Bilateral Closed Loop Deep Brain Stimulation for Freezing of Gait Using Neural and Kinematic Feedback

Informed Consent Form

NCT04043403

June 28, 2020

Are you participating in any other research studies? Yes No

You are invited to participate in a study of your movement for the treatment of your Parkinson's disease. You have been asked to participate because you are currently being evaluated for Deep Brain Stimulation (DBS) surgery to treat your movement disorder and this research study relates directly to this clinical intervention. This study is separate from the DBS surgery itself; however, you can only participate in the study if you receive DBS. Your decision whether or not to participate in the study will not affect your eligibility for DBS. Up to 15 people who qualify for DBS surgery will be enrolled into this study.

Kinematic analysis (computerized movement measurements) will be done in addition to standard clinical examinations and neural activity will be recorded using the investigational implantable Summit RC+S® Neurostimulator System, (Medtronic, Inc.). The information gathered from these measurements will be used to supplement the clinical evaluation. Some of it may also be used for clinical outcomes and research projects.

Key Information:

- Participation in this study is voluntary.
- The purpose of this study is to provide objective measurements of abnormal movements of the body in correlation with neural activity of the brain and to track how both of these metrics change over time.
- The expected duration of your participation in this study is approximately 2 years, with study visits every 3-4 months.
- The study's procedures consist of gait tasks, motor testing, speech testing, and the modulation of your deep brain stimulation parameters.
- There are risks associated with this study, including but not limited to: risks of brain recording and adaptive DBS, risks of stopping your PD medication, and risks of falling during gait tasks.
- You may not have any direct medical benefits; however, the information obtained from this study may benefit other patients with PD in the future.
- The alternative to the study is to not participate. You do not have to be in this study to be treated for Parkinson's disease. If you decide not to be in this study, there is other care available to you, including but not limited to: a publicly available, approved DBS System, another surgical procedure, medications, or you may choose no treatment at all.

PURPOSE OF RESEARCH

The purpose of this study is to provide objective measurements of abnormal movements of the body in correlation with neural activity of the brain and to track how both of these metrics change over time. The secondary purpose is to use brain and movement signals to regulate therapeutic deep brain stimulation within clinically safe limits. This may allow for the development of a DBS system that uses signals from your brain and movements to provide customized, real-time demand-based therapy in the future.

The Medtronic Summit® RC+S System being used in this study is considered investigational because it has not been approved by the US Food and Drug Administration (FDA). The details of the Medtronic Summit® RC+S System are explained below in the System description section. This study is being conducted to understand more about the brain signals that are involved in movement and is **not to test the non-FDA approved components of the device.**

The Summit® RC+S neurostimulator is a pulse generator (similar to a pacemaker) designed to deliver standard DBS therapy, as well as perform brain recordings for research purposes. The sensing function of the pulse generator is what enables adaptive DBS (aDBS). The device is rechargeable and may be used for up to nine (9) years before replacement. Although it has been tested in animal laboratories, it has only been tested in very few humans.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You may decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

If you receive the study neurostimulator, your participation in the study may last about 4 years. You will be asked to come in for study visits every 3-4 months with first visit scheduled 3 months after initial programming of traditional open loop DBS (olDBS) therapy, after the therapy has been optimized. Each visit will span 3 to 4 days. The length of each study day will not exceed 8 hours (including breaks) or the amount of time deemed tolerable by you. Throughout the course of testing, you will be closely monitored by the study team and the clinician to ensure that testing does

not continue past your limits.

At your standard clinical visits that occur after the surgery but before the first scheduled study visit, the research team will perform short technical checks for safety purposes and to inform the development of the subject-specific protocols. These technical checks may include: adverse event testing for intensity limits, voltage/current titrations with short resting state sensing recordings, and short periods of sensing during movement.

If your study neurostimulator is removed and not replaced or is replaced with a different neurostimulator, your participation in the study will end.

Dr. Bronte-Stewart and the clinical team will provide the DBS programming care for you during the study, using the investigational programmer and device. They will

also continue to perform the DBS programming for you if you choose to leave the study or are exited from the study, in coordination with your primary neurologist. If you choose to have the investigational system removed, the clinical team will coordinate replacement of the Summit RC+S device with an FDA approved DBS system.

PROCEDURES

If you decide to be in this study, Dr. Bronte-Stewart will collect information about you and your medical history. This includes any medication you currently take and any other information in your medical records related to your condition or treatment that may be relevant to your being in the study. The clinical examination will include an assessment of your movement disorder (such as the Unified Parkinson's Disease Rating Scale or other clinical rating scale). If you are currently taking medications for symptomatic relief of your movement disorder, you may be evaluated both OFF your medications and ON your medications. As most patients take little or no medication following DBS, this does not usually cause difficulty in your mobility.

If the study doctor decides that you should not be in this study, you will be exited from the study and no further study-related procedures will be done. Your doctor will continue to treat you as they would any other patient with Parkinson's disease. This may include additional surgery to receive a DBS System that is not part of this study.

As part of the study, you will be implanted with the Summit® RC+S

Neurostimulator. This device is investigational, which is similar to the FDA-approved commercial devices but has additional components for sensing and sending/receiving information from an external computer. The research portion of the study will not begin until after the device has been implanted.

For this study, your doctor will schedule visits before and after surgery, as is the standard of care for any patient with a standard DBS system. The number of visits scheduled will depend on what your doctor believes is best clinical practice for you. About three (3) months after your DBS surgery, your study visits will start. A typical visit will be three (3) or four (4) consecutive days long. You must make sure that you can come to each visit as scheduled.

Study Visit(s)

You will undergo computerized assessment of your motor function in the Stanford Human Motor Control and Balance Laboratory, OFF medication and OFF stimulation or under one of the study's different stimulation interventions, described below. During all visits and sessions, you will be blinded to the specific stimulation setting but will be able to give feedback throughout. If, during any intervention, you are unable to tolerate the therapy, that session will be stopped. The aDBS settings will form a separate group on the neurostimulator so that you can be immediately returned to your clinical DBS settings at any time. You will be instrumented with eleven (11) inertial measurement unit sensors (IMUs) to capture full-body kinematics (chest, lumbar (L5), left and right shanks, wrists, thighs, feet, and head). All experiments will have synchronized neural, kinematic and video recordings.

Day 1 of each visit: After the clinic visit, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered, per FDA mandate for all device related studies. The (C-SSRS) is a series of questions that help identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs. The C-SSRS will be done pre-operatively and at every research visit.

Baseline testing will then be administered. It will consist of the speech intelligibility test (SIT), quantitative measures of bradykinesia and tremor during repetitive wrist flexion extension (rWFE), the UPDRS-(I-IV), FOG-Q, and custom AE questionnaires.

Calibration tests will determine the stimulation parameter limits such that the investigational interventions will be safe and tolerable. A custom calibration safety and tolerability questionnaire will be administered during the aforementioned tests to determine which ramp rates and current amplitudes are optimally safe and tolerable.

A maximum tolerable current amplitude (I_{max}) related to adverse effects (AEs) will be determined by the clinician. The aDBS experiments will never exceed this I_{max} such as to avoid AEs.

You will be asked to perform kinematic tasks, stepping in place (SIP) and/or turning and barrier course (TBC), at different DBS intensities that will not exceed I_{max}. Motor performance and corresponding brain signals will be recorded and used to determine the neural and kinematic driven adaptive DBS parameters that will be used in the subsequent aDBS experiments.

Procedures to be performed during each visit*:
*Subject to change

Visit Number	Pre-Op	1				2				3				4				5				6			
Day Number		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
ENROLLMENT:																									
Informed Consent	X																								
Clinical Evaluation*	X																								
ASSESSMENTS:																									
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X				X				X				X				X				X			
Calibration*		X				X				X				X				X				X			
Custom Safety and Tolerability Questionnaire		X				X				X				X				X				X			
Baseline Testing*	X	X	X	X		X	X	X		X	X	X		X	X	X		X		X	X	X		X	X
Stepping in Place (SIP)	X	X	X	X		X	X	X		X				X				X	X	X	X				
Turning and Barrier Course (TBC)	X									X	X	X		X	X	X						X	X	X	X
FOG Questionnaire	X	X				X				X				X				X				X			
Custom Adverse Effects Questionnaire		X				X				X				X				X				X			
INTERVENTION/CONDITION:																									
OFF DBS Stimulation		X				X				X				X				X				X			
NaDBS 140 Hz		X	X	X						X	X	X													
oIDBS 140 Hz			X								X	X						X	X			X	X		
ioIDBS 140 Hz			X								X	X						X	X			X	X		
NaDBS 140 Hz + Medication				X								X													
NaDBS 60 Hz						X	X	X						X	X	X									

olDBS 60 Hz				X						X	X			X				X					
iolDBS 60 Hz				X						X	X			X				X					
iolDBS (changing frequency 140/60Hz)														X				X					
NaDBS 60 Hz + Medication					X							X											
KaDBS (changing current)														X	X			X	X				
KaDBS (changing frequency 140/60Hz)														X			X	X					X
KaDBS + Medication*															X	X				X	X		

Description of Interventions

Neural Adaptive Deep Brain Stimulation (NaDBS)

Neural adaptive deep brain stimulation contrasts with current continuous open loop DBS in that the stimulator can sense and respond to neural activity. This study will use subthalamic movement beta band burst power and duration to drive NaDBS. These neural signals will be tracked and computed in real-time using an external computer through the Summit® RC+S system (Medtronic Inc.), and the concurrent modulation of stimulation parameters will be based on a pre-defined control policy.

Kinematic Adaptive Deep Brain Stimulation (KaDBS)

Kinematic adaptive deep brain stimulation is another form of aDBS that modulates DBS parameters in a responsive fashion, this time responding to physiological signals that identify specific behaviors, such as walking. Behavioral features are extracted in real-time during movement-related tasks. The change in these behavioral features will indicate gait impairment and freezing, at which time the DBS will be modulated using custom control policy algorithms that may improve gait and FOG. Similar to NaDBS the behavioral signals will be tracked and computed in real-time and the commands to the neurostimulator to modulate DBS parameters will use an external computer through the Summit® RC+S system (Medtronic Inc).

Open-loop Deep Brain Stimulation (olDBS)

Open-loop DBS simply refers to the traditional method of delivering stimulation. It is not responsive and the stimulation parameters do not change in response to sensed, patient-specific physiological signals.

Intermittent Open-loop Deep Brain Stimulation (iolDBS)

Intermittent is a control for aDBS, where DBS intensity or frequency changes in a manner that mimics aDBS but is pre-determined and open loop rather than being

responsive to neural or kinematic signals.

aDBS + medication
The subjects will take medication during NaDBS and KaDBS trials and medication wash-in effect will be observed. The safety, tolerability and response of NaDBS and KaDBS as medication takes effect will be monitored, in addition to whether this reduces adverse effects seen with olDBS + medication.

Calibration Procedures
Custom Calibration Safety and Tolerability Questionnaire: a customized questionnaire that assesses the safety and tolerability symptoms experienced during the different current intensity ramp rates as well as when switching between stimulation frequencies.

Current Titrations to determine I_{min} and I_{max}: At the start of Day 1 of each visit, subject-specific DBS intensity ranges (I_{min} and I_{max}) will be determined. The procedure will involve setting the subject's device on different current intensities and then recording the neural/kinematic signals to obtain good characterization of signals. I_{max} will be determined at the clinical DBS programming by the patient's neurologist.

Current Titrations for SIP/TBC: The subject will be tested during different current amplitude settings (i.e. at 0, 25, 50, 75, and 100% of I_{max}) in a randomized order. At each current setting, the subject will stand for 10 seconds, followed by either 30 seconds of SIP or TBC. This will be followed by the next current setting using a pre-determined safe and tolerable ramp rate. Both neural and kinematic data will be recorded during this procedure. The minimum DBS intensity that results in tolerable performance will be defined as I_{min}.

Baseline Testing
Speech Intelligibility Test (SIT): Subjects will be recorded using a microphone as subjects repeat the sentences generated from a pool of 1,100 sentences (sentences range in length from five to 15 words).

Repetitive Wrist Flexion Extension (rWFE): Using solid-state gyroscopic sensors (Motus Movement Monitor, Motus Bioengineering Inc, Benicia CA) that measure angular velocity, subjects will perform self-paced repetitive wrist flexion extension (rWFE) for 30 seconds. The elbow will be kept at a 90 degree angle. The subject will perform the rWFE movement continuously until a verbal "stop" command is given. After resting for 30 seconds, a verbal "go" cue will be given and the subject will begin to move the other hand for 30 seconds until they hear

the verbal "stop" command again.

Unified Parkinson's Disease Rating Scale (numeric):

Part I: Mentation, Behavior and Mood
Part II: Activities of Daily Living
Part III: Motor Examination
Part IV: Complications of Therapy (includes dyskinesias)

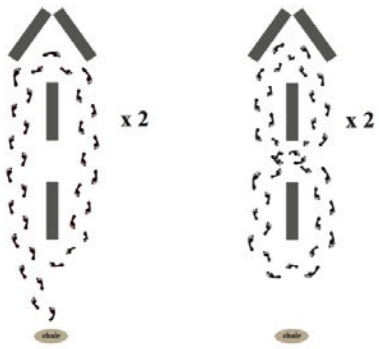
Freezing of gait questionnaire (FOG-Q, numeric): Validated questionnaire used to assess freezing of gait severity unrelated to falls in patients with PD.

Custom Adverse Effects Questionnaire: a customized questionnaire that monitors patient feedback and will assess any adverse effects such as muscle twitches and paresthesias, and records the frequency at which these are reported. The questionnaire will be administered at throughout and the end of each session.

Gait Tasks

Stepping in Place**:** Subjects will begin by standing in place for 30 seconds. On the 'go' command, subjects will complete 100 seconds of self-paced, repetitive, alternating stepping on two adjacent force plates. The subjects will wear a harness to protect them from falling and IMU sensors (chest, lumbar, left and right shanks, wrists, thighs, feet, and head) to capture full body kinematics. Sensors on the legs (shanks) will measure shank angular velocity as they step.

Turning and Barrier Course (TBC, pictured below): a forward walking "turning and barrier course" (TBC) using eight 6.5x4 ft^2 barriers on wheels, around and through which the patients turn and walk. After an initial standing, resting state period, the subject will sit. On the "Go" command, the subject will stand, first walking two ellipses around the dividers and then two "figures of eight", around and through the opening between the dividers, before sitting down again. The subject will repeat the task in the opposite direction, for a total of four ellipses and four figures of eight. The patient will wear eleven (11) IMUs.



Intentional Stopping During Gait Tasks: The same protocol will be performed with the subjects for either gait task (SIP or TBC) with the addition of two randomized conditions: (1) that they will make a decision to stop stepping/walking at a random time that they choose during the task ("Subject Initiated Stop"), and (2) that the research staff will instruct the subject to stop stepping/walking at a random time point in the task ("Researcher Initiated Stop"). In the "Subject Initiated Stop" condition, when performing each stop, subject will say 'stop' out loud and will stand still for five seconds after stopping. They will then be given the 'go' command to start stepping/walking again. There will be a total of three subject-initiated stops performed by the subject during the gait task. In the "Researcher Initiated Stop" condition, the same protocol as above will be used, with the exception that the researcher will be the one instructing the stops at random intervals.

Standing in Place and Swinging Arms: Subject will stand in place, arms at their side, at rest for 30 seconds. They will then be given the "go" command at which time they will begin swinging their arms, as they normally would while walking, maintaining a stationary position without moving their feet, for 30 seconds.

PARTICIPANT RESPONSIBILITIES

As a participant, you are expected to:

- Tell the study doctor about your medical and medication history;
- Attend all visits scheduled with the study doctor, most importantly, two days of study-specific testing at about six (6) months after your DBS surgery;
- Call the study doctor's office to reschedule if you cannot make a visit as soon as possible;
- Report any injuries, hospitalizations, emergency room visits, symptoms or complaints to the study doctor, study nurse or research personnel as soon as possible.

For Women of Childbearing Potential:

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to choose to have a pregnancy test done before beginning this research study

You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

WITHDRAWAL FROM STUDY

What happens to the study devices at the end of the study?
Your Summit® RC+S pulse generator is expected to require surgical replacement after nine (9) years of DBS therapy, as is expected for the rechargeable Activa® RC standard clinical pulse generator. The sensing function does not change the estimated battery life of the device compared to a non-research pulse generator, but may require you to recharge it more frequently. When your pulse generator requires replacement, it may be replaced with Activa® RC, the standard pulse generator model that delivers DBS therapy but has no ability to sense and store brain recordings, or it could be replaced with another Summit® RC+S.

Can I stop being in the study?
Yes. You can decide to discontinue your participation at any time by simply telling the study doctor or study staff. There are no specific tests that are required prior to leaving the study. If you are thinking about stopping your participation or if you have decided to withdraw, tell the study staff. They will instruct you how to stop your participation safely. It is important to tell the study staff if you are thinking about stopping so that your doctor can evaluate any risks from the brain recording and discuss what alternative follow-up care and testing could be most helpful for you.

You may be asked to come in for a final study neurostimulator check or visit. If you are still experiencing an illness or injury related to the RC+S System after you leave the study, your doctor may follow up with you at the end of the study to find out if your illness or injury has resolved. All of your health information collected for the study cannot be removed from the study data and will be used as described in this form.

The study doctors may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the

study is stopped.

The study doctor may take you out of the study without your permission if:

- It is in your best medical interest
- You do not follow your study doctor's instructions
- You do not attend the required study visits
- Your study neurostimulator is removed
- The study doctor determines that the Medtronic LFP Beta Adaptive DBS System is not right for you
- It is discovered you do not meet inclusion or exclusion criteria
- You were not implanted with a study neurostimulator
- The study sponsor or FDA stops the study

If this happens, you will be informed of the decisions and the reasons will be reasonably explained to you.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

You will receive a separate surgical consent form from your study doctor explaining the implant procedure and the risks of having the system implanted.

Study-Specific Risks

The tools used for kinematic analysis are non-invasive (do not enter your body). Physical sensors are applied to the surface of your body. The tests are not physically painful (other than in the removal of adhesive tape holding the sensors on the skin). You may become fatigued while performing the kinematic tasks due to changes in their stimulation settings. Any test of gait includes the potential of falling.

Brain recording and adaptive DBS risks:

- DBS close to the STN may cause transient electrical sensations in the body and/or muscle twitching and these are expected during testing of the placement of the DBS lead clinically. These are reversible.
- You may experience return or worsening of your usual movement disorders symptoms (such as bradykinesia, akinesia, rigidity, or tremor caused by temporarily turning off your DBS device, or from temporarily using less than the best (suboptimal) DBS settings. You may also experience symptoms

associated with over-stimulation such as dyskinesias associated with temporarily using suboptimal DBS settings.

- Possibility that the Summit® RC+S generator will fail to deliver brain stimulation that will effectively treat PD. The Summit® RC+S device contains the identical therapeutic stimulation components as those in the FDA-approved Activa® RC device and would be expected to function with the same level of reliability; however additional sensing technology has been added, making the device experimental. Thus, as an experimental device, with additional sensing circuits that have not yet been used in humans, there is a possibility that performance might not match the standard device. The actual risk of less effective brain stimulation is unknown.
- Most of the stimulation side effects can be avoided by reprogramming the neurostimulator or turning the neurostimulator off. Other side effects or complications may occur which are more unusual or are not yet known and cannot be predicted at this time.

Risks of stopping your PD medications:

- Your symptoms may temporarily return to untreated levels

Other Risks

Risks of long-term DBS therapy:

- The brain leads or lead/extension connectors may move. Further surgery to re-adjust the location may be needed.
- Components or parts of the brain stimulation system may suffer mechanical breakage resulting in loss of therapy. Further surgery to replace the system parts may be needed.
- The brain stimulation system could stop because of an electrical or software malfunction, which could require further surgery if noninvasive attempts to restore the software did not succeed.
- The battery in the pulse generator could be prematurely depleted, in spite of recharging. This would require further surgery. Pulse generator battery service life, with regular recharging, is expected to be nine (9) years.
- There may be an allergic reaction to the brain stimulation system. The system materials coming in contact with the tissues include titanium polyurethane, silicone, and nylon. The body could also reject the system (as a foreign body).
- There is the possibility of tissue damage resulting from the programming settings or a malfunction of one of the parts of the brain stimulation system.
- Turning on the stimulator may produce side effects such as difficulty

with speech, abnormal skin sensations, or abnormal eye movements.

Risks of post-implant MRI:

- The Summit System has not been evaluated for MR compatibility. The subjects should not have an MRI post-implant due to the INS (and possibly other hardware and/or implant locations) based on lack of Medtronic MR test data. If any of your medical care (i.e., knee replacements, vascular conditions) require regular MRIs, you cannot be included in the study.

Reproductive risks:

- The reproductive risks of participating in this study are unknown. Women who are breastfeeding or potentially could become pregnant will not be allowed to participate in this study.

Battery Recharging:

- <u>You must remember to regularly charge your pulse generator</u>. Study staff as well as your clinicians will help to show you how to recharge, and will check the device at study visits to make sure you are doing it correctly. Failing to recharge your device may result in loss of stimulation and loss of therapy.

Unknown Risks:

- Brain activity recording and adaptive DBS may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

You should talk to study staff about any side effects that you experience while taking part in the study.

Risks of the medical adhesive used:

- Reaction to the adhesive
- Adhesive particles released into the study neurostimulator pocket

There may be additional risks related to this study that are not yet known.

DBS System Revision Risks

The lead will remain implanted indefinitely unless a problem arises and your physician determines it requires removal.

When you visit the clinic or doctor, the energy level of the battery in your neurostimulator will be checked. The battery in your neurostimulator is expected

to last nine (9) years after which it will require surgical replacement. This is also true for the rechargeable Activa® RC standard clinical pulse generator.

Risks associated with taking out, replacing, or repositioning parts of your DBS System include all the risks of the original implant procedure and also:

- Potential damage to the lead(s) while the extension(s) is being taken out which may create a need to replace the lead(s) as well
- Any components or fragments of components left in the body may still be affected by electromagnetic interference (EMI) causing induced current, heating, shocking or jolting sensations, tissue damage, serious injury, or death

Procedures requiring safeguards

Be sure to let your physician and/or the technician know that you have an implanted DBS System before undergoing the following procedures:

- Computerized axial tomography (CT or CAT) scans (a special type of x-ray equipment that gives a cross-section view).
- Mammography (x-ray of breast tissue).

Interference with other devices

If you have an implantable device that senses electrical signals, such as a cardiac pacemaker or implantable defibrillator, you should tell the physician or cardiac doctor that you have a neurostimulator.

Certain surgical tools and therapy approaches, including cautery, electrocautery, external defibrillators, lithotripsy, dental drills, ultrasonic probes (used to clean teeth), electrolysis (removes unwanted hair), laser procedures, and radiation therapy may cause some damage to the neurostimulator or cause harm to you.
The safety of psychotherapeutic procedures using equipment that generates electromagnetic interference (e.g., electroshock therapy, transcranial magnetic stimulation) is not known and should be avoided. Make sure to inform your doctor if you have any implanted devices.

When the DBS System Should Not Be Used (Contraindications)

Diathermy: Implantation of Medtronic DBS System is contraindicated **(absolutely not allowed under any circumstances because the risk outweighs the benefits**) for patients exposed to diathermy. Inform anyone treating you that you **CANNOT** have any shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (also known as deep heat treatment) anywhere on your body because you have an implanted neurostimulation system. Energy from diathermy can be transferred through

your implanted system, can cause tissue damage and can result in severe injury or death. Diathermy can also damage parts of your neurostimulation system. This can result in loss of therapy from your neurostimulation system, and may require additional surgery to remove or replace parts of your implanted system. Injury or damage can occur during diathermy treatment when:

- Your neurostimulation system is turned 'on' or 'off.'
- Diathermy is used anywhere on your body (not just where you neurostimulation system is located).
- Diathermy is used to deliver heat or no heat.
- Any component of your neurostimulation system (lead, extension, neurostimulator) remains in your body.

Doctors, chiropractors, dentists, physical therapists, and occupational therapists usually provide diathermy treatments.

Transcranial magnetic stimulation therapy (TMS): Implantation of Medtronic DBS System is contraindicated (absolutely not allowed under any circumstances because the risk outweighs the benefits) for patients exposed to TMS therapy.

Patient Use of the Neurostimulator: You should not have a DBS System implanted if you are unable to operate the neurostimulator's patient programmer.

Warnings

Excessive stimulation: There is the possibility of brain tissue damage from high stimulation settings or a malfunction of one of the parts of the neurostimulator.

Case damage: If the neurostimulator is ruptured or pierced (punctured) after the implant due to outside forces, severe burns could result from exposure to battery chemicals.

Electromagnetic Interference (EMI): Electromagnetic interference is a field of energy (electrical, magnetic or a combination of both) that is generated by various equipment found in medical, work, and home environments. This equipment can create enough interference to cause the following:

- Serious injury or death, resulting from heating of the implanted system components, which can damage surrounding tissue.
- System damage, requiring surgical replacement; or result in a loss of, or change in, symptom control.
- Changes in your neurostimulator function, causing it to switch on or off, or reset to factory settings, which may result in loss of stimulation, return of symptoms, and require reprogramming by your doctor.

- Unexpected changes in stimulation, causing a momentary increase in stimulation or intermittent stimulation, which some patients have described as "jolting" or "shocking."

Your neurostimulator is designed to protect against most sources of EMI. However, strong electromagnetic fields and permanent magnets can interfere with your system. Even when the therapy is turned off, interference can affect the lead(s). If you suspect EMI, move away from the suspected source of the EMI. If possible, turn off the suspected source of EMI. Then, use your patient programmer to turn your therapy on or off.

Theft Detectors and Screening Devices: Walking through some theft detectors or security gates can cause an increase in stimulation or additional stimulation. It could also turn on or turn off your neurostimulator. Use care when approaching security arches or gates (such as those found in airports, libraries, and some department stores). If an airport security wand is used, ask the security personnel to avoid placing the wand over your neurostimulator. The DBS Patient Therapy Guide has more information about potential interference with electrical equipment.

Additional Equipment Exposure:

You may want to avoid the following equipment or environment. EMI from the following may affect or damage the neurostimulator:

- Antenna of a citizen band or ham (Amateur) radio
- Electric arc or resistance welding equipment
- Electric induction heaters used in industry to bend plastic
- Electrical steel furnaces, for example, the blast furnaces found in steel mills, not the furnaces found in your home
- Power lines
- Television and radio transmitting towers
- Electric substations and power generators
- Therapeutic magnets, if placed close to the neurostimulator

Depression, Suicidal Thoughts, and Suicide: Depression, suicidal thoughts, and suicide have been reported in patients receiving DBS Therapy. The factors responsible for these adverse events have not yet been established, more specifically, a direct cause and effect relationship to DBS has not been established. However, the seriousness of these adverse events requires attention from patients and caregivers. When considering DBS Therapy be sure to discuss any history of depression or suicidal thoughts or behaviors with your physician to determine if this therapy is an appropriate option for you. If you have an

implanted DBS System, it is important to attend ongoing follow-up visits and to immediately notify your physician of any episodes of depression, suicidal thoughts or behaviors, or changes in mood and/or impulse control so that they can help manage these symptoms appropriately. It is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide) to the appropriate authorities.

Medications, over-the-counter drugs, and nutritional supplements: Inform your doctor about any medications, over-the-counter drugs, or nutritional supplements that you are taking. Some may have harmful effects when combined with DBS Therapy.

Precautions

There are certain activities and medical treatments that should be avoided when you have an implanted DBS System. Some of these can cause problems with the components of your system like loss of therapy or damage that would require surgical replacement of parts or all of your DBS System. Others can cause extra energy to travel along the system which can cause tissue damage that may result in severe injury or death. Make sure to always tell any health care worker you visit about your implanted DBS System before any procedure is begun. The

following are activities and treatments that you should avoid or take precautions with as explained by your doctor for as long as you have your DBS System implanted:

Activities requiring coordination: Loss of coordination is a potential side effect of DBS Therapy. Patients should exercise reasonable caution when participating in activities requiring coordination, including those that they were able to perform prior to receiving DBS Therapy (e.g., swimming).

Activities requiring excessive twisting or stretching: Avoid activities that may put undue stress on the implanted components of your DBS System. Activities that include sudden, excessive, or repetitive bending, twisting, or stretching can cause component fracture or dislodgement. Component fracture or dislodgement may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component.

Pushing or twisting the implanted parts of your system: Avoid pushing or twisting the implanted parts of your system, such as the neurostimulator. This can damage the system or cause skin erosion. This may require surgery.

Scuba diving or hyperbaric chambers: You should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA). Pressures below 10 meters (33 feet) of water (or above 2.0 ATA) could damage the DBS System. Before diving or using a hyperbaric chamber, discuss the effects of high pressure with your doctor.

Skydiving, skiing, or hiking in the mountains: High altitudes should not affect the DBS System; however, you should consider the movements involved in any planned activity and take precautions to avoid putting undue stress on the implanted system. For example, during skydiving, the sudden jerking that occurs when the parachute opens may cause lead dislodgement or fractures, which may require surgery to repair or replace.

Effect on electrocardiograms (ECGs): Ensure the neurostimulator is programmed OFF prior to initiating an ECG. If the neurostimulator is on during an ECG, the ECG recording may be adversely affected, resulting in inaccurate ECG results.

Radio-frequency sources: Analog and digital cellular phones, AM/FM radios, cordless phones, and conventional wired telephones may contain permanent magnets. To prevent undesired turning on or off the stimulation, these devices should be kept at least 10 cm (4 in) away from the implanted neurostimulator.

Component failures: The DBS System may unexpectedly stop working due to the battery wearing out or other causes. The symptoms you had before your system was implanted will likely return if the device stops working.

Electromagnetic interference (EMI): Interference from EMI sources could cause: serious injury or death, system damage, changes in your neurostimulator function, and/or unexpected changes in stimulation (jolting or shocking).

Pregnancy: The safety of DBS therapy during pregnancy or delivery is not known.

Components: The use of non-Medtronic components with this system may result in damage to Medtronic components, less than adequate stimulation, or increased risks to the patient.

POTENTIAL BENEFITS

If you agree to be in this study, it is possible that you may not have any direct

medical benefits; however, the information obtained from this study may benefit other patients with PD in the future. We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not have to be in this study to be treated for Parkinson's disease. If you decide not to be in this study, there is other care available to you. You may be treated with a publicly available, approved DBS System, with another surgical procedure or with drugs. You may choose no treatment at all. You should discuss other treatments and associated risks/benefits with your doctor.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. All questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study. You may be asked to sign a new consent form if this occurs.

You have the right to refuse to answer particular questions.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The purpose of this research study is to obtain information on the safety and effectiveness of the Summit RC+S ® neurostimulator; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Your identity will be kept as confidential as possible, as required by law. Your research records may be disclosed outside of Stanford, but in this case, you will only be identified by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.
However, direct personal identifiers such as your name and the serial number of your study device cannot be removed from the electronic media (e.g. disks, CDs, USBs, etc.), which are saved for research purposes at implantation and at each study follow-up visit. Copies of these electronic media are sent to Medtronic as part of the study. The audio and video recordings will not be sent outside of Stanford. The files will be uploaded to an encrypted hard disk.

In accordance with our funding agreement, data from this study will be uploaded to the Data Archives for the BRAIN Initiative (DABI), which is administered by researchers at the University of Southern California and coordinated and funded by the National Institutes of Health (NIH). All data shared in this manner will be deidentified. The goal of DABI is to accelerate high-quality research to improve our understanding of the human brain by making data more accessible to the broader research community.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.
Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Certificate of Confidentiality from the NIH:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not

connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH/NINDS which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law regarding potential child abuse or neglect. It is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide) to the appropriate authorities.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to research the use of adaptive DBS. The study goal is to understand if the device being studied (LFP Beta aDBS System) works as intended, how it impacts PD symptoms and whether it could be used to improve DBS Therapy in the future.

Any data that may be published in scientific journals will not reveal your identity. Patient information may be provided to federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction. In addition, the records of this study may be inspected by your doctor and hospital.

Medtronic will keep your health information confidential in keeping with all applicable laws and regulations. Medtronic may use your health information to conduct this study. Medtronic may use your health information for other purposes, such as:

- Monitoring and improving the performance of its device;
- New medical research;
- Proposals for making new medical products or procedures; and/or
- Other business purposes.

Any reports or publications about the study or any other research will

not include your name or a description of you. Any records identifying you will not be made publicly available. Information received during the study will not be used to market to you nor will your name will not be placed on any mailing lists or sold to anyone for marketing purposes. The US Food and Drug Administration's regulations, as well as other applicable laws, control Medtronic's work in developing and assuring the safety and quality performance of its medical devices. Medtronic may disclose your health information to the FDA, as well as to other US and foreign government authorities responsible for assuring the safety of medical devices. Medtronic also may disclose your health information to institutional review boards and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research. You agree to allow Medtronic to use study data in these ways. You also agree to allow FDA and other governmental authorities to inspect your health information.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

Dr. Bronte-Stewart
300 Pasteur Drive, Room [redacted]

Stanford, CA 94305.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, name, date of birth, phone number, address, email, medical records, physical and neurological examinations, neuropsychological test results, MRI scans, x-rays, data acquired during the DBS surgical procedure, neural data acquired by the implanted stimulator, DBS programming data, videotaped evaluations, clinical rating scales (such as the UPDRS), and current or past medications may be used or disclosed in connection with this research study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director: Dr. Helen Bronte-Stewart
- The Study Nurse
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Medtronic, the "Study Sponsor" and its employees, agents, representatives, independent consultants and contractors who perform work related to the Research Study for the Study

Sponsor
- A court of law, if the court orders the disclosure
- Your health insurance provider or other payer, if necessary
- The Food and Drug Administration
- The National Institutes of Health (NIH/NINDS)

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on January 1, 2055 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment

For postoperative study visits, you will be reimbursed at the IRS rate for mileage driven from your home to Stanford Neuroscience Health Center and back. If you do not have a handicap placard, we will provide parking stickers to pay for parking at the Hoover garage. For patients living more than 60 miles away, you will be reimbursed for study visit related hotel fees according to federal per diem rate.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

Sponsor

Medtronic is providing financial support in the form of materials to Stanford Medical Center for this study. Dr. Helen Bronte-Stewart is a paid advisor to Medtronic, the company whose products are being used in this study.

This study is sponsored by the National Institutes of Health, Institute of Neurological Disorders and Stroke (NIH/NINDS).

COMPENSATION FOR RESEARCH-RELATED INJURY

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining

appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance**.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Study-specific Contact: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director. Dr. Bronte-Stewart can be reached at [redacted] You should also contact her at any time if you feel you have been hurt by being a part of this study.

If you need to change your appointment, please contact our research staff at [redacted].

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB: Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

VIDEO RECORDING (INCLUDING AUDIO) CONSENT

All kinematic testing and research procedures will be video (including audio) recorded. The video content will be used at a later time only by the research staff to review what happened during the experiment and to aid in data analysis accuracy. The video content will be stored on encrypted, password-protected hard drives that are stored in locked office cabinets.

I give consent to be videotaped during this study:

Please initial:_____Yes_____No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent