline Phase		aDBS Setup and Adjustment Phase		aDBS Evaluation Phase		Long-term Follow-up Phase				Extended Access Phase			
VISIT NAME	**Enrollment**	**LFP Screening**	**cDBS Baseline**	**aDBS Setup**	**Randomization**	**Visit 1**	**Visit 2***	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Extended Access Visits**	**Subject Withdrawal / Discontinuation**	**Unsched. Visit**	**System Mod.**
MDS-UPDRS Patient Questionnaire (Part IB & II) *Best condition*			X			X	X								
MDS-UPDRS III *On stim (cDBS) / On med*			X												
MDS-UPDRS III *Off stim (cDBS) / Off med*		X													
MDS-UPDRS III *On stim (aDBS) / On med*						X	X								
MDS-UPDRS IV			X			X	X								
PD Home Diary			X			X	X								
C-SSRS (follow-up)						X	X								
VHI *Worst condition*			X			X	X								
VHI *Best condition*			X			X	X								
PDSS-2			X			X	X								
BrainSense setup		X		X											
aDBS programming				X										X**	
Physician programming survey				X**										X**	
Patient preference questionnaire						X	X								

PHASE NAME		cDBS Baseline Phase		aDBS Setup and Adjustment Phase		aDBS Evaluation Phase		Long-term Follow-up Phase				Extended Access Phase			
VISIT NAME	**Enrollment**	**LFP Screening**	**cDBS Baseline**	**aDBS Setup**	**Randomization**	**Visit 1**	**Visit 2***	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Extended Access Visits**	**Subject Withdrawal / Discontinuation**	**Unsched. Visit**	**System Mod.**
Patient satisfaction questionnaire											X		X***		
GIC					X										
Preferred aDBS mode							X								
Wearable data			X			X	X	X	X	X	X				
Event Markers with LFP capture**								X	X	X	X				
Programming session upload via CDU	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X****
AEs	As they occur														
Device deficiencies	As they occur														
Protocol Deviations	As they occur														
Reason for exit													X		

* If two aDBS modes are set up

** Optional

*** If early discontinuation following aDBS Evaluation Phase

**** If INS is modified

9.3. Scheduled Follow-up Visit Windows

Data analyses include follow-up 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. Follow-up visit windows are listed in Table 4. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Table 4: Visit Windows

Visit	Visit ranges
LFP Screening	1-45 days after enrollment
cDBS Baseline	30-45 days after LFP Screening
aDBS Setup	1-45 days after Baseline
aDBS Adjustment	0-60 days after aDBS setup complete
Randomization / Day 0	No greater than 60 days after aDBS setup complete
aDBS Evaluation Visit 1	30-45 days after Day 0
aDBS Evaluation Visit 2*	30-45 days after Evaluation visit 1
Visit 3	45-60 days after Evaluation Visit 2 (or Evaluation Visit 1 if the subject is only configured to one aDBS mode)
Visit 4	45-60 days after Visit 3
Visit 5	90 +/- 14 days after Visit 4
Visit 6	90 +/- 14 days after Visit 5
Extended Access Visits	Every 180 +/- 60 days beginning after Visit 6 and every 6 months thereafter following the previous extended access visit

* If two aDBS modes are set up

9.4. Subject Screening

Subjects may be recruited through the investigator's practice, referring physicians, and/or the use of recruitment tools approved by the reviewing IRB/EC. Potential subjects may be identified through a study center database query (e.g. chart reviews) or as new or existing patients attend clinic visits.

The investigator, or authorized center personnel, will screen potential subjects by reviewing the study's inclusion/exclusion criteria. A screening log will be provided for use in tracking potential subjects. All subjects that are considered for the study must be included on the study screening log. The reason for

non-eligibility, as determined by the Investigator must also be recorded on the study pre-screening log. The screening log serves as a method for Medtronic to assess selection bias in the trial.

If a subject fails the inclusion/exclusion criteria, and is discontinued from the study, and it is the investigator's medical judgment that re-screening may be appropriate at a later date during the study, the investigator may contact the Medtronic study team to request approval to re-screen the subject prior to proceeding. Approval will be provided in writing by Medtronic for subjects who are permitted to repeat the screening process.

9.5. Prior and Concomitant Medications

All concomitant medications, except for over-the-counter medications and herbal supplements, will be collected for this study. All Parkinson's disease medications will be collected for this study. Subjects' Parkinson's disease medication must be stable at the time of enrollment in the trial through the end of the aDBS Evaluation Phase. During this time, the investigator should make only clinically necessary changes to PD medication.

There are no medication restrictions in the study unless they are investigational and may confound the study results, in which case, prior approval would be needed from Medtronic.

Parkinson's disease medications will be held prior to the LFP Screening and aDBS Setup visits. See Table 5: PD Medication Off/On Definitions.

9.6. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's IRB/EC and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the site IC and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be approved by the IRB/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 IRB/EC. Any adaptation of the sample IC must be reviewed and

approved by Medtronic and the IRB/EC reviewing the application prior to enrolling subjects or if the IC is updated at any time during the study.

The 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.

Templates for the study-specific subject IC and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language for this study are provided by Medtronic under a separate cover.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the IC Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law 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 investigator or other study site personnel. 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.

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.

When the subject decides to participate in the study, the IC must be signed and personally dated by the subject and investigator or authorized designee, as required by the IC, and ensured by the principal investigator or his/her authorized designee.

A copy of the IC and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, 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.

In the event the subject or legally designated representative cannot read, the IC process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The IC and any other information must be read aloud to the prospective subject or his/her legally designated representative. Whenever possible, either the subject or his/her legally designated representative shall sign and personally date the informed consent form. The witness signs and personally dates the IC attesting that the information was accurately explained and that informed consent was freely given.

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

The IC and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the study procedures must be able to review the subject's signed and dated IC and verify its completeness prior to proceeding with the aDBS setup. In the event the Medtronic Field personnel identify IC as being incomplete, the aDBS setup will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Consistent with the DoH, vulnerable adults (i.e. those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g. Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. This protocol defines vulnerable adult as those subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response." For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving IC. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

In some countries, patients must specifically opt-in for data use for other purposes than the study objectives. In those countries, patients will have the option to indicate that in the consent (e.g., via a checkbox or via a separate signature).

9.7. Enrollment and Screening Phase

This phase begins at consent and includes an Enrollment visit and an LFP Screening visit.

9.7.1. Enrollment

Subjects who have a complete Medtronic DBS system, including Percept PC, leads and extensions and whose cDBS parameters and PD medications are stable may be approached to participate in the study. From enrollment to the end of the aDBS Evaluation Period, the investigator should make only clinically necessary changes to cDBS settings.

A subject is considered enrolled when the consent process has been fully executed. The date the subject signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study will be maintained. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

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

The subject will arrive for the visit with PD medications and cDBS according to the center's standard procedures. After consent, the clinician will perform a Signal Test, using a commercially available Clinician Programmer System, to ensure the subject has adequate signal quality. The clinician should ensure the subject movement is minimized during this test.

If signal artifact is detected on all six aDBS sense pathways (3 each on both DBS leads), the Signal Test may be repeated. If signal artifact is persistent on all six aDBS sense pathways, the clinician should determine whether this precludes them from setting thresholds. If not, the subject can continue in the study. If the subject will not continue, device identification information will be collected, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU, and an AE and device deficiency assessment will be performed. The subject will then be discontinued from the study, and no further study-related procedures will be completed.

Following the Signal Test, data will be collected and assessments administered. The following data will be collected at enrollment:

- Demographics
- Medical & surgical history

- PD history
- Concomitant medications
- Columbia Suicide Severity Rating Scale (C-SSRS) (screening)
- Beck Depression Inventory II (BDI-II)
- Pregnancy test (for female subjects of child-bearing potential)
- Device identification information, including historical DBS implant information
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report
- AE and device deficiency assessment

The clinician 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 will be updated.

The subject will be instructed on the use of the PD Home Diary. For at least 3 consecutive days in the 14 days prior to the cDBS Baseline and aDBS Evaluation visits, the subject will record, in 30-minute intervals, whether they were Asleep, "Off," "On" without dyskinesia, "On" with non-troublesome dyskinesia, or "On" with troublesome dyskinesia. The subject will also be instructed on the use of the PKG Watch.

The subject will leave the visit on their current cDBS settings (including BrainSense settings).

9.8. cDBS Baseline Phase

This phase begins when the enrollment visit is complete and includes an LFP screening visit, cDBS Baseline period and cDBS Baseline visit.

9.8.1. LFP Screening Visit

1-45 days after Enrollment

The subject will arrive for the visit off PD medication and on cDBS. Confirm the subject's PD medication was appropriately withheld as specified in Table 5. If the subject's PD medications were not appropriately withheld, consider rescheduling the study visit.

Table 5: PD Medication Off/On Definitions

Term	Definition
Off PD Medication	Subject stops taking PD medication(s) for the following time periods prior to a study visit: • 72 hours extended-release forms of dopamine agonists • 24 hours regular form of dopamine agonists, controlled release forms of carbidopa/levodopa

	• 12 hours regular carbidopa/levodopa, entacapone, rasagiline, selegiline, amantadine
On PD Medication	Optimal motor response to PD medication ("best" On). The clinical symptoms should be stable for at least 10 minutes and both, patient and investigator should agree that the best On of the patient has been reached.
Current PD Medication(s)	Medication the subject is taking for treatment of PD on the day prior to initiating the hold requirements for the Off medication state

Data will be collected, including the following:

- MDS-UPDRS III (Off stim/Off med)
- BrainSense setup and Signal test
- Concomitant medications
- Time of last dose of PD medications taken prior to the visit
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

At the start of the visit, the clinician will turn off the subject's cDBS for approximately 15 minutes. Following this DBS washout, the trained rater will conduct the MDS-UPDRS III Off med/Off stim assessment.

Next, the clinician should follow the BrainSense setup workflow and perform a Signal Test, using the commercially available Clinician Programmer System, to assess LFP the screening inclusion criterion. The subject must have Alpha - Beta band amplitude ≥ 1.2 µVp detected on at least one (left or right) DBS lead on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11.

If the subject does not meet all of the LFP screening inclusion criteria and/or meets the LFP screening exclusion criterion, they will be exited from the study following the process in Section 9.19, including a programming session upload to Medtronic via CDU. No further study-related procedures will be completed, and subjects will be followed according to the center's standard procedures.

At the end of the visit, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU. The subject may resume taking their normal PD medication.

The subject will be reminded of the use of the PD Home Diary and the use of the PKG Watch.

The subject will leave the visit on their current cDBS settings with BrainSense set to Passive Sensing Only in all groups where BrainSense setup was utilized.

9.8.2. cDBS Baseline Period

The subject will remain on cDBS with BrainSense set to Passive Sensing Only for the duration of the period.

Prior to the scheduled cDBS Baseline visit, the PKG Watch will be given to the subject or mailed to the subject's home. Upon receipt, the subject will put on and activate the PKG Watch. The PKG Watch will be worn on the most affected side for at least 6 consecutive days in the 14 days prior to the scheduled cDBS Baseline visit. After the recording, the subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at the visit.

The PD Home Diary will also be provided to the subject in advance of the visit and will be completed for at least 3 consecutive days in the 14 days prior to the scheduled cDBS Baseline visit. If possible, the PD Home Diary will be completed at the same time as the PKG Watch is worn.

Some assessments may be completed prior to each scheduled visit. See Section 9.15 for detailed information about the administration of each assessment.

Subjects should be contacted prior to the cDBS Baseline Visit to remind them to complete the required between-visit activities (PKG Watch, PD Home Diary and assessments (if applicable)).

9.8.3. cDBS Baseline Visit

30-45 days after LFP screening

Baseline data will be collected, including the following:

- PDQ-39
- EQ-5D-5L
- VHI (worst condition)
- VHI (best condition)
- Parkinson's Disease Sleep Scale (PDSS-2)
- MDS-UPDRS I (Part A) – trained rater
- MDS-UPDRS Patient Questionnaire (Part IB and II) (best condition)
- MDS-UPDRS Patient Questionnaire (Part IB and II) (worst condition)
- MDS-UPDRS III (On stim (cDBS)/On med) – trained rater
- MDS-UPDRS IV – trained rater
- Collect PD Home Diary and review for completeness
- Concomitant medications
- Collect PKG Watch or confirm it was returned
- AE and device deficiency assessment
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report

Following cDBS baseline data collection, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.

9.9. aDBS Setup and Adjustment Phase

This phase consists of an aDBS Setup Visit and an optional aDBS Adjustment period and ends with randomization. Subjects will be blinded to the aDBS mode during the aDBS Setup and Adjustment Phase. If the blind is broken, document the reasons for unblinding in the subject's source documentation and report as a deviation.

9.9.1. aDBS Setup Visit

1-45 days after cDBS Baseline visit

The aDBS Setup visit may be conducted in one day or may occur over two days, with the final day being no more than 45 days following the cDBS Baseline visit. The aDBS Setup visit should be conducted on sequential days, but when non-sequential days are scheduled there must be no more than 14 days between the visit days.

The subject will arrive for the visit off PD medication and on cDBS. Confirm the subject's PD medication was appropriately withheld as specified in Table 5. If the subject's PD medications were not appropriately withheld, consider rescheduling the study visit.

Data will be collected, including the following:

- Concomitant medications
- Time of last dose of PD medications taken prior to the visit
- PD medication dose given at the visit (if applicable)
- Adverse Event and device deficiency assessment

The clinician should follow the BrainSense setup workflow using the investigational Clinician Programmer System. The subject must have Alpha - Beta band amplitude ≥ 1.2 µVp detected on at least one (left or right) DBS lead on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11.

Utilizing Signal Test, if the subject no longer meets the LFP screening inclusion criterion, it is allowable to re-assess LFP inclusion criterion, at the investigator's discretion, at the start of the first day of aDBS Setup Visit. If the subject does not meet the inclusion criterion, they will be exited from the study following the process in Section 9.19, including uploading the programming session, with BrainSense data included in the JSON session data report, to Medtronic via CDU. No further study-related procedures will be completed, and subjects will be followed according to the center's standard procedures.

The clinician will set up both aDBS Dual and Single Threshold Modes while the subject is Off PD medication. As part of the Off PD medication aDBS setup, the clinician configures the stimulation

amplitude which is automatically adjusted based on the changes to sensed brain signals. Streaming transition schemes and wrist flexion tasks may be utilized as assessments for each mode. Following the Off PD medication aDBS setup, the clinician will assess the programmed aDBS settings (both Dual and Single Threshold Modes) while the subject is On PD medication.

In cases where only one hemisphere has LFP Alpha - Beta signal which meets the inclusion criterion, the following configurations will be used to set up aDBS.

Dual Threshold (DT) Mode:

If only one hemisphere has LFP Alpha - Beta signal >=1.2µVp when setting up the Dual Threshold mode, the clinician should configure adaptive therapy in both hemispheres, using sensing from the hemisphere with LFP Alpha - Beta signal >=1.2µVp.

For example, when utilizing BrainSense Setup, if the Left hemisphere has LFP Alpha - Beta signal >=1.2µVp, and the Right hemisphere does not, then proceed with the following:

- Set up Dual Threshold mode in the Left hemisphere with the sensing electrode configuration that has met the LFP Alpha - Beta signal inclusion criterion (Preferably the active cDBS card).
- In the Right hemisphere, at Signal Test, select Left STN/GPi as the sensing configuration.
- Note: the stimulation electrode(s) or cathode(s) in the Right hemisphere is not constrained to a sensing configuration.

Single Threshold (ST) Mode:

If only one hemisphere has LFP Alpha - Beta signal >=1.2µVp when setting up Single Threshold mode, the clinician should configure adaptive therapy in only that hemisphere with LFP Alpha - Beta signal >=1.2µVp.

- cDBS should be setup in the hemisphere with LFP Alpha - Beta signal <1.2uVp (set to Passive Sensing, if possible).
- Note: that the stimulation electrode(s) or cathode(s) in the hemisphere set to cDBS is not constrained to a sensing configuration.

If one aDBS mode cannot be set up, the subject should continue with the study using only the mode that can be set up and the subject will not be randomized.

If neither aDBS mode can be set up, the subject will be exited from the study following the process in Section 9.19, including uploading the programming session, with BrainSense data included in the JSON session data report, to Medtronic via CDU. No further study-related procedures will be completed, and subjects will be followed according to the center's standard procedures.

Following each aDBS setup visit day, the programming sessions, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.

Once aDBS is set up, and prior to the subject leaving the study center On aDBS, the subject's commercially available Patient Programmer System will be replaced with an investigational-marked Patient Programmer System, and the subject will be given the investigational patient labeling. The

clinician or appropriately delegated study personnel will assist the subject to pair the investigational Patient Programmer System with the INS.

Subjects will be instructed on how to pause aDBS any time they feel like the therapy is not working for them by selecting Pause Adaptive Therapy. This Pause Adaptive Therapy (amplitude last delivered in that group prior to starting aDBS therapy (i.e. the suspend amplitude)) is defined by the clinician as part of the aDBS setup process, following the streaming transition schemes testing and prior to starting adaptive therapy. Subjects will notify the investigator when they pause aDBS to assess the scenario and need for any adjustments.

If the visit occurs over 2 days, the clinician may program the subject to one aDBS mode between visit day 1 and visit day 2.

At the end of the aDBS Setup Visit, the subject may resume taking their normal PD medication. The physician may also be surveyed to understand rationale for programming settings. The investigator may determine that additional aDBS programming adjustments are needed for one or both of the aDBS modes, or the subject may proceed directly to randomization, or. If additional adjustment is planned for only one aDBS mode, the investigator will send the subject home in that mode for as much time as needed within the aDBS Adjustment Period. If additional adjustment is planned for both aDBS modes, the investigator will send the subject home in one of the aDBS modes to start the aDBS Adjustment Period. The investigator and subject will determine how and when to adjust the other aDBS mode within the aDBS Adjustment Period (if applicable). Event markers may be set up to further capture information about the patient's out of clinic experience with aDBS.

Every attempt will be made to blind the subject to the aDBS mode being adjusted. The clinician should set on the investigational Clinician Programmer the group names of the aDBS modes being adjusted in a manner which will not unblind the subject. For example, "aDBS 1" and "aDBS 2" or "aDBS" and "Do not use." These group names will be displayed on the investigational Patient Programmer.

9.9.2. aDBS Adjustment Period (optional)

0-60 days after aDBS setup complete

Additional visits for the clinician to adjust settings for one or both aDBS modes may be conducted as needed for up to 60 days following the final aDBS setup visit to ensure the aDBS mode(s) will be acceptable to the subject. These visits will be completed either at the study center, by telephone or telehealth/video consult. The subject will remain blinded to the programmed aDBS mode. Any aDBS adjustment visit will be recorded as an unscheduled visit (see Section9.13). The physician may also be surveyed to understand rationale for programming settings.

If programming sessions or device interrogations occur, these sessions with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.

9.9.3. Randomization

Day 0 (no greater than 60 days after aDBS setup complete)

Randomization may occur at the aDBS setup visit, at an unscheduled visit during the aDBS Adjustment Period, or as a standalone visit. All subjects for whom aDBS was set up will complete this visit.

The investigator will assess each aDBS mode that was set up utilizing the aDBS Global Impression of Change (GIC) provided in Appendix A - aDBS Global Impression of Change Score (GIC). Efficacy and side effects are assessed on a scale from 1 to 21. The lower the score the better the efficacy and the less side effects. A score of 8 or less indicates the aDBS mode is acceptable. The investigator will also ensure that the subject is comfortable remaining in the aDBS mode(s) for the duration of the trial.

If only one aDBS mode was set up for a subject, they will not be randomized, but the physician should still complete the aDBS GIC and data collection for the visit.

Data will be collected, including the following:

- Concomitant medications
- GIC value for each aDBS mode that was set up
- Adverse Event and device deficiency assessment

For subjects in whom both aDBS modes are acceptable as compared to cDBS (using the aDBS GIC), unblinded site personnel will obtain the randomization assignment via Remote Data Capture (RDC). The randomization assignment can be obtained upon completion of the aDBS GIC and randomization CRFs.

Randomization will occur to one of two possible treatment sequences if both aDBS modes are acceptable as compared to cDBS (using the aDBS GIC) (dual threshold mode followed by single threshold mode or vice versa) and will be stratified by target site location (STN/GPi). The two sequences will be randomly permuted in blocks of two and four. If an aDBS mode is unacceptable as compared to cDBS (using the aDBS GIC), that subject will be assigned the mode which was acceptable. The randomization schedule will be prepared by Medtronic and it will be maintained at Medtronic. Subjects will continue to be blinded to the aDBS mode during the aDBS Evaluation Phase. If the blind is broken, document the reasons for unblinding in the subject's source documentation and report as a deviation.

Following randomization, the clinician will program one group to the randomized aDBS mode.

Subjects for whom one aDBS mode is unacceptable as compared to cDBS (using the aDBS GIC) or for whom only one mode could be acceptably configured will not be randomized and will complete one aDBS evaluation visit in the aDBS mode that was acceptable to the subject.

In order to blind the subject to the aDBS mode assigned, the clinician will set the group name of the aDBS mode being evaluated during each period to "aDBS," and the group name of the mode not being evaluated to "Do not use" on the Clinician Programmer. These group names will be displayed on the Patient Programmer.

If neither aDBS mode is acceptable to the subject, the subject will be exited from the study following the process in Section 9.19. No further study-related procedures will be completed, and the subject will be followed according to the center's standard procedures.

If randomization is conducted as a separate visit, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.

The subject will be instructed on the use of the PKG Watch and PD Home Diary in the aDBS Evaluation Phase.

9.10. aDBS Evaluation Phase

This phase consists of up to two treatment periods; one per acceptable aDBS mode. After each treatment period, there is an aDBS evaluation visit. The subject's PD medications will remain stable from enrollment through the end of the aDBS Evaluation Phase, unless changes are clinically necessary.

During the aDBS Evaluation Phase, the subject may return to the study center for further aDBS adjustment in each randomized aDBS mode. All adjustments must be completed at least 14 days prior to the evaluation visit for that mode. Any adjustments will be recorded as unscheduled visits. Any adjustments during the 14 days prior to the evaluation visit will be considered a protocol deviation.

Prior to each scheduled aDBS Evaluation visit, the PKG Watch will be given to the subject or mailed to the subject's home. Upon receipt, the subject will put on and activate the PKG Watch. The PKG Watch will be worn on the most affected side for at least 6 consecutive days. After the recording, the subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at the visit. The subject will also be provided with the PD Home Diary in advance of the visit and will complete it for at least 3 consecutive days in the 14 days prior to each scheduled aDBS Evaluation Visit. If possible, the PD Home Diary will be completed at the same time as the PKG Watch is worn.

Some assessments may be completed prior to each scheduled visit. See Section 9.15 for detailed information about the administration of each assessment.

Subjects should be contacted prior to each aDBS Evaluation Visit to remind them to complete the required between-visit activities (PKG Watch, PD Home Diary and assessments (if applicable)).

9.10.1. Evaluation Visit 1

30-45 days after randomization

The subject will arrive for the visit on their normal PD medications and on aDBS.

The clinician will confirm the subject is in the assigned mode for the visit. If the subject is not in aDBS, the clinician will program the subject to the assigned aDBS mode and all On stim assessments will be

performed in the assigned mode. If the subject completed the evaluation period in the incorrect aDBS mode, all On stim assessments will be performed in the incorrect aDBS mode.

The following data will be collected:

- PDQ-39
- EQ-5D-5L
- C-SSRS
- MDS-UPDRS I (Part A) – trained rater
- MDS-UPDRS Patient Questionnaire (Part IB and II) (best condition)
- MDS-UPDRS Patient Questionnaire (Part IB and II) (worst condition)
- MDS-UPDRS III (On stim (aDBS)/On med) – trained rater
- MDS-UPDRS IV – trained rater
- VHI (worst condition)
- VHI (best condition)
- PDSS-2
- Patient preference questionnaire
- Collect PD Home Diary and review for completeness
- Concomitant medications
- Collect PKG Watch or confirm it was returned via mail
- Adverse Event and device deficiency assessment

At the end of the visit, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.
Next, the clinician will program the subject to the other assigned aDBS mode and label that group "aDBS." The group for the aDBS mode the subject just completed evaluation of will be re-labeled "Do not use" on the Patient Programmer.

The subject should be reminded that they will receive the PKG Watch prior to the aDBS Evaluation Visit 2 and will put on and activate the PKG Watch upon receipt. The subject will wear the PKG Watch for at least 6 consecutive days in the 14 days prior to the scheduled aDBS Evaluation Visit 2. After the recording, the subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at the visit. The subject will also be reminded that they will be provided with the PD Home Diary in advance of the visit and will complete it for at least 3 consecutive days in the 14 days prior to the next aDBS Evaluation Visit.

If only one aDBS mode is being evaluated, the subject will continue into the Long-term Follow-up phase and skip aDBS Evaluation Visit 2.

9.10.2. Evaluation Visit 2

If two aDBS modes are being assessed

30-45 days after Evaluation visit 1

The subject will arrive for the visit on their normal PD medications and on aDBS.

The clinician will confirm the subject is in the assigned mode for this visit. If the subject is not in aDBS, the clinician will program the subject to the assigned aDBS mode and all On stim assessments will be performed in the assigned mode. If the subject completed the evaluation period in the incorrect aDBS mode, all On stim assessments will be performed in the incorrect aDBS mode.

The following data will be collected:

- PDQ-39
- EQ-5D-5L
- C-SSRS
- MDS-UPDRS I (Part A) – trained rater
- MDS-UPDRS Patient Questionnaire (Part IB and II) (best condition)
- MDS-UPDRS Patient Questionnaire (Part IB and II) (worst condition)
- MDS-UPDRS III (On stim (aDBS)/On med) – trained rater
- MDS-UPDRS IV – trained rater
- VHI (worst condition)
- VHI (best condition)
- PDSS-2
- Patient preference questionnaire
- Collect PD Home Diary and review for completeness
- Concomitant medications
- Patient and physician preferred aDBS mode and reason for selecting preferred mode (at end of visit)
- Collect PKG Watch or confirm it was returned via mail
- Adverse Event and device deficiency assessment

At the end of the visit, the programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU.

Following the final aDBS visit, the clinician will program the subject to the chosen DBS mode (clinician & patient preference) for the long-term follow-up phase and record the reason for selecting that mode.

If the chosen DBS mode is cDBS, the subject will be exited from the study following the process in Section 9.19. No further study-related procedures will be completed, and the subject will be followed according to the center's standard procedures.

The subject should be reminded that they will receive the PKG Watch prior to the next visit and will put on and activate the PKG Watch upon receipt. The subject will wear the PKG Watch on the most affected side for at least 6 consecutive days in the 14 days prior to the scheduled visit.

9.11. Long-term Follow-up Phase

Once subjects complete the aDBS Evaluation Phase (one or two evaluation visits), they enter a Long-term Follow-up Phase. During this Phase, the investigator may choose to switch aDBS modes as needed, so long as the subject received both modes during the aDBS Evaluation Phase. Any changes to the aDBS mode must be done at a study visit, either scheduled or unscheduled.

Prior to each scheduled long-term follow-up visit (visit #3 through #6 inclusive), the PKG Watch will be given to the subject or mailed to the subject's home. Upon receipt, the subject will put on and activate the PKG Watch. The PKG Watch will be worn on the most affected side for at least 6 consecutive days in the 14 days prior to each visit. After the recording, the subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at the visit.

The PDQ-39 and EQ-5D-5L may be completed prior to each scheduled visit. See Section 9.15 for detailed information about the administration of each assessment.

In the Long-term Follow-up Phase, subjects may choose to participate in optional data collection of Events with LFP capture (snapshots). The clinician may set up a maximum of 4 event types, selected from the following options: *dyskinesia, tremor, rigidity, freezing, sleep disturbance, took PD medication.* Study personnel will instruct the subject on how to record each event type utilizing the Patient Programmer System.

9.11.1. Visit 3

45-60 days after Evaluation Visit 2 (or Evaluation Visit 1 if the subject is only configured to one aDBS mode)

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

Data collection:

- Concomitant medications
- PDQ-39
- EQ-5D-5L
- Collect PKG Watch or confirm it was returned via mail
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

The subject should be reminded that they will receive the PKG Watch prior to the next visit and will put on and activate the PKG Watch upon receipt. The subject will wear the PKG Watch on the most affected side for at least 6 consecutive days in the 14 days prior to the scheduled visit. The subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at Visit 4.

9.11.2. Visit 4

45-60 days after Visit 3

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

Data collection:

- Concomitant medications
- PDQ-39
- EQ-5D-5L
- Collect PKG Watch or confirm it was returned via mail
- Programming session upload to Medtronic, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

The subject should be reminded that they will receive the PKG Watch prior to the next visit and will put on and activate the device upon receipt. The subject will wear the PKG Watch on the most affected side for at least 6 consecutive days in the 14 days prior to the scheduled visit. The subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at Visit 5.

9.11.3. Visit 5

90 +/- 14 days after Visit 4

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

Data collection:

- Concomitant medications
- PDQ-39
- EQ-5D-5L
- Collect PKG Watch or confirm it was returned via mail
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

The subject should be reminded that they will receive the PKG Watch prior to the next visit and will put on and activate the device upon receipt. The subject will wear the PKG Watch on the most affected side for at least 6 consecutive days in the 14 days prior to the scheduled visit. The subject will return the PKG Watch in the pre-paid mailer or bring it to the site for return at Visit 6.

9.11.4. Visit 6

90 +/- 14 days after Visit 5

Data collection:

- Concomitant medications

- PDQ-39
- EQ-5D-5L
- Patient satisfaction questionnaire
- Collect PKG Watch or confirm it was returned via mail
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

At the completion of this visit, if aDBS is not commercially approved, the subject may choose to continue participation in the study as described in Section 9.12. If the subject chooses to exit the study after this visit and before aDBS is commercially approved, aDBS will be turned off as directed in Section 9.19.

9.12. Extended Access Phase

Following the final long-term follow-up visit (Visit 6), subjects will be allowed extended access to aDBS through aDBS is commercially approved in the geography in which the subject is enrolled. The subject will continue the study in aDBS and return for a visit every 6 months or until aDBS is commercially approved or closure of the study, whichever comes sooner.

9.12.1. Extended Access Visits

Every 180 +/- 60 days beginning after Visit 6 and every 6 months thereafter following the previous extended access visit

Data collection:

- Concomitant medications
- PDQ-39
- EQ-5D-5L
- Programming session upload to Medtronic, with BrainSense data included in the JSON session data report
- Adverse Event and device deficiency assessment

9.13. Unscheduled Visit

Any time the subject has a visit (in person, by telephone and/or telehealth/video consult) for aDBS programming adjustment/optimization (including resuming aDBS if it was unintentionally turned off) or for an Adverse Event, the following data will be collected:

- Reason for the visit
- Concomitant medications
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report (if applicable)
- Adverse Event and device deficiency assessment

9.14. System Modification

System modifications made to the DBS System will be completed according to the center's standard procedures. If the system modification occurs prior to randomization, the subject should be exited, prior to receiving the system modification if possible, and considered for re-enrollment as applicable. If the system modification occurs after randomization, the investigator should assess if the subject should be exited from the study or proceed to the long term follow up phase on aDBS. The subject will not complete or repeat the aDBS evaluation period(s). If the subject proceeds to the long term follow up phase, aDBS will be programmed after (s)he is healed and stable on cDBS. aDBS can be programmed by either performing the full aDBS setup or by using the subject's prior aDBS parameters and assessing for acceptability. Any visits for aDBS setup due to a system modification will be recorded as unscheduled visits. Once aDBS is set up, the subject will enter the long-term follow-up. If aDBS cannot be acceptably set up, the subject will be exited from the study following the process in Section 9.19.

Data collection:

- Device information (if applicable)
- Concomitant medications
- Programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report (if INS is being modified)
- Adverse Event and Device deficiency assessment

9.15. Assessment of Efficacy and Device Performance

9.15.1. Parkinson's Disease (PD) Home Diary

The Parkinson's Disease Home Diary (Copyright © The University of South Florida, 2000. All rights reserved) is a standard home diary to assess functional status in patients with PD. In 30-minute intervals, patients record whether they were in the "On" condition, with or without dyskinesia, "Off" condition, or asleep.[a] In the On condition with dyskinesia, patients record whether they were On with troublesome or non-troublesome dyskinesia. For the purposes of the PD home diary, at least 3 consecutive days means at least 3 consecutive 24-hour periods.

[a] Hauser, et al. "A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia." Clinical Neuropharmacology. 2000 Mar-Apr;23(2):75-81.

9.15.2. Total Electrical Energy Delivered (TEED)

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:

$$TEED = (Voltage^2 * Frequency * Pulse\ width) / Impedance$$ [b]

The calculation of TEED when using constant current is:

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

9.15.3. Wearable Data

Wearable data will be collected via the PKG Watch as a continuous measure of bradykinesia score (BKS), dyskinesia score (DKS) and the % of wear time with Tremor. A Fluctuation and Dyskinesia score (FDS) will also be derived from the wearable data.

9.15.4. European Quality of Life – 5 Dimensions (EQ-5D-5L)

The European Quality of Life – 5 Dimensions, version 5L (EQ-5D-5L), is a standardized measure of health status developed by the EuroQol Group and a widely used validated tool to determine health-related quality of life.[c] The EQ-5D descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems, extreme problems. The subject will be asked to indicate his/her health state by selecting the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined into a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. In a second step, the responses to the five EQ-5D dimensions (i.e. an EQ-5D health state or profile) will be converted into a single number called an index value using the United Kingdom value

[b] Koss AM, et al. "Calculating Total Electrical Energy Delivered by Deep Brain Stimulation Systems." Annals of Neurology. Vol 58. No 1. July 2005. P. 168-169.
[c] The EuroQol Research Foundation. "EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument." https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

set. The index value reflects how good or bad the health state is according to the preferences of the general population of a country/region.

This assessment may be completed either in person, or over the telephone a maximum of 7 days prior to the study visit.

9.15.5. Parkinson's Disease Questionnaire (PDQ-39)

The Parkinson's Disease Questionnaire is a self-completion Patient Reported Outcome (PRO) designed to address aspects of functioning and well-being for those affected by Parkinson's disease.[d] There are 39 questions in the long form Parkinson's Disease Questionnaire, with 8 discrete scales:

- mobility (10 items)
- activities of daily living (6 items)
- emotional well-being (6 items)
- stigma (4 items)
- social support (3 items)
- cognitions (4 items)
- communication (3 items)
- bodily discomfort (3 items)

Patients are asked to think about their health and general well-being and to consider how often in the last month they have experienced certain events (e.g. difficulty walking 100 yards). Patients are asked to indicate the frequency of each event by selecting one of 5 options (Likert Scale): never/occasionally/sometimes/often/always or cannot do at all.

This assessment may be completed either in person, or a copy may be sent to the subject to be completed a maximum of 7 days prior to the study visit.

9.15.6. Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a MDS-sponsored revision of the UPDRS clinical rating scale for Parkinson's disease. It has been the most widely used scale to assess impairment and disability in PD. The MDS-UPDRS is a comprehensive 50 question assessment of both motor and non-motor PD symptoms. The assessment has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living),

[d] Oxford University Innovation. "Parkinson's Disease Questionnaire (PDQ-39 and PDQ-8)." https://innovation.ox.ac.uk/outcome-measures/parkinsons-disease-questionnaire-pdq-39-pdq-8/

Part III (motor examination) and Part IV (motor complications).[e] Parts 1A, III and IV are assessed by the trained rater and Parts IB and III are a self-administered patient questionnaire that is completed with or without the aid of the caregiver.

Each question is scored from 0 to 4 reflecting the subject's usual level of function; Normal, Slight, Mild, Moderate and Severe. Each part (I-IV) can be reported as sub-scores, or all parts can be reported as an overall score.

This assessment must be completed in person whenever possible. In the event the assessment cannot be completed in person, Parts IA, IB, II and IV may be administered via telephone/telehealth a maximum of 7 days prior to the study visit, and a protocol deviation recorded.

9.15.7. Parkinson's Disease Sleep Scale 2 (PDSS-2)

The PDSS-2 assesses a wide spectrum of disease-specific sleep problems and is administered as a patient self-rating scale.

The PDSS-2 consists of 15 questions about various sleep and nocturnal disturbances which are to be rated by the patients using one of five categories, from 0 (never) to 4 (very frequent). PDSS-2 total score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance).[f]

This assessment must be completed in person whenever possible. In the event the assessment cannot be completed in person, the assessment may be administered via telephone a maximum of 7 days prior to the study visit, and a protocol deviation recorded.

9.15.8. Voice Handicap Index (VHI)

The VHI has been designed to evaluate the quality-of-life specific to dysphonia. It was developed and validated with patients with a wide range of disorders, including neurological disorders and quantifies the patients' perceptions of the handicap they experience in everyday life due to speech disorders.

The 30-item self-administered questionnaire consists of a 10-item functional subscale, a 10-item emotional subscale, and a 10-item physical subscale. Patients are asked to read each item and circle one of five response comprising an equal-appearing five-point scale. The scale has the words "never" and "always" anchoring each end and the words "almost never", "sometimes", and "almost always"

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[e] Movement Disorder Society. "MDS-UPDRS." https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_English_FINAL_Updated_June2019.pdf

[f] Trenkwalder C, et al. "Parkinson's Disease Sleep Scale – Validation of the Revised Version PDSS-2." Movement Disorders. Vol. 26. No. 4. March 2011. P. 644-652.

appearing in between. An “always” response was scored 4 points, a “never” response was scored 0 points, and the remaining options were scored between 1 and 3 points. [g]

This assessment may be completed either in person, or a copy may be sent to the subject to be completed a maximum of 7 days prior to the study visit.

9.15.9. Patient Preference

Patient preference for aDBS vs. cDBS and Single vs. Dual Threshold aDBS modes (if both were evaluated) will be assessed by a Medtronic-developed questionnaire.

This assessment may be completed either in person, or a copy may be sent to the subject to be completed a maximum of 7 days prior to the study visit.

9.15.10. Patient Satisfaction

Patient satisfaction with aDBS as assessed by a Medtronic-developed questionnaire.

This assessment may be completed either in person, or a copy may be sent to the subject to be completed a maximum of 7 days prior to the study visit.

9.15.11. aDBS Global Impression of Change

Acceptability of each aDBS mode is be assessed by a Medtronic-developed aDBS Global Impression of Change. Efficacy and side effects are assessed on a scale from 1 to 21. Lower scores represent better efficacy and fewer side effects. A score of 8 or less indicates the aDBS mode is acceptable.

9.16. Assessment of Safety

Subjects will be assessed for all potential Adverse Events and device deficiencies, as applicable, at each study visit from the time the study informed consent form is signed until discontinuation from the study. Safety data collected for this study will include all device deficiencies, and all reportable AEs. Refer to Section 11: Adverse Events and Device Deficiencies.

[g] Jacobson B, et al. “The Voice Handicap Index (VHI): Development and Validation.” American Journal of Speech-Language Pathology. Vol 6. No 3. August 1997. P. 66-70.

9.17. Recording Data

The 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 (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).

In general, eCRFs (or paper copies) may not serve as source documents. Subject questionnaires (e.g. PD Home Diary, MDS-UPDRS, VHI, PDQ-39, PDSS-2) and physician assessments (e.g. C-SSRS, GIC, MDS-UPDRS) may be collected on paper forms provided by the sponsor to be entered into the RDC system by the center personnel. If used, the paper forms of the questionnaires will be retained at the center as original source documentation. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents. Data reported on the CRFs, which are derived from source documents, must be consistent with the source documents and discrepancies need to be justified with documented rationale, and approved by the principal investigator or delegate. The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

The study will use the Oracle Clinical (OC) RDC system which allows the study centers to enter study data into the sponsor's database over a secured internet connection. The system controls user access, ensures data integrity, and maintains an audit trail on entries, changes or corrections in CRFs. The principal investigator will ensure that only appropriately delegated study personnel are given access to the RDC system; user IDs and passwords may not be shared.

Programming session files, with BrainSense data included in the JSON session data report, will be collected for the study and uploaded via CDU to the NPU (Neuro Programmer Upload) server and study database.

9.18. Deviation Handling

A study deviation is an event within a study that did not occur according to the clinical investigation plan, CTA, investigator agreement, IRB/EC policies or applicable standards, laws and regulations.

The 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 investigator's control (eg, subject failure to attend a scheduled follow-up visit, inadvertent errors, equipment failure). All deviations must be documented in the study database 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 case report form.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with IRB/EC policies, local laws, and/or RA requirements. Refer to Section 15.8.1 for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or RAs.

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

- Failure to obtain subject informed consent prior to beginning study activities
- Subject does not meet general inclusion/exclusion criteria after the enrollment visit
- Failure to report AEs or Device Deficiencies per Table 9: Safety Reporting Requirements
- Failure to collect CIP-required assessments
- Subject missed visit or visit outside of window
- Subject unblinding
- Programming adjustments during the 14 days prior to each aDBS Evaluation Visit
- For subjects with the SenSight system enrolled in the Primary Cohort: change of programming from ring mode to directional stimulation before the end of the aDBS Evaluation Phase
- For subjects enrolled in the Directional Stimulation Cohort: change of programming from directional stimulation to ring mode before the end of the aDBS Evaluation Phase

Deviations will be reviewed by Medtronic on an ongoing basis. Medtronic 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). Repetitive or serious investigator compliance issues may suggest a need to implement a corrective action plan with the investigator and study center. If needed, subject enrollment may be suspended until the compliance issues are resolved. If compliance issues are left unresolved, the investigator's participation in the study may be terminated.

Medtronic will provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

During the aDBS Evaluation Phase, every effort should be made to keep the subjects in the study, with applicable protocol deviations reported as necessary.

9.19. Subject Exit, Withdrawal or Discontinuation

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

Prior to early discontinuation, or after the completion of the final study visit if aDBS is not commercially available, subjects will return to the study center to have aDBS turned off and be programmed back to standard cDBS Therapy. This is done by interrogating the subject's INS with a commercially available Clinician Programmer System. The subject will return the investigational Patient Programmer System to the study center and the investigator will re-pair the subject's INS with a commercially available Patient Programmer System. A final device interrogation will be obtained to confirm that aDBS has been turned off. The programming session, with BrainSense data included in the JSON session data report, will be uploaded to Medtronic via CDU. BrainSense and passive sensing functionality will be on or off at the discretion of the clinician. Once aDBS is no longer active, the subject's INS is no longer considered Investigational, and subjects will be discontinued and followed according to the study center's standard procedures.

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

After study discontinuation, the updates for ongoing, and for any new events (eg, AEs or device deficiencies), will be reported through Neuromodulation Customer Quality as required by regulation.

9.19.1. Study Exit

A study exit eCRF 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 (visit #6)
- 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 (prior to randomization)
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- Neither aDBS mode is acceptable

The 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 BrainSense data included in the JSON session data report upload to Medtronic via CDU (after aDBS has been turned off)
- A brief description of why the subject discontinued (if applicable)
- Patient satisfaction questionnaire (if early discontinued after the aDBS Evaluation Phase)

9.19.2. Study Completed

At the completion of Visit 6, subjects may exit from the study. Both the CRFs for Visit 6 and a Study Exit CRF need to be completed. If aDBS is not commercially approved at the time the subject completes all study visits, the subject may choose to continue participation in the study until aDBS is commercially approved or closure of the study, whichever comes sooner.

9.19.3. 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., one letter and one phone record, or two letters) must be documented in the subject's medical record. In addition, regulation set forth by the governing IRB/EC must be followed.

When subjects are lost to follow-up the investigator will make efforts to confirm the vital status of the subject, as described in the informed consent.

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

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e., the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing IRB/EC. Permission may be requested to follow up with the subject outside of the study due to withdrawal based on problems related to the investigational feature safety or performance.

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

- Adverse event and device deficiency assessment
- Final device interrogation and data upload via CDU (after aDBS has been turned off)
    - Export JSON Session Data
- A brief description of why the subject discontinued (if applicable)

9.19.5. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If the subject was randomized, it is preferred to keep the subject in the study and perform study procedures/collect data to the extent possible. If an investigator withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Adverse event and device deficiency assessment
- Final programming session upload to Medtronic via CDU, with BrainSense data included in the JSON session data report (after aDBS has been turned off)
- A brief description of why the subject was withdrawn by the investigator

9.19.6. Conditional Disengagement

After a subject is enrolled/randomized every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to occur. In these cases we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be collected because the subject has not revoked consent, or exit when study participation is completely ended. In randomized subjects, modified data collection is always preferred over exit.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location but telephone follow-up still acceptable)
- Investigator deems conditional disengagement necessary (e.g. medically justified)

If the subject wishes to disengage from the study, or the investigator deems it necessary, the study site is required to document the reason. Prior approval from the study team is required and a Limited Data Collection CRF needs to be completed. Data collection requirements no longer apply, but study sites are encouraged to collect as much data as possible on the regular CRFs.

10. Risks and Benefits

10.1. Potential Risks

Deep Brain Stimulation Therapy is a reversible procedure (,i.e., the system can be turned off or removed in most cases) with stimulation parameters that are adjustable to minimize or reverse complications and maximize therapeutic effects. Deep Brain Stimulation Therapy has CE Mark, Health Canada and FDA approval, and is commercially available in the European Union, Canada and the United States. The risks associated with the Medtronic DBS Therapy are included in commercially available product information.

The risks, precautions, warnings, cautions, and contraindications associated with the Medtronic DBS Therapy and each system component are included in the product labeling. These risks may be temporary or permanent and must be continuously monitored, assessed and documented by the investigator.

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk management process for the aDBS feature is being performed in accordance with ISO 14971 and will ensure that the level of risk is acceptable prior to starting the study.

10.1.1. 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 have a negative pregnancy test at enrollment and agree to not become pregnant during the study by using a medically acceptable method of birth control. Should a pregnancy occur during the study, the subjects are instructed to notify their physician immediately and the 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 physician.

10.1.2. 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.

10.1.3. Potential Study Procedures Risks

The clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the clinical investigation plan. Potential risks related to study procedures include:

- Subjects may experience skin irritation from the PKG watch. Should irritation occur, the subject should remove the watch
- There may be risks or side effects which are unknown at this time.

10.1.4. Potential Study Procedure Inconveniences

- The patient assessments subjects are required to complete for the study may be burdensome.
- The patient assessments that are required for the study may request information of a personal nature

10.2. Risk Minimization

The potential risks associated with the aDBS feature were identified and have been successfully mitigated as far as possible (Table 6). Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP. Medtronic has also attempted to minimize risk to subjects implementing a DMC to review safety issues as part of the study.

Risks will be minimized by careful assessment of each subject prior to, during, and after enabling aDBS. In addition, investigators will be actively involved in the follow-up of the subjects with aDBS enabled on their Percept PC device.

Medtronic has further minimized the possibility of risks by: performing required laboratory and pre-clinical testing prior to the ADAPT-PD study, implementing design assurance and quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Table 6: Potential Risks and Risk Minimization

Potential Risk	Risk Minimization
Non-optimum stimulation, due to noise to LFP	• System requirements ensures that patient has the capability to switch from aDBS to cDBS, if needed. • Product requirements and software requirements ensure that aDBS works reliably as designed.

10.3. Potential Benefits

Some subjects may experience benefits from aDBS, such as: Parkinson's disease symptom management, improvement of movement symptoms, improved quality of life and/or energy savings of their device.

The information gained from this study might benefit 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. All the potential risks have been controlled to a level as far as possible. Based on the risk acceptance criteria for the ADAPT-PD Trial laid out in the Study Risk Management Plan, the study-specific residual risk is determined to be acceptable given the expected benefits.

10.5. Risk Determination

The Percept PC INS used in the ADAPT-PD Trial meets the definition for a significant risk device in 21CFR§812.3(m), because it is an implanted device and presents a potential for serious risk to the health, safety, or welfare of a subject.

The Percept PC INS used in the ADAPT-PD Trial is currently classified as AIMD in accordance with 90/385/EEC and in the future will be classified as Class III in accordance Annex VIII, Rule 8 of EU Regulation 2017/745. The Percept PC INS is considered an investigational device in the ADAPT-PD Trial once aDBS is enabled.

As per Schedule 1 of the Canadian Medical Device Regulations (SOR-98-282), the Percept PC INS used in the ADAPT-PD Trial is classified as a Class IV Medical Device according to Rule 1(2): *A surgically invasive device that is intended to diagnose, monitor, control or correct a defect of the central cardiovascular system or the central nervous system or of a fetus in utero is classified as Class IV.*

As per Schedule 1 of the Canadian Medical Device Regulations (SOR-98-282), the PKG Watch used in the ADAPT-PD Trial is classified as a Class II Medical Device according to Rule 10(1), *which states: Subject to subrule (2), an active diagnostic device, including any dedicated software, that supplies energy for the purpose of imaging or monitoring physiological processes is classified as Class II.*

11. Adverse Events and Device Deficiencies

11.1. Adverse Events

AE definitions are provided in Table 7. All AE information will be collected throughout the study duration, starting at the time of signing the IC.

Reporting of these events to Medtronic will occur on an AE eCRF. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

In all geographies, UAE, listed in Table 7, need not be reported unless the adverse event worsens or is present outside the stated timeframe post-system modification.

For AEs that require immediate reporting (see Table 9), initial reporting may be done by phone, email, or on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.

All non-subject AEs will be collected throughout the study duration

Subject deaths are also required to be reported. Refer to Section 11.6 for Subject Death collection and reporting requirements.

11.2. Device Deficiency

The Device Deficiency (DD) definition is provided in Table 7. All DD information will be collected throughout the study 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.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require reporting according to the timeframes listed in Table 9.

11.3. 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 eCRF. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, 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.

After study discontinuation, subjects will be followed according to the study center's standard procedures and updates for AEs that are ongoing, and any new events (eg, AEs or device deficiencies) will be reported through Neuromodulation Customer Quality as required by regulation.

11.4. Definitions/Classifications

This study will be following ISO14155:2020 and will collect all Adverse Events and Device Deficiencies from the time of enrollment through study exit/discontinuation. It is the responsibility of the Investigator to identify the occurrence of all adverse events and device deficiencies and to ensure the required information is accurately documented in the medical records and reported to Medtronic. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system, and includes but is not restricted to the components listed in Table 1: Medtronic DBS System Components and the PKG Watch.

Table 7: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device. Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

	NOTE 3: this includes 'comparator' if the comparator is a medical device (ISO 14155:2020, 3.1)
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Note 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	
Relationship of Adverse Events	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 or disease based on the following definitions: • 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 • Each of the relatedness classifications will be assessed for causality using five different levels of causality based on the following definitions: • Not Related: relationship to the device, comparator or procedures can be excluded when: o the event has no temporal relationship with the use of the investigational device or the procedures related to application of the investigational device; o 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; o 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 adverse 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 underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); ○ the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; 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 adverse event • Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. • Possible: the relationship with the use of the investigational device or comparator 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 were relatedness cannot be assessed or no information has been obtained should also be classified as possible. • Probable: the relationship with the use of the investigational device or comparator seems relevant and/or the event cannot reasonably be explained by another cause • Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: ○ 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 investigational device use/application or procedures; ○ the event involves a body-site or organ that ▪ the investigational device or procedures are applied to; ▪ the investigational device or procedures have an effect on; ○ the serious adverse 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 adverse 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 investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/ procedures and the serious adverse event. Events are considered "related" to the investigational medical device if their relationship to the device, procedure, or therapy is classified as "possible", "probable", or "causal".
Seriousness	
Serious Adverse Event (SAE)	<u>AE that led to any of the following:</u> a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) A life-threatening illness or injury, or 2) A permanent impairment of a body structure or a body function, including chronic diseases, or 3) In-patient or prolonged hospitalization, or 4) Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment. Note 1: Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (US 21 CFR§812.3(s))

Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk assessment. (ISO14155:2020 3.51)
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals. (ISO 14155:2020, 3.46)
Unavoidable Adverse Event (UAE)	An AE inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:

Event Description	**Timeframe (hours) from the Surgical Procedure**
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or 37.8°C)	48
Pocket site / Incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to laying on table	72
Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72

The following are not considered an AE for the study.

- Pregnancy

- Documented pre-existing conditions unless the intensity, duration, or frequency of the condition is worsened from the time of enrollment
- Programming adjustment (optimizations) 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 quality-of-life patient-reported outcome scores (e.g. EQ-5D-5L, PDQ-39, PDSS-2, VHI, MDS-UPDRS Part IB & II)
- Expected side-effects of Parkinson's disease medication

11.5. Reporting of Adverse Events

All reportable AEs and device deficiencies must be recorded in the subject's medical record, the study CRF, and promptly reported to Medtronic or its designee. 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 (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 investigator to identify the occurrence of reportable AEs and DDs and to ensure the required information is accurately documented on the CRF.

For emergency reporting of SAEs and SADEs, the following Medtronic contact information may be used:

Phone: +1 763.514.4000
Email : rs.ADAPT-PDTrial@medtronic.com
Address: 7000 Central Avenue NE, RCE375 | Minneapolis, MN 55432 | USA

11.5.1. Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE/DD at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary, will request clarification and/or additional information

from the Investigator. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE/DD based on the information provided by the investigator. Copies of de-identified source documentation regarding an adverse event or device deficiency (eg, clinician notes or summaries) will be provided to Medtronic upon request.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 9 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs will be classified according to the standard definitions as outlined below in Table 8:

Table 8: Event Classification Responsibilities

What is Classified	Who Classifies	Classifications
Relatedness*	• Investigator • Sponsor	• Relationship to the: ○ Procedure ○ Device ○ Therapy/Stimulation ○ Disease under study
USADE/UADE potential	Sponsor	USADE/UADE
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by investigator

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

In addition, all ADEs and deaths will be reviewed and adjudicated (seriousness, relationship/causality) by an independent Clinical Events Committee. Refer to Section 12.2.

11.5.2. Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB/EC. Refer to Table 9: Safety Reporting Requirements for more details related to reporting timelines.

Table 9: Safety Reporting Requirements

SAE	
Investigator shall submit to:	
Medtronic	**Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event or of new information in relation with an already reported event. **All other geographies:** Report to the sponsor, without unjustified delay, all serious adverse events
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.
SADE	
Investigator shall submit to:	
Medtronic	**Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event or of new information in relation with an already reported event **US:** Report to the sponsor, without unjustified delay, all serious adverse device events
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All other geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.
UADE	
Investigator shall submit to:	
Medtronic	**US:** As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
IRB/EC	**US:** As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
Regulatory Authority	**US:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**US:** Submit to IRB/EC as per local requirement.

Regulatory Authority	**US:** Reporting timeframe as per local requirement.
USADE	
Investigator shall submit to:	
Medtronic	**Canada:** USADEs on the patient, the user or any other person must be reported within 72 hours after it comes to the attention of the qualified investigator. **Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event or of new information in relation with an already reported event.
IRB/EC	**Canada:** Submit to IRB/EC as per local requirement. **Europe:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**Canada:** USADEs on the patient, the user or any other person must be reported within 72 hours after it comes to the attention of the qualified investigator. **All other geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.
Deaths	
Investigator shall submit to:	
Medtronic	**All geographies:** Without unjustified delay after learning of a subject's death, regardless of whether the death is related to the device system or therapy.
IRB/EC	**Canada:** All subject deaths must be reported the EC as soon as possible, but no more than 72 hours of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. **All other geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.
All other AEs	
Investigator shall submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.

Investigational DDs with SADE potential	
Investigator shall submit to:	
Medtronic	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event or of new information in relation with an already reported deficiency. **US:** Reporting timeframe as per local requirement
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All other geographies:** As per local requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.
All other Device Deficiencies	
Investigator shall submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the device deficiency
IRB/EC	**All geographies:** Reporting timeframe as per local IRB/EC requirement.
Sponsor shall submit to:	
IRB/EC	**All geographies:** Submit to IRB/EC as per local requirement.
Regulatory Authority	**All geographies:** Reporting timeframe as per local requirement.

IRB/EC and Competent Authority (CA) reporting must be completed in accordance with the local reporting policies of the governing IRB/EC and CA.

11.6. Subject Death

The investigator must notify Medtronic and the governing IRB/EC (as required) without unjustified delay after learning of a subject's death, regardless of whether the death is related to the device system or therapy. The 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 eCRF 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 per Section 6.10, Product Return.

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, and investigator summary of the death is acceptable. Additionally, device disposition information should be updated.

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
- 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)

11.7. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints 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 investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of 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. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

12. Data Review Committees

12.1. Data Monitoring Committee

The main objective of the ADAPT-PD Trial Data Monitoring Committee (DMC) is to advise Medtronic regarding the continued safety of study subjects and those yet to be recruited to the study; and to ensure the validity and scientific merit of the study.

The DMC will be external to Medtronic and independent of the study investigators. The physician members will have specialties appropriate to the therapeutic area and all members will meet requirements established in the DMC charter.

The DMC will be responsible for:

- Assessing the progress of the ADAPT-PD trial, including the accumulation of safety data
- Evaluating study conduct (eg, data quality) for the impact on validity and scientific merit of the ADAPT-PD Trial
- Considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- Recommending to the sponsor whether to continue, modify, or stop the study

Medtronic personnel (eg, statistician, Medtronic study management team) may facilitate the DMC meetings, provide study progress updates and answer questions. Medtronic personnel will not be voting members.

The DMC Charter will define the DMC processes for member selection, meeting frequency, roles and responsibilities, procedures, and record keeping. The DMC may call additional meetings whenever there are concerns regarding any aspect of the study.

12.2. Clinical Events Committee

This study will utilize a Clinical Events Committee (CEC) to review and adjudicate all reportable stimulation/therapy, procedure and device related (S)AEs and deaths for seriousness and relationship to the procedure, device, and therapy/stimulation using the definitions provided in Section 11.4. The CEC Charter will define the CEC processes for member selection, meeting frequency, roles and responsibilities, procedures, and record keeping.

Prior to making a final adjudication decision, the CEC may request clarification and/or additional information from the principal investigator who reported the event. If the conclusion of the review differs from the principal investigator's assessment, both opinions will be reported back to the investigator and noted in the final study report. Incidence rates will be tabulated using the final CEC determination.

13. Statistical Design and Methods

13.1. General Aspects of Analysis

The ADAPT-PD Trial will be considered successful when the primary objective of the study is met for one or both aDBS algorithms independently or the algorithms combined.

The main analysis of the study objectives will use the Full Analysis Set (FAS) which includes all Primary Cohort subjects, using the intention-to-treat (ITT) principle, who initiate the aDBS Evaluation Phase using the randomized treatment assignment for each subject that was randomized and the programmable treatment assignment for those subjects that may only be configured to one aDBS mode (dual or single threshold).

The main analysis will include data from all contributing geographies and centers. A poolability analysis for a center effect will be performed as described in Section 13.2.10.

The subjects' baseline status will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation for continuous variables. Safety data will be summarized as specified in Section 13.6.

Subject disposition will be illustrated in a CONSORT diagram and attrition will be identified and summarized.

The handling of missing data for the primary and secondary objective is described generally in Section 13.2.5 and also with each objective. Subgroup analyses are described in Section 4.1.4

13.2. General Statistical Considerations

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used to analyze the study results.

Additional details of the analyses outlined in this section will be described in a separate Statistical Analysis Plan prior to the data freeze for the Primary Analysis Report. Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Primary Analysis Report, as appropriate or in an amended CIP, if applicable.

13.2.1. Analysis sets

All-Consented (AC): includes all subjects who properly signed the study-specific informed consent (IC). This patient set will be used to summarize patient disposition.

Full Analysis Set (FAS): includes all Primary Cohort subjects, using the intention-to-treat (ITT) principle, who initiate the aDBS Evaluation Phase using the randomized treatment assignment for each subject that was randomized and the programmable treatment assignment for those subjects that may only be configured to one aDBS mode (dual or single threshold).

As-Treated (AT): includes all Primary Cohort subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) during the cDBS Baseline Evaluation Phase and/or the aDBS Evaluation Phase, and Long-term Follow-up Phase and uses the observed treatment used for each subject in each phase.

All-Randomized (AR): includes all Primary Cohort subjects who were randomized in the aDBS Evaluation Phase, excludes those that were not configured to both modes.

Complete-Case (CC): FAS without imputation that includes all Primary Cohort subjects who have available measures for the respective analysis and are analyzed in their randomization group for those randomized or the programmable treatment for those configured to one aDBS mode.

Directional Stimulation As-Treated (DSAT): includes all Directional Stimulation Cohort subjects who have SenSight leads in a directional stimulation configuration who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) during the cDBS Baseline Evaluation Phase and/or the aDBS Evaluation Phase, and Long-term Follow-up Phase and uses the observed treatment used for each subject in each phase.

Directional Stimulation Complete-Case (DSCC): includes all Directional Stimulation Cohort subjects who completed the aDBS Evaluation Phase.

13.2.2. Factors That May Compromise the Outcome or Interpretation of the Results

Missing PD Home Diary Data

PD Home Diary non-compliance or incorrect completion are most concerning in the assessment of the primary effectiveness objective. PD Home Diaries will be collected, regardless of completeness or accuracy of completion. PD Home Diaries and other efficacy data collected while the subject is in the wrong treatment assignment or stimulation is inactive will be included in analyses, following Section 13.4.5.

PD Home Diary compliance will be continuously monitored throughout the duration of the study to ensure that compliance is maintained.

13.2.3. Familywise error rate and hypothesis testing

The familywise error rate will be controlled using one-sided tests with an overall alpha-level of 0.025. Each primary hypothesis (one for each aDBS mode) will be assigned a Bonferroni corrected alpha (0.0125) for the respective primary hypothesis (0.025/2, see Section 13.4.1). The primary hypothesis will serve as a gatekeeper for the secondary hypothesis within each mode.

13.2.4. Sample size rationale

Since the device implant will occur outside of the study and the study requires participants to be stable on cDBS prior to enrollment, the standard deviation of the change from cDBS to aDBS in “On” time without troublesome dyskinesia will be used to establish a threshold for assessing the performance goal. The threshold will be set as 1 standard deviation. If the difference between aDBS and cDBS (aDBS-cDBS) for a subject is at least -1 standard deviation, the threshold will be met for the subject. Using this threshold, the proportion of subjects who exceed the threshold will be computed.

The sample size was estimated using a binomial distribution for a one-sided exact test (alpha=0.0125) for a proportion (PASS 2011 module Tests for One Proportion [Differences]) to compare to a performance goal of 50%. Assuming the alternative hypothesis of 85% of subjects exceeding the threshold, a minimum of 36 subjects achieves at least 90% power to reject a performance goal of 50%.

Simulations have shown that this sample size is sufficient to cover possible deviations from normality such as a uniform distribution. The threshold criterion will remain the same as the standard deviation is robust to moderate departures from normality.

Sample size in the Primary Cohort may be increased to a maximum of 55 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase to obtain at least 8 subjects per

aDBS mode and 8 subjects per target site (STN/GPi). Criteria for increasing sample size is described in Section 13.2.6.

For the safety analyses, a minimum of 30 subjects followed for approximately 30 days with aDBS out-of-clinic in the subjects' real-world environments provides at least 95% probability that all events with a true event rate of at least 10% would be reported at least once.

It is estimated that approximately 70-100 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled in the study to obtain 40 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. Accounting for a 10% dropout during the aDBS Evaluation Phase, a minimum of 36 subjects (at least 8 per brain target site (STN/GPi) and 8 per aDBS mode) will complete the aDBS Evaluation phase.

In addition, approximately 15 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS and SenSight system will be enrolled in the Directional Stimulation Cohort to obtain 9 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. Accounting for dropout during the aDBS Evaluation Phase, a minimum of 8 subjects will complete the aDBS Evaluation Phase.

13.2.5. Handling of missing data

All attempts will be made to minimize missing data. If 5% of the data or fewer are missing for the analysis, no imputation will be used.[h] Otherwise, if missing data are observed, multiple imputation will be used for the analysis of the primary and secondary objectives, as described in the objective sections below. If an aDBS mode is not programmable to a subject no imputation will occur for those subjects for that aDBS mode.

Appropriate standard errors will be computed to account for the multiple imputations.[i,j] A Complete-Case Analysis Set and As-Treated Analysis Set will be used for sensitivity analyses of the primary and secondary objective analyses.

[h] Buhi, E, Goodson, P, Neilands T. Out of Sight, Not Out of Mind: Strategies for Handling Missing Data. Am J Health Behav. 2008 Jan-Feb;32(1):83-92, doi: 10.5555/ajhb.2008.32.1.83.
[i] Rubin, D. B. (1976). "Inference and Missing Data." Biometrika 63:581–592.
[j] Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

13.2.6. Interim sample size adjustment

Sample size for the Primary Cohort may be increased to a maximum of 55 subjects based on acceptability of the aDBS modes during the aDBS Setup Phase and to ensure a minimum number of subjects in each target site (STN/GPi) as described in 13.2.9.

13.2.7. Reports

Annual reports of study progress and safety data will be provided. After all aDBS treated subjects in the Primary Cohort have reached the end of their aDBS Evaluation Phase (randomized or programmable mode) a Pre-Market Approval (PMA) supplement will be submitted to request FDA approval of aDBS; a Technical Document will be submitted to request TUV approval of aDBS. These requests will include available data through the final aDBS Evaluation Phase visit and any available safety data for those subjects in the long-term follow-up phase. A final study report, which will include data covering all phases of subject follow-up, will be prepared after all subjects have completed the study.

13.2.8. Demographics and baseline variables

Demographics and baseline characteristics will be summarized for the AC, FAS, and DSCC analysis sets.

13.2.9. Pooling of aDBS mode

Most planned analyses for the Primary Cohort are to be done separately for each mode. Summary statistics will be computed to summarize the percentage who were programmed to each mode and subject characteristics of each subgroup. If fewer than 24 subjects are programmed to one of the aDBS modes because aDBS is unacceptable as compared to cDBS (using the aDBS GIC), the evaluation of aDBS effectiveness will use data from the first period of the aDBS Evaluation Phase from all subjects. If the modes are considered poolable, the modes would be combined and the alpha level of the test would be alpha=0.025 (one-sided). To test for a treatment difference in the first period by aDBS mode group, subjects will be categorized based on the modes they are programmable to: aDBS – Dual Threshold only; aDBS – Single Threshold only; and aDBS – both modes. The Freeman and Halton's extension of Fisher's exact test will be computed testing for differences between aDBS modes in the proportion of subjects exceeding threshold for the primary outcome using data only from the first period. The same categorization of mode will be used and tested using F-tests using linear regression models for the secondary outcome measure. P-values >0.1 for the tests of association with aDBS mode group will be deemed as supporting the assumption of no aDBS mode group effect and the data will be considered poolable across aDBS mode groups. If the aDBS mode group factor approaches statistical significance

(defined as ≤0.1),[k] the data will not be considered poolable. A minimum of 8 subjects per aDBS mode will be required for the pooled analysis using the first period outcome data.

If data are pooled, missing data observed in the cDBS Baseline Phase and aDBS Evaluation Period 1 will be imputed as described in 13.2.5.

13.2.10. Center pooling

All investigators in the proposed study will conduct the study according to a common protocol and utilize the same CRFs to collect study data. Throughout the trial, efforts will be made to ensure consistency among investigative sites in selection of patients and conduct of the study procedures. In addition, site study personnel training will be conducted prior to initiation of the study at each site and periodic monitoring will be conducted by Medtronic to ensure compliance with protocol requirements.

Data will be pooled across centers for all analyses. Each study center will stop enrollment in the Primary Cohort after they have identified a maximum of 8 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase (~25% of the total planned number of subjects). For the Directional Stimulation Cohort, each study center will stop enrollment after they have identified a maximum of 5 subjects for whom at least 1 aDBS mode is acceptable and who enter the aDBS Evaluation Phase. The actual number of subjects at a study center may be slightly larger due to the number of subjects that are enrolled prior to cessation of enrollment. This restriction is intended to reduce the possibility that the results from one study center will be overly influential in the overall study results.

Tests for a treatment difference in the Primary Cohort among centers are described in the supporting analyses of the objective sections below. When testing for differences between centers, centers with 5 or more FAS subjects will each be tested as separate centers. Those with less than 5 FAS subjects will be combined into a “pooled” pseudo-center to minimize the impact of small samples on the analysis. If the pseudo-center contains more than 50% of the subjects, the centers will be combined into more than one pseudo-center. If more than one pseudo-center is needed, the centers will be randomly ordered and divided as near the midpoint as possible. If ambiguity between assigning a center to the first or second pseudo-center exits, the center will be assigned to the first pseudo-center.

13.3. Analysis Execution

A formal analysis for the ADAPT-PD Trial will occur when all active subjects in the Primary Cohort have completed the Evaluation Phase of the study. Analysis will include both the primary and secondary

[k] Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993; 2(2):121-45.

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 Long-Term Follow-up Phase or have been exited. The inferential analysis for the primary and secondary objectives will not be updated for the final report. Additional objectives will be addressed based on complete data.

13.4. Primary Objective

To demonstrate that the proportion of aDBS subjects with "On" time without troublesome dyskinesia during the Evaluation Phase exceeds a performance goal of 50%.

13.4.1. Hypothesis

Two hypotheses are being tested for the primary objective in order to compare each aDBS mode relative to cDBS at baseline, separately. The alternative hypotheses are:

- H_{11}: The proportion of subjects with "On" time without troublesome dyskinesia during aDBS dual threshold mode Evaluation Period exceeding threshold > 50%
- H_{21}: The proportion of subjects with "On" time without troublesome dyskinesia during aDBS single threshold mode Evaluation Period exceeding threshold > 50%

13.4.2. Endpoint definition

The primary endpoint is the proportion of aDBS subjects with "On" time without troublesome dyskinesia that exceed threshold. This endpoint will combine the diary categories of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia. Since the device implant will occur outside of the study and the study requires participants to be stable on cDBS, the within-subject standard deviation of the change between cDBS and DBS in "On" time without troublesome dyskinesia will be used to establish a threshold for assessing the performance goal. The threshold will be set as 1 standard deviation. If the difference between aDBS and cDBS (aDBS-cDBS) for a subject is at least -1 standard deviation, the threshold will be met for the subject. Using this threshold, the proportion of subjects who exceed the threshold will be computed. The primary endpoint proportion of subjects above threshold will be compared to a performance goal of 50% using a binomial exact test. The lower bound of the 97.5% confidence limit will also be presented. Data will be imputed as described in 13.2.5 prior to computing the mean "On" time without troublesome dyskinesia for all periods when using the FAS.

Rationale for endpoint

Continuous Deep Brain Stimulation (cDBS) is a proven FDA-approved therapy in the treatment of Parkinson's disease symptoms. This study aims to show that aDBS is a viable optional feature that can provide similar benefit and safety to cDBS for some subjects. The primary endpoint for this study compares aDBS to cDBS directly for each subject to ensure some level of consistent comparability

between cDBS and aDBS. The endpoint of PD Home Diary was chosen to determine the threshold of success as it is a measure of the subject response to DBS therapy over time, the aDBS algorithm will adapt the therapy over time, and the PD Home Diary has been used as an endpoint in previous DBS trials.

Rationale for 1 standard deviation threshold

A unit of one standard deviation was chosen as it is an acceptable amount of statistical variability in the PD Home Diary endpoint given the fluctuating nature of Parkinson's disease and the percentiles of a normal distribution.

Rationale for 50% performance goal

A performance goal of 50% was chosen for this study in order to demonstrate that at least 50% of the subjects are able to achieve the threshold with 95% confidence demonstrating some level of efficacy.

13.4.3. Sample size justification

The sample size justification for the primary objective is provided in Section 13.2.4.

13.4.4. Analysis methods

The primary analysis will use the FAS as described in Section 13.2.1 The PD Home Diary will be collected for at least 3 consecutive days (24 hour "periods") prior to each visit to evaluate the primary objective. Complete diary periods collected anytime during the cDBS Baseline period will be used for analysis as subjects should be on stable cDBS stimulation from enrollment through the end of this period. In the aDBS Evaluation Phase, diary periods will be defined starting with the first completed diary record which is no more than 14 days prior to the visit. If diary is collected more than 14 days prior to the visit, the diary may be used for analysis if there is no change in aDBS stimulation settings. Complete diary periods are defined as any diary period where at least 21 hours[I] (defined as 42 30-minute records) of diary were completed during the 24-hour period, and only complete periods will be used for analysis. If the diary is collected for more than 3 complete periods, up to 7 which are closest to the visit will be used for the

[I] Neurostimulation for Parkinson's disease with early motor complications. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group. N Engl J Med. 2013 Feb 14;368(7):610-22. doi: 10.1056/NEJMoa1205158.

analysis, while if a subject has zero complete periods, their diary will be considered missing. Diaries with at least 1 complete period available will be used for analysis. Data from non-contiguous complete periods may be used in the analysis.

The change in daily "On" time without troublesome dyskinesia from cDBS to aDBS will be computed for each subject. The overall standard deviation of the change will be computed for the FAS. The threshold will be set as 1 standard deviation. If the difference between aDBS and cDBS (aDBS-cDBS) for each subject is at least -1 standard deviation, the threshold will be met for the subject. Using this threshold, the proportion of subjects who exceed the threshold will be computed. The proportion with "On" time without troublesome dyskinesia during the respective aDBS Evaluation Period that exceed the threshold will be compared to the performance goal of 50% for each aDBS mode separately using a binomial exact test. The objective will be considered passed if the p-value is less than 0.0125. The lower bound of the 97.5% confidence interval will also be presented.

13.4.5. Handling of missing data

All attempts will be made to minimize missing data. If 5% of the data or fewer are missing (as defined in Section 13.4.4) for the analysis, no imputation will be used and the data will be analyzed as specified in the previous section. Otherwise, if missing data are observed, multiple imputation will be used for the analysis of the key primary objective.

Prior to the MI, the distribution of the continuous variables will be assessed for normality (using the Shapiro-Wilk test) to determine whether regression ($P \geqslant 0.05$) or predictive mean matching ($P<0.05$) multiple imputation will be used for each variable. First, multiple imputation will be applied to impute missing values in continuous hours of "On" time without troublesome dyskinesia for each mode separately (aDBS single threshold, aDBS dual threshold). Variables for target site (STN or GPi) and cDBS hours of "On" time without troublesome dyskinesia will be considered for the model. The fully conditional specification (FCS) method within SAS (version 9.4 or higher) with 5 repetitions and 100 burn-in iterations will be used for imputation. No limits will be defined for imputed values. Following imputation, the "On" time without troublesome dyskinesia will be assessed against the "On" time threshold, and the estimate for the proportion of subjects meeting threshold will be determined for each imputation and combined using MI analysis methods. The lower bound of the 97.5% confidence limit will be determined from the MI Clopper-Pearson mean success approach[m]. In addition, the

[m] Mandan, Arpita (2018). Two Applications of Summary Statistics: Integrating Information Across Genes and Confidence Intervals With Missing Data. Master's thesis, Duke University. Retrieved from https://hdl.handle.net/10161/17533

objective will be tested by comparing the lower bound to 50% for each imputation, and the overall p-value will be computed as the median of the p-values from the multiply imputed datasets.[n]

13.4.6. Supporting analyses

Supporting analyses for the primary objective in the Primary Cohort include verifying the lack of a period or carryover effect (randomized subjects only), a target site effect (STN/GPi), a lead type effect (legacy Models 3387 and 3389 compared to SenSight Models B33005 and B33015), or a center effect. Summarized results from the Directional Stimulation Cohort will be provided as supporting analyses to the Primary Cohort results. In addition, sensitivity analyses will be conducted using the CC and the AT Analysis Set.

An analogy of Prescott's test[o] will be computed to test for a period or carryover effect and p-values >0.1 will be deemed as supporting the assumption of no period or carryover effect in the proportion of subjects exceeding threshold for the primary outcome using data from both periods. If the assumption of no period or carryover effect is accepted, target site (STN/GPi), lead type, and center pooling assessments will be made using data from all subjects treated with aDBS in the aDBS evaluation phase. If a period effect exists, only data from the first period will be used for the analysis.

To test for a treatment difference by target site (STN/GPi), lead type, and center within each mode, Fisher's exact test and Freeman and Halton's extension of Fisher's exact test, respectively, will be computed testing for differences between target sites, lead type, or centers in the proportion of subjects exceeding threshold for the primary outcome using data from both periods. P-values >0.1 will be deemed as supporting the assumption of no target site effect, lead type effect, or center effect, respectively, and the data will be considered poolable across the respective variable. If the p-value approaches statistical significance (defined as ≤0.1),[k] the proportion exceeding threshold and the lower bound of the 97.5% confidence interval will also be estimated at each target site, lead type, or center, as applicable (eg, if the target sites (STN/GPi) do not allow for pooling the analysis will be conducted by target site for that mode.)

If center(s) causing the significance are identified, variables relating to patient characteristics and other factors will be analyzed to try to identify why this center is showing a different treatment effect.

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[n] Ekhout, I., van de Wiel, M.A., and Heymans, M.W. (2017), Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: power and applicability analysis. BMC Med. Res. Methodol.17: 129. doi: 10.1186/s12874-017-0404-7

[o] Nagelkerke, N.J.D., Hart, A.A.M. and Oosting, J. (1986), The Two Period Binary Response Cross - Over Trial. Biom. J., 28: 863-869. doi:10.1002/bimj.4710280715

As part of the additional objectives, "On" time without troublesome dyskinesia will be summarized as absolute change from cDBS Baseline Phase to the Evaluation Phase.

13.5. Secondary Objective

13.5.1. Secondary Objective

To demonstrate decreased stimulation energy use during the aDBS Evaluation Phase as compared with cDBS.

13.5.2. Hypothesis

Two secondary hypotheses are being tested using independent gatekeeper procedures to control the alpha-level as described in Section 13.4.1. The two secondary alternative hypotheses comparing aDBS (Evaluation Phase) to cDBS (Baseline Phase) separately, are:

- H_{12}: Mean Difference between aDBS dual threshold (Evaluation Phase) minus cDBS (Baseline Phase) for TEED < 0
- H_{22}: Mean Difference between aDBS single threshold (Evaluation Phase) minus cDBS (Baseline Phase) for TEED < 0

13.5.3. Endpoint definition

The secondary endpoint is to decrease energy use as measured by TEED during the aDBS Evaluation Phase as compared with TEED during the cDBS Baseline Phase. The Total TEED will be calculated as a sum of the energy use in the left and right leads. There will be one value per patient for each mode evaluated (eg, cDBS, aDBS Dual Threshold, aDBS Single Threshold).

The reduction in TEED will be calculated as:

$$\text{TEED } \Delta_{\text{aDBS dual threshold mode}} = \text{TEED}_{\text{aDBS dual threshold mode}} - \text{TEED}_{\text{cDBS}}$$

and

$$\text{TEED } \Delta_{\text{aDBS single threshold mode}} = \text{TEED}_{\text{aDBS single threshold mode}} - \text{TEED}_{\text{cDBS}}$$

Computing TEED in cDBS

To compute TEED using the formula in Section 9.15.2 in the cDBS mode, the current drain, pulse-width, frequency, and impedance will be determined from the JSON session data at the cDBS Baseline visit.

Computing TEED in aDBS

To compute TEED using the formula in Section 9.15.2 in an aDBS mode, the average current drain from the JSON session data will be computed using the average stimulation currents from the timeline feature. 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). Included days should be in the 14 days prior to the visit. The pulse-width, frequency, and impedance will be determined from the JSON session data at the aDBS Evaluation visit.

Impedance

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. In case electrode impedance was not collected at cDBS Baseline or aDBS Evaluation Phase, impedance from aDBS Setup would be used.

13.5.4. Sample Size justification

The sample size was estimated using a one-sided test (alpha=0.0125) for one mean (PASS 2011 module Tests for One Mean) to compare the difference in aDBS TEED to cDBS TEED of 22 and a standard deviation of 35, a minimum of 36 subjects achieves at least 90% power.

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 35 and 22 units for aDBS single threshold mode and aDBS dual threshold mode, respectively. A SD of 36 results in a medium to large effect size of 0.629.

13.5.5. Analysis methods

The secondary analysis will use the FAS Analysis Set as described in Section 13.2.1. Change in TEED will be used to evaluate the secondary objective. A paired t-test will be used to compare the difference in TEED for each aDBS mode (Evaluation Phase) to cDBS (Baseline Phase), separately. 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.

13.5.6. Handling of missing data

All attempts will be made to minimize missing data. If 5% of the data or fewer are missing for the analysis, no imputation will be used and the data will be analyzed as specified in the previous section. Otherwise, if missing data are observed, multiple imputation will be used for the analysis of the secondary objective.

Prior to the MI, the distribution of the continuous variables will be assessed for normality (using the Shapiro-Wilk test) to determine whether regression ($P\geq0.05$) or predictive mean matching ($P<0.05$)

multiple imputation will be used for each variable. First, multiple imputation will be applied to impute missing values in TEED for each mode separately (aDBS single threshold, aDBS dual threshold). Variables for target site (STN or GPi) and cDBS TEED will be included in the model. The fully conditional specification (FCS) method within SAS (version 9.4 or higher) with 5 repetitions and 100 burn-in iterations will be used for imputation. No limits will be defined for imputed values. Following imputation, the mean and standard error of the change in TEED will be determined for each imputation and combined using MI analysis and tested with a t-statistic comparing the value to no change.

13.5.7. Supporting analyses

Supporting analyses for the secondary objective in the Primary Cohort include verifying the lack of a period or carryover effect (randomized subjects only), tests for poolability by target site (STN/GPi), tests for poolability by lead type (legacy Models 3387 and 3389 compared to SenSight Models B33005 and B33015), and tests for poolability by center. The test for a carryover effect will use a two-sample t-test, all other supporting analysis tests will use linear regression models. In addition, results from the Directional Stimulation Cohort will be described as a supportive analysis. The test of no period or carryover effect will be computed first, and if the assumption of no period or carryover effect is accepted, data from both periods from all subjects treated with aDBS in the aDBS Evaluation Phase will be used for the models to assess poolability by target site, lead type, and center. The models will use the change between aDBS and cDBS and include an intercept and a covariate for the respective parameter. P-values >0.1 for the terms testing the effect of the respective parameters will be deemed as supporting the assumption of no period or carryover effect, target site effect, lead type effect, or center effect, respectively, and the data will be considered poolable across the respective variable. 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 secondary endpoint may be transformed (e.g., log-transformation) or apply non-parametric method for the supporting analyses.

In addition, sensitivity analyses will be conducted using the CC and AT Analysis Sets without imputation.

13.6. Safety Assessment

The safety assessment is to characterize:

- Stimulation-related adverse events during the aDBS evaluation and the cDBS baseline phases.
- Serious adverse events, adverse events, and device deficiencies throughout the study.

Stimulation-related adverse events will be summarized during the cDBS Baseline and aDBS Evaluation Phases for all subjects, with tabulations individualized by aDBS mode in the Primary Cohort, by target site in the Primary Cohort, by lead type in the Primary Cohort, and the Directional Stimulation Cohort (DSAT analysis set). Summarized results from the Directional Stimulation Cohort will be provided as supporting analyses to the Primary Cohort results. In the Primary Cohort, if statistical comparisons of

poolability across mode, lead type, and target site are accepted, overall tabulations will be provided as appropriate. To test for a difference in safety by target site (STN/GPi) and lead type, Fisher's exact test will be computed testing for differences between target sites and lead types in the proportion of subjects with a stimulation-related adverse event during the aDBS evaluation phase using data from both periods. A repeated measures logistic regression model will be used to test for a difference between aDBS modes in the proportion of subjects with stimulation-related adverse events. P-values >0.1 will be deemed as supporting the assumption of no target site, lead type, or mode effect, respectively, and the data will be considered poolable across the respective variable. If the p-value approaches statistical significance (defined as ≤0.1),[k] safety summaries will not be provided as a combined summary for that variable.

Serious adverse events, adverse events, and device deficiencies that occur from the time of enrollment 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.

13.7. Additional Objectives

To characterize each aDBS mode as compared to cDBS, the additional objectives described in Section 4.1.4 will be evaluated for the FAS separately for each aDBS mode. In addition, the subgroup analyses as described in Section 4.1.4 will be performed for the FAS and DSAT.

Summary statistics will be presented for continuous measures (N, means, medians, standard deviations, minimums and maximums) and categorical measures (N, percentage, frequency distributions) with 95% confidence intervals as appropriate. No adjustment will be made for multiple testing of the additional study objectives.

13.8. 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 Evaluation Phase
- Randomized crossover to evaluate the dual threshold and single threshold modes

In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

14. Ethics

14.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The ADAPT-PD Trial was designed to reflect the Good Clinical Practice (GCP) principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. AE and DD handling in the ADAPT-PD Trial is ISO 14155:2020 compliant for all participating geographies.

The principles of the DoH have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all study sites in all geographies will follow and comply with:

- Principles of DoH
- ISO 14155:2020
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The CTA
- The procedures described within this CIP
- Local IRB/EC Requirements
- Local regulatory authority requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 54: Financial Disclosure by Clinical Investigators
  - 56: IRBs
  - 812: IDEs
- In Canada, SOR/98-282, section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1)).

- In Europe the study will be conducted in compliance with the AIMDD 90/385/EEC and EU MDR 2017/745, and DoH version 2013.

The study will be publicly registered prior to the first enrollment in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Study investigators will be required to sign and date an investigator agreement or CIP signature page stating their intent to adhere to applicable regulations.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical EC or IRB.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned groups prior to implementation of the revised CIP at the study site.

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

15. Study Administration

15.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (all clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Contact information for the study monitoring:
Medtronic Clinical & Regulatory Solutions
8200 Coral Sea Street, N.E., MVS33
Mounds View, MN 55112

15.1.1. Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

15.2. Data Management

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; investigators and center 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 Oracle Clinical Remote Data Capture (RDC) system is a fully validated system and 21CFR§11 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.

CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable local regulations.

The Principal Investigator, or designated representative, 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 a person only authorized to complete CRFs makes changes to an already signed CRF, the system will require the principal investigator, or authorized delegate, to re-sign the CRF.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

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

Device data, including BrainSense data, will be uploaded to secure servers. Upon receipt, device data will be maintained in the NPU database and retrieved for analysis and reporting.

GKC will store information collected by the wearables and provide this data to Medtronic for use in analysis.

15.3. Direct Access to Source Data/Documents

Medtronic or third-party auditors representing Medtronic may perform clinical center audits to verify the performance of the monitoring process and study conduct, and to ensure compliance with applicable regulations. IRBs/ECs, representatives for regulatory bodies such as the FDA, CA and Notified Body may also perform center inspections related to this clinical study. The investigator and/or institution shall permit Medtronic, IRBs/ECs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

15.4. Confidentiality

Subject confidentiality is assured through use of subject identification numbers, and the de-identifying of photocopies or records obtained by the Sponsor. In addition to the review of records at the center, release of de-identified records to Medtronic may be necessary, such as in the evaluation of adverse events. The investigational center personnel must de-identify and label source documentation with the subject's study-specific identification number prior to submission to Medtronic.

Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

Health Insurance Portability and Accountability Act (HIPAA) language will be required to be included at every center in the United States. HIPAA language may be included within the IC according to the center's policy.

15.5. Liability/Insurance Information

The compensation and covered liability associated with this study conduct will be documented in a separate financial agreement signed by Medtronic, the Principal Investigator, and/or the management of study site/institution. Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the IRB/EC.

15.5.1. Insurance (Canada)

Medtronic of Canada Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the EC.

15.5.2. Insurance (Europe)

Medtronic Bakken Research Site B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC.

15.6. CIP Amendments

Clinical investigation plan amendments may be initiated by Medtronic to address changes to the scope or conduct of the study. Protocol amendments will be submitted to the appropriate regulatory authorities for their approval, if required, and to the IRBs/ECs. Prior to a study center's implementation of a CIP amendment and/or associated changes to the IC, approval must be obtained, in writing, by the reviewing IRB/EC and Medtronic except:

- When necessary to eliminate an immediate/or apparent immediate hazard to participating subjects
- When the change involves purely administrative or logistical aspects of the study

15.7. Record Retention

The principal investigator is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years after the date the investigation is completed or terminated or the records are no longer required to support a marketing application (or longer in compliance to local requirements). The retention period may be longer if required by Medtronic or local or global regulatory requirements. Medtronic will not store any personal data longer than necessary and always in line with the required storage periods defined by the applicable laws.

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

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

15.7.1. Investigator Records

At a minimum, the investigator is responsible for the preparation, review, and retention of the records listed below. The below records pertaining to the study, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- Correspondence with another investigator, an IRB/EC, the sponsor, a monitor or regulatory body (eg, FDA, CA, Notified Body) including required reports
- Device receipt/use/disposition records (i.e., product accountability)
- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation), such as:
    - Signed and dated IC (In U.S. and Canada, signed by subject. In Europe, Middle East, Africa, signed by subject and investigator)
    - Observations of AEs/ADEs/DDs
    - Medical records, including, for example, progress notes of the physicians, the subject's hospital and clinic chart(s) and the nurse's notes
- Subject Screening log and Enrollment log
- Signed and dated CTA
- Signed investigator agreement

- Current Curriculum vitae of principal investigators and key members of investigation study site team
- Documentation of delegated tasks
- IRB/EC approval documentation. Written information that the investigator or other study staff, when member of the IRB/EC, did not participate in the approval process. Approval documentation must include the IRBs/ECs composition, where required per local law.
- RA notification, correspondence and approval, where required per local law.
- All approved versions of the CIP, IC and IB/Report of Prior Investigations
- Signed financial disclosure forms for all investigators
- Study personnel training records
- Insurance certificates (Europe and Canada only)
- Final Study Report including the statistical analysis

A list of the study sponsor staff, and a list of the investigator names, emergency contact details, addresses and professional positions of the principal clinical investigators will be kept separately from the CIP. The sponsor will maintain updated lists.

15.7.2. Sponsor Records

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

- All correspondence which pertains to the investigation
- Investigational device traceability record containing Model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates.
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements, FD (if applicable) and current CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Randomization records
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- RA correspondence, notification and approval as required by national legislation
- Insurance certificates (Europe, Canada)
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, IB and study related reports, and revisions
- Study training records for study site personnel and 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 password-protected 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 the required storage periods defined by the applicable laws.

15.8. Reporting Requirements

15.8.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB/EC with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety reporting requirements are listed in Table 9. The investigator shall prepare and submit in a complete, accurate and timely manner the applicable reports listed in this section (Table 10, Table 11 and Table 12).

Table 10: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Final Report	IRBs/ECs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

Table 11: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress report	Sponsor and IRB/EC	The investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/EC, and the FDA/applicable RA. If the deviation does not affect these issues then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs/ECs	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor, IRBs/ECs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An investigator shall, upon request by a reviewing IRB/EC, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Table 12: Investigator reports applicable to Europe, Middle East and Africa per ISO 14155

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	Report if required by local law.
Progress Report	Sponsor IRB/EC	Provide if required by local law or IRB/EC.
Study Deviations	Sponsor, Competent Authority and IRB/EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When required, ECs, CAs or the appropriate RAs should be informed by sponsor. (ISO 14155:2020)
Failure to obtain IC	Sponsor and IRBs/ECs	IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020)

15.8.2. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of the reviewing IRB/EC, RA or FDA, provide accurate, complete and current information about any aspect of the investigation.

Table 13: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant regulatory authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).

Report	Submit to	Description/Constraints
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities, and Health Canada	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study center specific study deviations will be submitted to investigators periodically.

Table 14: Sponsor reports for Europe, Middle East and Africa

Report	Submit to	Description/Constraints
Normal closure of the clinical investigation	Investigators, IRB/EC, and Relevant regulatory authorities (if applicable)	Provide prompt notification of national/global study closure.
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant regulatory authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Withdrawal of IRB/EC approval	Investigators, Head of Institution, and relevant regulatory authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Withdrawal of CA approval	Investigators, Head of Institution, IRB/EC	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.

Report	Submit to	Description/Constraints
Progress Reports	IRB/EC and Regulatory authorities	This will be submitted to the IRB/EC only if required by the IRB/EC and regulatory authorities).
Final report	Investigators, IRB/EC, and RAs if required	• The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal Investigator in each study center should be obtained. (ISO 14155:2020)
Study deviation	Investigators and Regulatory authorities	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study center specific study deviations will be submitted to investigators periodically.

Table 15: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Investigators, IRB/EC, and FDA	Notification within five working days of receipt of notice. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators and IRB/EC	Notification within five working days of receipt of notice. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. (21 CFR 812.150(b)(4))
Progress Reports	IRB/EC and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)

Report	Submit to	Description/Constraints
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Final report	Investigators, IRB/EC, RAs upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/ECs within six months after completion or termination of this clinical study. (21 CFR 812.150(b)(7))
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study center specific study deviations will be submitted to investigators periodically.
Other	IRB/EC, FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))
Premature termination or suspension of clinical study	IRB/EC, Investigators, and RAs, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB/EC and RAs.

15.9. Publication and Use of Information

Publications from the ADAPT-PD Trial will be handled according to Standard Operating Procedures and as indicated in the CTA.

15.9.1. Publication Committee

Medtronic may form the ADAPT-PD Trial Publication Committee from study investigators. 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.

The Publication Committee's role is to: 1) develop the final Publication Plan under separate cover, 2) execute the Publication Plan, 3) oversee the publication of primary, secondary and ancillary study results, 4) review and prioritize publication proposals, 5) provide input on publication content, and 6) 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.

15.9.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the CIP.

An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this study, and clinicians not participating in this study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

15.9.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “Medtronic ADAPT-PD Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

15.9.4. Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested

15.10. Suspension or Early Termination

Medtronic reserves the right to suspend or terminate the study at any time. Reasons for study suspension or termination may include, but are not limited to:

- Insufficient enrollment to complete the study within the expected timeframe
- Identification of unacceptable safety profile (suspicion of an unacceptable risk will result in a suspension, confirmation of an unacceptable risk will result in termination)
- Product performance/product supply issues

15.10.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Refer to Section 9.19 for additional information regarding study exit procedures.

15.10.2. 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 and distribution of the product. This is possible for the whole study or a single study site.

15.10.2.1. 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 or RA (where the study is operating under RA)
- Recommendation of early termination by the DMC

15.10.2.2. Investigator/study site termination or suspension

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

- IRB/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 study center personnel
- Insufficient or lack of investigator oversight
- IRB/EC suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

15.10.3. Procedures for Termination or Suspension

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

If applicable, an attempt will be made to transfer active subjects to another study center prior to termination whenever possible.

Individual study centers may be closed by Medtronic if all subjects have completed the study or no active subjects are actively being followed.

15.10.3.1. Medtronic-initiated and regulatory authority initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the IRB/EC will be promptly informed as required per local regulation
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

15.10.3.2. Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)

- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities
- The investigator 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

15.10.3.3. Ethics Committee-initiated

- The investigator 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 investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects with the rationale for the study termination or suspension
- The investigator will promptly inform the RAs

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Appendix A - aDBS Global Impression of Change Score (GIC)

17. Version History

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	[redacted]
2.0	4. Updated visit schedule to move LFP screening earlier in the study as a standalone visit 5. Corrected motor diary to PD Home Diary and updated patient diary categories 6. Removed risks of commercially available DBS and included reference to labeling 7. Added sections: • 7: Study Site requirements	1. CIP V1.0 not approved by regulators or distributed for use; internal version only 2. Updated to new Medtronic template CIP 3. Additional revisions made to improve execution of CIP procedures	Not Applicable	1. IC 2. CRFs	[redacted]

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	• 9.19.6 Conditional disengagement • 10.2 Risk Minimization • 11.3 Processing Updates and Resolution • 11.5.1 AE and DD Classification • AE and DD Reporting requirements • 11.7 Product Complaint Reporting • 13.1 General Aspects of Analysis • 13.8 Minimization of Bias • 15.1.1 Monitoring Visits • Clerical updates				
3.0	1. Clerical updates throughout 2. Removed Prof Andrea Kühn as lead PI 3. Updated the following sections to add	1. None 2. No longer participating 3. New study subject cohort 4. New SW version available 5. Clarification 6. TH91 is a box, not a medical device	None	• IC • CRFs • IB	[redacted]

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	Directional Stimulation Cohort • 2 Synopsis • 3 Purpose • 4 Objectives and Endpoints • 5 Study Design • 6 Product Description • 8 Selection of Subjects • 9 Study Procedures • 10 Risks and Benefits • 13 Statistical Design and Methods 4. Section 6.1: updated software versions for Model A610 5. Section 6.5: Equipment. Clarified that PKG watch will be used under an ITA in Canada 6. Section 6.8: Clarified that TH91 package kit will not be tracked	7. Technical requirement for SenSight 8. Detected artifact may not preclude programming of aDBS 9. COVID-19 restrictions 10. Expansion of the visit window from 3 days to 1 day after the previous visit does not change the expectation for the subject to be fully withdrawn from PD medication. The increased window allows for subjects who do not take controlled release carbidopa/ levodopa or dopamine agonists to be seen earlier as they will have fully withdrawn from medication (per Table 5) in 12 hours. 11. Clarification 12. Clarification 13. Clarification to improve execution of CIP procedures 14. Added more detail to improve execution of CIP procedures 15. Clarification			

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	7. Section 8.3: Added inclusion #9 8. Section 8.4: Updated exclusion #16 9. Updated Section 9 Study Procedures to allow administration of assessments outside of the visit when necessary. Section 9.15 provides guidance on which assessments may be done remotely and in what time frame. 10. Section 9.3: updated visit windows for LFP screening and aDBS setup visits from 3-45 days to 1-45 days 11. Moved blinding language earlier in Section 9.9 and clarified that unblinding at any time during aDBS	16. Updated per final published ISO14155:2020; Germany no longer participating 17. Updated per Medtronic procedure 18. No longer following MEDDEV			

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	setup and adjustment is a deviation 12. Re-ordered Section 9.9.1 for better flow 13. Added clarification to Section 9.9.1 that if the visit occurs over 2 days, the clinician may program the subject to one aDBS mode between visit day 1 and visit day 2 and may have more freedom for naming aDBS modes. 14. Section 9.15 added aDBS Global Impression of Change description 15. Section 10.5, added information about PKG watch classification in Canada 16. Section 11.4, table 7 updated AE definition				

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	Note 3; removed Germany SAE definition 17. Section 11.4, table 7 updated causality definitions 18. Section 11.7 removed MEDDEV definitions				
4.0	1. Glossary: Added definitions for directional stimulation, Primary Cohort and ring mode; updated SADE definition 2. Section 5: defined primary cohort, ring mode and directional stimulation 3. Section 7.1: Clarified that all investigators must be trained and experienced in DBS and management of PD 4. Section 7.2: removed “as required” from CV	1. Clarification/correction 2. More clearly defined the cohorts and which programming configurations fall within each 3. Clarification 4. Required per ISO14155 5. Reminder per GDP 6. More clearly defined the cohorts and which programming configurations fall within each 7. Real-world experience shows non-cardiac artifact may vary over time and based upon patient state and LFP signal may be affected by factors	None	1-5, 7-28: None 6: CRFs	[redacted]

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	5. Section 8.2: added note that the date of IC signature must be documented in the subject's medical records. 6. Section 8.3: Updated general inclusion criterion #5 for both Primary and Directional Stimulation Cohort 7. Section 9.4: removed prohibition for re-screening due to signal artifact and inadequate LFP signal 8. Section 9.7.1: clarified signal artifact requirement and actions to be taken 9. Section 9.9.1: Clarified re-testing procedure for LFP inclusion criterion	other than medication (e.g. movement) 8. Clarification 9. Clarification 10. Clarification 11. Clarification 12. In current practice, clinicians can adjust therapy parameters as the subject's disease state dictates. Investigators have always been allowed to make changes in programming outside of the study Enrollment to aDBS Evaluation Phase (allowed only when clinically necessary). This update clarifies that a change in aDBS mode is considered a change in programming. The investigator may only change modes if subject received both in the aDBS Evaluation Phase. 13. Same as #11			

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	10. Section 9.9.1: Re-worded instructions for Dual and single threshold setup when only one hemisphere has signal meeting the LFP screening inclusion criterion 11. Section 9.9.1: re-ordered end of visit instruction 12. Section 9.11: Added allowance that investigator may choose to switch aDBS modes as needed in the Long-term Follow-up phase. 13. Section 9.12: clarified that the subject will continue into the Extended Access Phase in aDBS, not necessarily the preferred mode. 14. Sections 9.19 & 11.3: updated RTG to	14. Update in Medtronic business name 15. Clarification 16. Correction, this is not collected 17. Correction. Data will continue to be retained in accordance with applicable local regulations. 18. Clarification 19. Correction: records will continue to be retained in line with applicable laws 20. Reformatting and clarification 21. Additional administrative information 22. Administrative change			

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	Neuromodulation and removed RTG from Glossary 15. Section 11.4: Added clarification as to what "device" means in the context of AE definitions 16. Section 11.5.1, Table 8: Removed "An underlying condition or disease" from relatedness classification 17. Section 15.2: removed "indefinitely" from data retention description 18. Section 15.4: Clarified third party data access 19. Section 15.7: Updated record retention information 20. Section 15.9: moved to new Section 15.9.4 Transparency				

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	21. New Sections 15.9.2 & 15.9.3: added information regarding publication and authorship 22. Moved content from Section 15.10.2.2 to 15.10.3				
5.0	1. Updated the CIP Template vE and v5.0. 2. Added Competent Authority Number 3. Updated Glossary of terms – Alpha – Beta, Globus Pallidus Internus, Multiple Imputations 4. Definition updated Beta to Alpha - Beta throughout document 5. Added sub-group analysis of selected mode	1.Updated template and version. 2.Update only - Added Competent Authority number 3. Updated and added missing terms 4. Updating name of frequency range to accurately describe frequency ranges in accordance with current literature and align with EEG	1-15: No impact	1 – 5: CIP 6 (duration) – CIP, ICF 7-11, 13-20: CIP 12 (addition of Impartial Witness) – CIP, ICF	[redacted]

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	6. Section 5.1 – updated study duration from 2.5 to 5 years 7. Removed reference to A610 Clinician Programmer Application v2.0 throughout documents 8. Section 6.1.2.1 Investigational DBS system– updated number of patient programmers from 40-70 9. Section 6.10 Product Return– aDBS feature should be disabled	Standardized terminology[16],[17]. Frequency updated to 8-30 Hz 5.Updated to include sub-group analysis in long-term and extended phase 6.Updated timeline to accommodate regulatory review and study closure 7.All sites now on A610 v3.0 8.Updated to account for DS cohort and number of subjects enrolled			

[16] Kane N, Acharya J, Benickzy S, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clin Neurophysiol Pr*. 2017;2:170-185. doi:10.1016/j.cnp.2017.07.002

[17] Kane N, Acharya J, Beniczky S, et al. Corrigendum to "A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017" [Clin. Neurophysiol. Practice 2 (2017) 170–185]. *Clin Neurophysiol Pr*. 2019;4:133. doi:10.1016/j.cnp.2019.06.001

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	prior to explant and is then no longer considered investigational 10. Section 9.3 Scheduled f/u windows, Table 4, and Section 9.12.1 Extended Access visits - follow-up windows clarified that Extended Access continues until commercialization, study exit and/or closure 11. Section 9.5 Prior and Concomitant Medications– add clarification of no medication restrictions 12. Section 9.6 Subject Consent– added impartial witness statement to CIP and ICF 13. Section 9.13 unscheduled visits - Programming adjustments/optimizations are not reportable events	9.Clarification 10.Clarification 11. Template update 12. Update – with the progression of PD addition of a witness to facilitate obtaining informed consent for subjects with visual difficulties 13. Clarification – programming adjustments/optimizations not			

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	14. Section 9.18 Deviation Handling - Changes after the aDBS Evaluation Phase would not be considered a deviation. 15. Section 19.1 Study Exit and 9.19.2 Study Completed - Study Completion definition clarified 16. Section 11.4, Table 7, Table 8 Definitions/Classifications – Table 7 - removed definition of underlying condition. Table 8 - removed redundant definition 17. Section 13.4.4 – Clarified diary period analysis 18. Section 13.5.3 – Endpoint Definition and Section 13.5.7 Supporting analyses - TEED calculation with missing impedance and test for carryover effect	triggered by a change in clinical symptoms are not reportable events. 14.Clarification – changes made after the aDBS Evaluation phase does not affect the analysis and therefore would not be considered a deviation. 15.Clarification – subjects may exit at visit #6 or continue until commercialization. 16. Update – redundant definitions. UADE/USADE already listed in table 17. Clarification - In order to reasonably and accurately accommodate more actual diary data used in the analysis. This was allowed as the programmed parameters were still relevant to the analysis at the time of data collection. 18. Clarification - In order to obtain an impedance for the TEED calculation and considering that impedance would be generally stable over the trial period,			

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	19. Section 15.3 – updated name of MDT monitoring group 20. Section 17 deleted – duplicate section	impedance values were used from the aDBS Setup visit or the closest visit to that time. 19. Updated – Name updated 20 Duplicate section to Appendix A			

Appendix A - aDBS Global Impression of Change Score (GIC)

This scale is used to help assess for acceptability of an aDBS mode vs. cDBS for an individual subject. A lower number is better in terms of acceptability (ie, greater efficacy with minimal side effects).

- "Acceptable": A selection appearing in the white (unshaded) boxes means the mode has been deemed "acceptable" and is available for selection for that subject in the aDBS Evaluation Phase. The subject may be programmed with this mode.
- "Unacceptable": A selection appearing in the grey shading means the mode has been deemed "unacceptable" and is eliminated for selection in the aDBS Evaluation Phase. The subject will not be programmed with that mode.

To decide if a mode is acceptable to a subject, the following table will be used:

	Side effects			
Efficacy	*None*	*Does not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Side effects experienced outweigh efficacy*
Vast improvement	01	02	Fail:10	Fail:11
Decided improvement	03	04	Fail:12	Fail:13
Slight improvement	05	06	Fail:14	Fail:15
Unchanged	07	08	Fail:16	Fail:17
Worse	Fail:18	Fail:19	Fail:20	Fail:21