Adaptive Closed Loop Neuromodulation and Neural Signatures of Parkinson's Disease

Study Protocol, Statistical Analysis Plan, and Informed Consent Form

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2. REPORT OF PRIOR INVESTIGATIONS

For prior investigations with Medtronic DMF 2010 – Activa PC+S Neurostimulation System, please refer to Medtronic Right of Reference Letter located in **Appendix B** and [redacted] Master File # [redacted] (PDF Page 58).

Clinical investigations of the standard DBS system

The Bronte-Stewart Lab has performed several clinical investigations using the FDA approved Medtronic device, the Activa PC Deep Brain Stimulation (DBS) system, since 2005. From here on, this term - the DBS system - will refer to the standard (nonsensing) implantable pulse generator (IPG), its connectors, leads and the four electrodes that are implanted in the brain. We were the first to show that the presumed brain biomarker of Parkinson's disease (PD), specifically the beta rhythm, was attenuated after short periods of DBS[1]. We subsequently showed that the resting beta rhythm was stationary and was similar across hemispheres in individuals but different among people with PD, and that there was evidence that this abnormal rhythm in the brain in PD was a property of a widespread bilateral sensorimotor network[2, 3]. We demonstrated that there was a gradient in the power of this rhythm within the main target nucleus for DBS in PD, the subthalamic nucleus (STN), and that DBS both at this site and dorsal to the nucleus attenuated the beta rhythm power in a voltage-dependent fashion in PD and showed prolonged attenuation of beta power after longer periods of DBS[2,4,5]. We have also reported that such abnormal electrophysiology is seen in both primary and secondary dystonia in the brain and that DBS also attenuates beta rhythm power in dystonia in the target nucleus, the globus pallidus interna (GPi). We are in the pilot stages of our investigations of abnormal electrophysiology during tremor and movement and the effects of DBS on such. With the technological development of the sensing IPG, we will be able to move these experiments from the operating room to the laboratory.

3. INVESTIGATIONAL PLAN (Study 2: Adaptive Closed Loop Neuromodulation for Parkinson's Disease)

3.1. Purpose

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), internal segment of the globus pallidus (GPi), and/or thalamus has become the standard of care FDA-approved treatment for Parkinson's disease (PD), tremor, and dystonia. DBS consists of the implantation of chronic stimulating electrodes (leads) - Medtronic models 3387 or 3389 - into the nucleus of choice. The DBS leads are connected to an implantable neurostimulator called Activa PC (already FDA approved). Medtronic has developed a new DBS implantable system called Activa PC+S. Activa PC+S will have therapy equivalent to Activa PC.

Activa PC+S's new sensing capability allows for chronic recording of neural activity in the presence of stimulation or when stimulation is turned off. Furthermore, the new device permits non-invasive data transfer of recorded neural signals.
The Nexus-D system is a newly developed research technology allowing for bidirectional communication of information between the Activa® PC+S and a portable computer (PC).

Currently, cDBS is limited to "open-loop" stimulation without real-time adjustment for the patient's state of activity, fluctuations and types of motor symptoms, medication dosages, or neural markers of the disease. The purpose of this proposed study is to determine if an adaptive DBS system, responding to patient-specific clinically relevant neural or kinematic feedback, is more effective than continuous DBS on the motor Unified Parkinson's Disease Rating Scale (UPDRS III) and specific phenotypic measures in Parkinson's Disease.

Used in conjunction, the Nexus-D and Activa® PC+S devices will allow us to begin to investigate "closing the loop" and will allow for the implementation of adaptive neuromodulation (aDBS) which adjusts stimulation parameters in real-time to account for patients' symptoms and actions. The Nexus-E system firmware update, when used in conjunction with Nexus-D, allows for neural recording without data compression in order to analyze the effect of adaptive DBS on LFP power.

Currently, there are a myriad of possible algorithms to inform aDBS based on numerous potential kinematic and neural options for use as input signals. Preliminary studies have shown improvement in items of the motor Unified Parkinson's Disease Rating Scale (UPDRS III), and predicted decreased energy when using aDBS triggered by resting state beta band (13-30 Hz) peak power compared to continual feed-forward DBS and randomized stimulation[1]. However, it is unknown if peak beta power is the optimal neural classifier for tremor, bradykinesia, freezing, and/or when the patient is undergoing their activities of daily life. The tools available in the
Activa® PC+S, Nexus-D and Nexus-E System will allow the opportunity to test such algorithms within safe and externally-controlled boundary conditions for the first time in human subjects with PD.

3.2. Protocol

3.2.1 Background and significance

The proposed study will mark the first clinical implementation of the Nexus-D/E device to create a closed-loop stimulation system. Neuromodulation and changes of stimulation parameters will be implemented by computer algorithms using neural and kinematic triggers

imputed to the PC and communicated to the Activa® PC+S neurostimulator using the Nexus-D/E system.

Concurrent synchronized kinematic signals will be recorded using an analog-to-digital converter (CED, Cambridge Electronic Design Limited, Cambridge, England). These will be used to determine classifier algorithms for the states of tremor or bradykinesia using angular velocity sensors strapped to the hands. Patient-specific kinematic triggers of tremor amplitude and movement velocity will be used to trigger aDBS. By optimizing neurostimulation outside the clinical setting, aDBS will reduce the number of office visits and travel for many PD patients. The ideal aDBS system would also adjust to therapies and motor states over time, preventing harmful side effects. Additionally, aDBS may allow for significantly less total energy delivered compared to cDBS since neurostimulation is only turned ON when disease-pertinent classifiers are present. This should prolong battery life and reduce the necessity and frequency of neurostimulator replacement surgeries which reduces overall surgical risk. Adaptive or "intelligent" deep brain stimulation will allow for the continuous optimization of therapy on an individual basis, maximizing motor improvement and minimizing adverse effects.

We believe that the field of neurostimulation is about to undergo a significant paradigm shift, similar to the revolution in cardiac pacing when demand-based pacemakers were realized that could pace the heart in response to abnormal heart rhythms. This research will allow us to identify the abnormal brain signals or brain "arrhythmias" responsible for abnormal motor behavior in PD and will ultimately allow the design of demand or feedback brain pacemakers.

3.2.2 Specific Aims

SA1: Determine the efficiency and effectiveness on PD signs of aDBS, triggered by patient-specific resting or movement state neural activity, compared to cDBS, using the UPDRS III and validated high-resolution kinematic metrics of tremor, bradykinesia and freezing of gait (FOG).

Primary Hypothesis: Resting state aDBS will reduce energy consumption compared to cDBS as well as improve overall motor outcome, but may have differing effects on the individual PD motor signs.

SA1a. Determine the neural classifier of the resting or movement state to use as a trigger for aDBS. Hypothesis: Patient-specific beta band synchrony is a classifier of the off therapy resting or movement state in PD and can be used as a trigger for aDBS[1,2]. Using individualized algorithms, resting or movement state neural activity will be tested as the stimulation trigger, activating aDBS when beta power is above a specific threshold. SA1b. Compare the efficiency and effectiveness on PD symptoms of aDBS (using the patient specific resting state neural classifier) compared to cDBS at the same neurostimulation parameters**.**

SA2: Determine whether aDBS using a kinematic classifier pertinent to the patientspecific phenotype is more efficient and/or effective on PD symptoms than aDBS using the using the patient's specific resting or movement state neural classifier and/or cDBS.

Secondary Hypothesis: Different PD motor phenotypes may respond better to aDBS triggered by the kinematic classifier respective to that state than to aDBS triggered by the resting or movement state neural classifier or to cDBS.

SA2a. Determine the kinematic classifiers for the states of tremor and bradykinesia, and develop the control policy algorithms of optimal DBS settings that improve each motor abnormality. SA2b. Compare the efficiency and effectiveness on PD symptoms of tremor or bradykinesia kinematic aDBS versus resting or movement state neural aDBS and cDBS.

SA3: Determine whether aDBS is more efficient and effective than cDBS in the optimized on medication state after six months of cDBS.

Tertiary Hypothesis: Neural and/or kinematic classifiers and control policy algorithms will need to be adapted to different medication states, making aDBS more or less useful. After six months of cDBS plus medication, SA1 and SA2 will be repeated in the optimized on medication state. The control policy algorithms will be adjusted as necessary to adapt to this state**.**

3.2.3 Study Design, Setting/Location

This is an open-label pilot study of up to 30 people with Parkinson's disease. All experiments will be performed in the Stanford Human Motor Control and Balance Laboratory in the department of Neurology and Neurological Sciences at Stanford University Medical Center. A unique aspect of the Stanford Movement Disorders Center is the Stanford Human Motor Control and Balance Laboratory, in which we have developed several quantitative measures of motor control and a parallel line of research in human motor control in movement disorders. These measures have been validated with the clinical scale most widely used in PD research, the UPDRS III, as stated above.

Study Population

The study will be carried out in up to 30 people with moderate to advanced PD who will have been evaluated and approved to have subthalamic deep brain stimulation to treat their motor signs. Subjects who have been implanted with Activa PC+S and are participating or have completed Study 1 will be asked to complete Study 2. In order to account for study attrition additional subjects (up to 30) will be recruited into study 2.

Battery life on the Activa PC + S (research device) and the Activa PC (FDA-approved clinical device) is estimated to last approximately 3-5 years. A limited number of subjects will be invited to be replaced with an Activa PC+S, should they chose to remain in the study. Invitations to receive a replacement Activa PC+S will depend on the focus of future experiments, quality of signal, and device availability. If the patient would prefer not to continue in the study, or if they are not invited to continue, they may proceed with the standard implantation of the non-research device.

3.2.4 Eligibility Criteria

The eligibility criteria are the same as those used for Study 1

Inclusion criteria:

1. A diagnosis of idiopathic Parkinson's disease with bilateral symptoms at Hoehn and Yahr Stage ≥ II.
2. Documented improvement in motor signs on versus off dopaminergic medication, with a change in the Unified Parkinson's Disease Rating Scale motor (UPDRS III) score of ≥ 30% off to on medication.
3. The presence of complications of medication such as wearing off signs, fluctuating responses and/or dyskinesias, and/or medication refractory tremor, and/or impairment in the quality of life on or off medication due to these factors.
4. Subjects should be on stable doses of medications, which should remain unchanged until the DBS system is activated. After the DBS system is optimized (during which time the overall medication dose may be reduced to avoid discomfort and complications such as dyskinesias), the medication dose should remain unchanged, if possible, for the duration of the study.
5. Treatment with carbidopa/levodopa and with a dopamine agonist at the maximal tolerated doses as determined by a movement disorders neurologist.
6. Ability and willingness to return for study visits at the initial programming and after three, six, and twelve months of DBS.
7. Age > 18

Exclusion criteria:

1. Subjects with significant cognitive impairment and/or dementia as determined by a standardized neuropsychological battery.
2. Subjects with clinically active depression, defined according to the Diagnostic and Statistical manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and as scored on a validated depression assessment scale.
3. Subjects with very advanced Parkinson's disease (Hoehn and Yahr stage 5 on medication (non-ambulatory)).
4. Age > 80.
5. Subjects with an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator, or medication pump.
6. Subjects who are pregnant, are capable of becoming pregnant, or who are breast feeding.
7. Subjects with an MRI showing focal brain lesions that could indicate a non-idiopathic movement disorder.
8. Subjects having a major comorbidity increasing the risk of surgery (prior stroke, severe hypertension, severe diabetes, or need for chronic anticoagulation other than aspirin).
9. Subjects having any prior intracranial surgery.
10. Subjects with a history of seizures.
11. Subjects who are immunocompromised.
12. Subjects with an active infection.
13. Subjects who require diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition.
14. Subjects who have an inability to comply with study follow-up visits.
15. Subjects who are unable to understand or sign the informed consent

Subgroups: We will attempt to recruit an equal number of tremor-dominant and tremor absent people as well as an equal number of people with documented freezing episodes and those without. Some with tremor may or may not freeze and vice versa. We will also attempt to recruit women and minorities, although the incidence of PD is higher in men and highest in Caucasians, so with only 30 subjects in this pilot trial, there may be more men than women and more Causasians than other ethnic groups in our cohort.

3.2.5 Study outcomes

Beta power, UPDRS III, and quantitative measures of tremor (rest tremor recording for 1 minute), bradykinesia (WFE task), speech and FOG (using a Stepping in Place (SIP) task[4]/Gait Analysis), and time DBS ON over the time on aDBS.

3.2.6 Recruitment

Subjects with Parkinson's disease who have been accepted for DBS implantation will be asked if they wish to participate in this study. All subjects will have undergone challenged on medication and practically defined off medication evaluations by a fellowship-trained movement disorders neurologist and detailed neuropsychological testing by a neuropsychologist prior to being presented at the movement disorders surgical review board. The movement disorders surgical review board consists of the neurosurgeons, movement disorders neurologists, psychiatrist, neuropsychologist, and nurse specialists, who evaluate each candidate's suitability for surgery and reach a consensus decision about each person. If s/he is accepted for DBS, s/he is scheduled to meet the neurosurgeon. At this visit they will be met in person by the research coordinator, who will with permission sit down in person with them and any family present to explain the study and review the informed consent. Feasibility of and time for recruitment: on average the Stanford Movement Disorders Surgical Review board accepts 6 – 10 patients for DBS per month. If it is assumed conservatively that 50% of patients asked will consent, then the recruitment of 15 subjects will take a maximum of five months. We recruit subjects currently for intra-operative investigations, which we think would be harder to recruit for than the current study and our acceptance rate is higher than 80%.
We will also recruit subjects who are participating in or have completed Study 1 to consent to and complete Study 2. In order to account for study attrition additional subjects (up to 10 additional) will be recruited into study 2.

Sample Size/Power Analysis: Our preliminary data: change ON versus OFF DBS (mean +/- std dev): beta band power = 57 +/- 6[2], UPDRS = 58 +/- 22%[5], Vrms 45% +/- 63%[3]. Power analysis (paired t-test, p=0.8, alpha =0.001, to allow for multiple comparisons) on the above data gave the largest sample size required for significant outcomes = 27 (STNs), which is similar to the sample size (21) needed to detect difference between aDBS and cDBS reported in previously published results[1].

3.2.7 Study procedures

Medical Adhesive Use: During Activa PC+S implantation surgery, a small amount of medical adhesive (Medtronic Part #080118, Dow Corning Medical Adhesive) is placed on the Activa PC+S Implantable Neurostimulator (INS) (Model 37604) header setscrew grommets and the header bore where the lead extensions are inserted and secured. For further information regarding use of medical adhesive during Activa PC+S implantation and replacement please see **Appendix K** (PDF Page 179), **Appendix L** (PDF Page 181) and **Appendix M** (PDF Page 190).
Nexus E Firmware Update: Subjects enrolled in study 2 will sign an updated informed consent, please see **Appendix N** (PDF Page 197) and undergo a Nexus E Firmware update at their next study visits. Subjects who have not yet been implanted with Activa PC+S will undergo Nexus E Firmware update at their initial programming visit. The Nexus E firmware update will take approximately 30 minutes to perform. During the firmware update the

subject will not receive any therapeutic stimulation. For further information regarding Nexus E please see **Appendix E** (PDF Page 120) and **Appendix F** (PDF Page 150.)

SA1: Determine the efficiency and effectiveness on PD signs of aDBS, triggered by patient-specific resting state or movement neural activity, compared to cDBS, using the UPDRS III and validated, high-resolution kinematic metrics of tremor, bradykinesia and freezing of gait (FOG).
SA2: Determine whether aDBS using a kinematic classifier pertinent to the patient specific phenotype is more efficient and/or effective on PD symptoms than aDBS using the using the patient's specific resting or movement state neural classifier and/or cDBS.

Aim 1 and 2 will be done at the time of initial programming of the DBS system and at the first follow-up visit for subjects who consent before DBS implantation. For subjects who already have the Activa PC+S implanted, Aims 1 and 2 will be performed after they have completed Study 1:

1. Patients will arrive in the off medication, OFF DBS state. Medication will be stopped 72 hours (extended release forms of dopamine agonists), 24 hours (regular form of dopamine agonists, controlled release forms of carbidopa/levodopa (CD/LD)) and/or 12 hours (regular CD/LD, entacapone, rasagiline, selegiline, amantadine) before testing. The DBS system will not have been activated after implantation or will be turned off as per the protocol in Study 1.
2. An interval history, examination, and UPDRS III will be performed. LFPs will be recorded from the DBS leads at rest during the repetitive wrist flexion-extension task and during stepping in place.
3. Real-time STN LFP beta band power will be calculated both OFF DBS and during "therapeutic" DBS. DBS will be applied through the electrode (1 or 2) that lies in between the electrode pair (0-2 or 1-3) with the greatest beta power. Therapeutic DBS: 140 Hz, 60 microsec at 3 volts OR the highest voltage <3V, that does not cause adverse effects.
4. We will determine if the therapeutic DBS will attenuate rest beta power by >= 40%[4].
5. Patients will be seated at rest, or while performing self-paced repetitive wrist flexion-extension (WFE) for periods of 10 seconds after a "Go" signal with angular velocity sensors attached to the hand.
6. <u>SA1a and SA2a (Initial Programming or Initial visit):</u> Determination of classifier thresholds: 1. Resting or movement state neural: ON and OFF triggers when the beta band power is greater than or less than different thresholds of the resting or movement state beta power differential (beta power OFF – ON therapeutic DBS). 2. Kinematic (tremor/bradykinesia): ON and OFF triggers when rectified tremor amplitude/root mean square angular velocity (Vrms) of WFE is greater than or less than different thresholds of tremor/Vrms differential (OFF – ON therapeutic DBS) respectively. <u>SA1b and SA2b (First Followup Visit):</u> Outcomes will be measured after 30 minutes of aDBS or cDBS. For neural and tremor aDBS, the Activa® PC+S will be updated in real time (see delays). For bradykinesia aDBS, the Activa® PC+S will be updated with the Vrms from 10 second epochs of WFE that the PD subject will perform every 2 minutes during the 30 minute trial (rwFE, angular velocity sensors, Motus Motion analysis system, and EMG). **SA3:** Determine whether aDBS is more efficient and effective than cDBS in the optimized on medication state after six months of cDBS.

Aim 3 will be completed after 6 months of continuous DBS and optimized therapeutic medication.

7. Patient arrives in on medication/on stimulation state. Patient is instructed to bring appropriate doses of medication to take throughout the day at pre-set intervals.
8. An interval history, examination, and UPDRS III will be performed. LFPs will be recorded from the DBS leads during some of the clinical assessments such as the repetitive wrist flexion-extension task and during stepping in place.
9. Real-time STN LFP beta band power will be calculated both on medication/OFF DBS, and during "therapeutic" DBS. DBS will be applied through the electrode (1 or 2) that lies in between the electrode pair (0-2 or 1-3) with the greatest beta power. Therapeutic DBS: 140 Hz, 60 microsec at 3 volts OR the highest voltage <3V that does not cause adverse effects.
10. We will confirm that the therapeutic DBS will attenuate rest beta power by >= 40%[4].
11. Patients will be seated at rest, or while performing self-paced repetitive wrist flexion-extension (WFE) for periods of 10 seconds, after a "Go" signal with angular velocity sensors attached to the hand.

12. SA3: Determination of classifier thresholds: 1. Resting or movement state neural: ON and OFF triggers when the LFP band power or variability is greater than or less than different thresholds of the resting or movement state LFP power differential (LFP power OFF – ON therapeutic DBS). 2. Kinematic (tremor/bradykinesia): ON and OFF triggers when rectified tremor amplitude/root mean square angular velocity (Vrms) of WFE is greater than or less than different thresholds of tremor/Vrms differential (OFF – ON therapeutic DBS) respectively.

13. Outcomes will be measured during trials up to 8 hours of aDBS or cDBS. For neural and tremor aDBS, the Activa® PC+S will be updated in real time (see delays). For bradykinesia aDBS, the Activa® PC+S will be updated with the Vrms from 10-60 second epochs of WFE that the PD subject will perform throughout during the trial (rwFE, angular velocity sensors, Motus Motion analysis system, and EMG).

Blinding: The PD subject, investigators (certified) performing the UPDRS III, and investigator analyzing data will be blinded to the type of DBS used for a particular experiment. All experiments will be videotaped and two additional independent certified raters will rate the UPDRS III.
Randomization: The order of aDBS, cDBS, and all motor tasks will be randomized for each subject and enough time will be given in between for patient rest and for return to baseline of beta power, tremor, and bradykinesia.

3.2.8 Clinical Assessments

Clinical Assessments	Pre-surgery Baseline	Initial programming	1 mo. Post IP	6 mo. post IP
	Off Meds	Off Meds	Off Meds	On Meds
Repetitive Wrist Flexion-Extension Movement	x	x	x	x
Tremorography	x	x	x	x
Stepping in Place (SIP)	x	x	x	x

Gait Analysis		x	x	x
UPDRS III / H&Y	x	x	x	x
Medical History	x	x	x	x
Physical Exam	x			
MOCA	x			
Columbia Suicide Severity Scale	x	x	x	x
Electromyography (EMG)		x	x	x
Local Field Potentials		x	x	x
Adaptive DBS Testing (Kinematic and Neural triggers)			x	x

Note: The subjects will be given practice trials for all of the quantitative tasks listed below to ensure that the goal and the instructions of the task are understood before each assessment is performed. At the baseline visit, the baseline version of the Columbia Suicide Severity scale (CSSS) will be used. At every subsequent visit, the "Since last visit" version of the CSSS will be used.

1. **Repetitive wrist flexion-extension movement – rwFE:** Using solid-state gyroscopic sensors (Motus Motion analysis system) that fit like a glove on the patient's hands and surface EMG sensors (Delsys Bagnoli 2 EMG System) placed on the wrist flexor and extensor muscles, the wrist movement and the muscle activation patterns will be quantified. Specifically, we will directly measure angular velocity and muscle activations. The patient's arm will be kept at 90 degrees in elbow flexion with the forearm in a neutral position. The patient will perform a wrist flexion-extension movement continuously from the "go" to the "stop" command. This test will assess the subject's bradykinesia state.
2. **Tremorography:** If the subject shows visible tremor of the hands using the above mentioned angular velocity sensors, his/her resting or postural tremor behavior will be measured. Surface EMG sensors will be placed on forearm muscles to capture the muscles' activation pattern.
3. **Repetitive alternating finger tapping (RAFT) keyboard task:** RAFT is a computerized objective measure of movement velocity, speed of movement, and timing using an engineered keyboard (Quantitative DigitoGraphy) with two adjacent keys. The subject will alternatively finger tap (trill) on the keyboard. The test will be performed twice for each hand. The patient will be seated at a table on which the keyboard is placed with the hand that does not perform the task placed in his/her lap. The subject will be instructed to tap as fast as s/he can while maintaining the alternating movement. This test will quantify a set of movement abnormalities seen in Parkinson's disease patients such as bradykinesia, freezing of movement, tremor, or fatigue.

4. **Stepping in place (SIP) task:** The subject will be asked to step in place repetitively on two adjacent force plates (Smart EquiTest, Neurocom Inc) with each foot on each forceplate. The subject will step at a speed similar to his/her normal walking. A baseline quiet stance will be acquired at the beginning and the end of the test. The subject will wear a harness to protect him/her from falling. This test will quantify measures such as gait asymmetry, gait rhythmicity, and left-right step coordination. These metrics may provide clues to underlying mechanisms involved in freezing of movement in PD. Our lab showed that the SIP metric has a high sensitivity (93%) and specificity (87%) for identifying freezers from non-freezers[5].
5. **Unified Parkinson's Disease Rating Scale part III – Motor Examination (UPDRS III):** The clinical motor assessment of the subject will be performed using the UPDRS III scale.
6. **Gait Analysis**: Subjects will wear sensors on their hands, arms, chest, trunk, feet and legs (Opal sensors, APDM, Inc). These tasks will quantify measures such as gait asymmetry, gait rhythmicity and left-right step coordination during subjects normal walking. Subjects may be asked to do regular forward walking as well as walking around obstacles (such as chairs, or small room dividers) or turning in place. These obstacles and turning in place will be used in order to elicit freezing, which often occurs in constrained spaces. This type of freezing is frequently encountered in subjects' daily lives. Subjects will be monitored carefully by research team in order to ensure their safety and comfort.

7. **Cognitive Testing**: Subjects will be administered the Montreal Cognitive Assessment at visits after the pre-surgery baseline visit. In both the resting and movement state, subjects will perform cognitive tasks that include but are not limited to reciting the months of the year backwards and serial 7s.

8. **Speech Assessment**: While wearing a voice-recording headset, subjects will be performing speech tasks that include reading sentences and phonation.

9. **Vibrotactile Stimulation:** Subjects may be asked to perform the above gait tasks with sensory cueing using the VibroGait system. Intermittent vibrotactile stimulation may be applied to the wrists, or another body part with intact sensation, in a manner that is either coordinated with or unrelated to the subject's gait cycle in real time. Subjects will be allowed to practice with the VibroGait on before completing the tasks.

In addition to Nexus testing, subjects attending clinical programming follow-up visits will come in off medication and on stimulation and will be asked to repeat quantitative assessment of motor function and simultaneous LFP recording. Subjects come in for programming visits every 3-6 months for 1-3 years post device implantation. Patients who receive replacement Activa PC+S devices will continue to complete the same assessments listed above in order to further the aims of both Study 1and 2. These experiments will allow us to collect data related to longer term disease tracking. Disease tracking includes monitoring the patients' beta band over time, in accordance with SA3 from study 1 (SA3: Determine the long-term effects of STN DBS on neural signatures and motor behavior; ascertaining whether long-term DBS changes the underlying neural signatures and dose response characteristics of PD behavioral states).

Testing for disease tracking will include quantitative digitography (QDG), quantitative range of motion analysis (Motus, LG G Watch, APDM System), tremorography, surface electromyography (EMG), and computerized dynamic posturography, SIP, gait analysis, cognitive testing and UPDRS III. Testing for replacement device patients will also include aDBS experiments, with the same protocol as detailed above. The subjects will perform these

assessments in the on clinical stimulation state and will repeat all or a subset of these tests in the off stimulation state.

3.2.9 Adverse Event Reporting

We will report any unanticipated adverse device effects to Medtronic and IRB as soon as possible after the event occurs (within 10 working days after first learning about event). Evaluations of unanticipated adverse device effects will be reported to the FDA, IRB, and Medtronic within 10 days after receiving notice of effect and in accordance with guidance 812.150. We do not expect any adverse events related with the functionality of the implanted device.

3.2.10 Data Analysis

Experimental outcomes: Beta power, UPDRS III and quantitative measures of tremor (rest tremor recording for 1 minute), bradykinesia (WFE task) and FOG (using a Stepping in Place (SIP) task and gait analysis), and time DBS ON over the 30 minutes on aDBS.
Number of arms: (One) Patients will be used as their own controls.
All quantitative data will be post-processed using custom MATLAB software (The MathWorks, USA).

1. **Repetitive wrist flexion-extension movement – rwFE:** The Motus motion analysis system will be used to obtain an objective quantitative assessment of bradykinesia by measuring hand angular velocity during a quantitative repetitive wrist flexion-extension task (rwFE). The system consists of sensors in which vibrating quartz crystals act like solid-state gyroscopes and produce an analog signal whose voltage is proportional to the angular velocity when rotated about its measurement axis. These sensors are unlike conventional accelerometers in that they are indifferent to their orientation with respect to gravity. Each sensor weighs about 60 g, has a maximum range of 1,900 degrees per second, a low noise level of 1 degree per second RMS, and a flat response to 30 Hz. The angular velocity data will be digitized at a rate of 100 samples per second per sensor. The root mean square velocity of angular movement (Vrms) will be used as an indication of the average speed at which the flexion-extension task is performed. The frequency spectrum of the angular velocity will be analyzed using a fast Fourier transform (FFT) analysis in each trial to ensure that patients' movements are not dominated by a fast-action tremor (7–12 Hz).
2. **Tremorography;** Using the above mentioned angular velocity sensors, the angular velocity data during rest and/or postural poses will be digitized at a rate of 100 samples per second per sensor and the frequency spectrum will be will be analyzed using an FFT analysis to detect and quantify the type of tremor (rest 4-6 Hz or action/postural 712 Hz) that is present.
3. **Muscle activation patterns:** The Delsys Surface EMG System will be used to collect electromyography signals from the wrist flexor and extensor muscles. The signals will be filtered using a fourth-order band pass Butterworth (20-300 Hz) applied in the forward and reverse directions to prevent phase distortions. The linear envelope of the rectified signals will be calculated by finding the absolute value of the signal and then calculating the RMS value at every 50 ms. The signals will be normalized by the average of the three greatest peak values of each muscle for comparing amplitude of muscle activity within tasks for each patient and also across patients.
4. **Repetitive alternating finger tapping (RAFT) keyboard task**: The engineered keyboard outputs a calibrated analog signal that corresponding to the displacement of the keys. The downstrike velocity, interval between strikes, and duration of keystrikes will be extracted from the recorded signal.

5. **Stepping in place (SIP) task;** During the SIP task, ground reaction forces will be captured at 100 Hz with two force plates (Advance Mechanical Technology Inc, Watertown, MA, USA). A freezing episode (FE) will be defined when the patient is unable to completely lift a foot from the force plates (i.e. when the vertical forces did not reach 100% (foot in stance) and 0% (lifting phase)). FEs will be identified only if detected visually and with the computerized algorithm. The experimenter will document the occurrence of FEs to compare with the offline force plate data analysis. A computerized algorithm to automatically detect freezes will be performed in MATLAB. Signals from the force plates will first be low-pass filtered at 12 Hz with a second order Butterworth filter. Peaks reaching values below 15% and above 85% and separated by more than 400ms
will be detected. If fewer than 20 peaks are detected on one of the force plates, the entire trial will be considered a FE and the analysis will be terminated. For each signal, abnormally long intervals will be defined as intervals between two maxima or two minima whose duration is longer than either 1.2 times the average duration of the intervals between the corresponding extrema in the three previous cycles, or longer than twice the average interval duration in the whole trial. A FE will be defined as an episode of abnormally long intervals detected concurrently on the two force plates. Finally, using the same criterion as for visual detection, when fewer than four minima and fewer than four maxima on each force plate (fewer than three strides) separated two FEs, these will be combined into a long FE. The stepping cycle symmetry and rhythmicity of SIP will be calculated for the first 25 s of each SIP trial and will be averaged over the three trials. According to previous studies, asymmetry and rhythmicity were defined as: SIP cycle asymmetry = 100 x [ln(SSWT/LSWT)], where SSWT and LSWT correspond to the leg with the shortest and longest mean swing time over the trials, respectively and rhythmicity = the mean stride time coefficient of variation (CV) of both legs. A large stride time CV would be indicative of a less rhythmic gait.
6. **Gait Analysis:** Standard quantitative gait metrics including but not limited to freezing episode duration, gait speed, gait asymmetry, gait rhythmicity, swing phase and left-right step coordination.
7. **Speech Analysis:** Audio recordings of the speech tasks will be analyzed to obtain metrics that include but are not limited to diadochokinesis rate, speaking rate, intelligibility rate, and communication efficiency ratio.

3.3. Risk Analysis

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).

The VibroGait is non-invasive and provides mild sensory feedback in the form of vibration, set to a frequency and intensity similar to a cell phone on vibrate mode. The vibration should not be painful, but if subjects do experience discomfort or pain they will be able to stop using the VibroGait at any time.

The Nexus-D/E System does not allow the clinician to change the stimulation configuration beyond what a patient programmer (model 37642) is capable of changing; therefore, a research system utilizing the Nexus-D/E system can effectively act only as an automated patient programmer when updating stimulation parameters.

Just like the existing patient programmer, the Nexus-D/E system provides the host computer with the capability of changing stimulation only within physician-configured neurostimulator limits programmed with the model 8840 Clinician Programmer (e.g. – incrementing or decrementing stimulation amplitude). Since the only stimulation updates allowed are those that stay within the physician limits, all risk mitigations implemented by the model 8840 Clinician Programmer are in full effect with no new stimulation-related risks introduced by the use of the Nexus-D/E System. Furthermore, the Nexus-D/E system is used under the direct supervision of the clinician and is not used outside of the acute clinical setting (i.e. – not taken home by the patient).

The Nexus D/E system does not make any stimulation update decisions. The system acts only as a conduit for data and commands between a host computer and the implanted neurostimulator. All decisions are made by the clinician who implements the host application. The Nexus E system is used in conjunction with Nexus D for improved fidelity of neural recordings. The Nexus E system firmware update takes approximately 30 minutes to perform. During the firmware update the subject will not receive any therapeutic stimulation.

Prior to all experiments performed using Nexus D and/or Nexus E system, the clinician will manually test the transition rise and fall times ("ramp rates") used during closedloop functionality. These manual tests will confirm patient comfort during adaptive DBS research protocols. Following all in-clinic experiments including closed loop experiments with Nexus-D or Nexus-E, patients will always be set back to their clinical stimulation settings before leaving the laboratory and will not be sent home with any aDBS settings.

The application of medical adhesive prevents observation of cardiac artifact in Activa PC+S brain recordings. Neither application of medical adhesive nor observation of cardiac artifact in Activa PC+S brain signal recordings impacts standard Deep Brain Stimulation (DBS) patient therapy or patient safety. Please see [redacted] Master File # [redacted] and **Appendix L** (PDF page 181) for further details.

There may be risks associated with the other unapproved Activa PC+S and Nexus-D components. Please reference **Appendix G and H** risk assessment for Nexus-D, Nexus E and Activa PC+S and [redacted] Master File # [redacted]

3.4. Description of Device

Please see **Appendix C** (PDF Page 60) for description of Activa PC+S Neurostimulator System and **Appendix D** (PDF page 69) for description of Nexus-D System. Please see **Appendix E - F** (PDF page 120 and 150) for information regarding Nexus-E system. Please see **Appendix K-M** (PDF Page 179, 181 and 190) for information regarding medical adhesive.

Wireless Nexus-D System Infrared Interface Update

The Nexus-D consists of a reprogrammed Medtronic sensing programmer telemetry module (SPTM) to create a communication channel to the implanted Activa neurostimulator. A host application on a desktop computer can access this communication channel through a commercially available USB to IrDA (infrared data association) bridge (an Actisys IR224UN). The Nexus-D system is comprised of this combination of the reprogrammed SPTM and the commercially available USB to IrDA bridge. It is important to note that the bridge is purely a translator between the USB interface from the PC and the infrared communication interface. No command generation, interpretation or parsing of data is

performed in the bridge of any kind. It simply passes any data communicated over USB directly to the Nexus SPTM and viceversa.

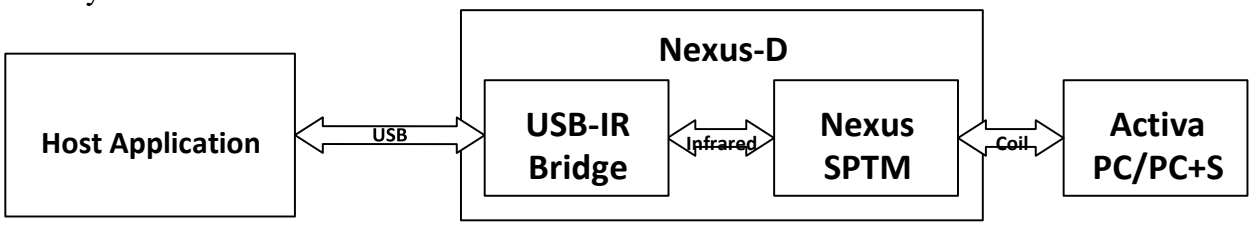

Figure 1 Nexus-D Block Diagram

Due to the fact that this bridge is a commercially available device that is unneeded for the overall functionality that the Nexus-D system provides, we have decided that it would be advantageous to remove it from the system. Our collaborators at University of Washington-Biorobotics lab (UW-BRL) have built a system that instead communicates directly to the Nexus SPTM over the infrared interface.

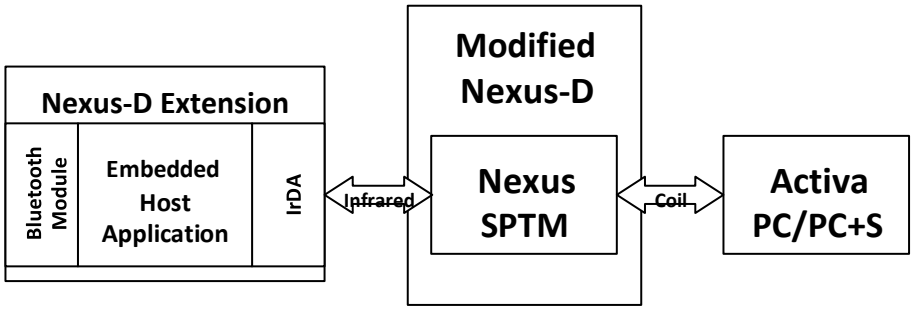

Figure 2 UW BRL Nexus Modification

In this system all of the safety mechanisms and functionality of the Nexus-D is maintained. However, this system give us the advantage of building battery-powered embedded systems that will allow for studies in ambulatory patients without the need to be tethered to a PC for the duration of the experiments.

3.5. Monitoring Plan

Same Monitoring Plan as Study 1

The project will be monitored to ensure the rights and well-being of the patients who consent to it; to ensure that the technical aspects of the study are carried out in a safe, accurate, and consistent manner; and to ensure that the data is collected and stored in a secure manner and is accurate, complete and verifiable.

Prior to the initiation of the experiments, monitors will review the protocol, inspect the laboratory and the equipment to be used, ensure that the data will be collected and stored in a secure and reliable manner, and that the investigators are trained in the protocol. Monitors will participate in “dry runs” of the experiments with the investigators to document the above readiness before the study will commence.

The monitors will verify that the investigators have adequate qualifications and resources which remain adequate throughout the trial period; and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period. The monitors will have formal meetings with the protocol director, Dr. Bronte-Stewart, and the investigative team every two months to review the number of patients recruited; to document that the data is being collected and stored correctly; and to document any adverse events, equipment issues and or data concerns. Monitors will formalize these with a report which will be provided to the IRB annually. Monitors will agree to meet on an ad hoc basis if there are any concerns that need to be

addressed immediately. They will have the authority to recommend that the study be terminated if they believe that this is in the best interest of the subjects enrolled.

Monitor Names & Addresses

Matthew Petrucci, MS, PhD
Stanford University Medical
Center 300 Pasteur Drive,
[redacted] Stanford, CA 94305

Dr. Petrucci has a MS in mechanical engineering and PhD in neuroscience. He has expertise in biomechanics, neurophysiology, mechatronics, engineering controls, and signal analysis in MATLAB, Simulink, C++. He has previous experience with closed-loop DBS protocols and PC+S recordings. His role as an engineer is to help oversee the technological and data aspects of the study.

Brent Bluett, DO
Stanford University School of Medicine,
213 Quarry Rd [redacted] Stanford, CA 94305

Dr. Bluett is a Fellowship trained Movement Disorders neurologist and a Clinical Assistant Professor in the Department of Neurology and Neurological Sciences at Stanford University School of Medicine. Dr. Bluett has special expertise in the management of patients with implanted DBS devices as well as research experience with Parkinson's disease. Dr. Bluett will monitor all the clinical aspects of the protocol and experiments.

Robert Fisher, MD
Stanford University Medical Center 300 Pasteur Drive, [redacted] Stanford, CA 94305

Dr. Robert Fisher is the Maslah Saul Professor in the Department of Neurology and Professor, by courtesy, of Neurosurgery at the Stanford University Medical Center. He has extensive experience in conducting clinical trials including a stage III trial for DBS therapy treatment of epilepsy.

3.6. References

1. Little, S., Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., Foltynie, T., Limousin, P., Ashkan, K., FitzGerald, J., Green, A. L., Aziz, T. Z. and Brown, P., *Adaptive deep brain stimulation in advanced Parkinson disease*. Ann Neurol., 2013. **74**: 449–457.
2. Bronte-Stewart, H., Barberini, C., Miller Koop, M., Hill, B.C., Henderson, J.M., Wingeier, B., *The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation*. Experimental Neurology, 2009. **215**:20-28.
3. Wingeier, B., Tcheng, T., Miller Koop, M., Hill, B.C., Heit, G., Bronte-Stewart, H., *Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease*. Experimental Neurology, 2006. **197**:244-251.
4. Miller-Koop, M., Andrzejewski, A., Hill, B.C., Heit, G., Bronte-Stewart, H.,

Improvement in a quantitative measure of bradykinesia after microelectrode recording in patients with Parkinson's disease during deep brain stimulation surgery. Movement Disorders, 2006. **21**(5):673-678.
5. Nantel, J., de Solages, C., Bronte-Stewart, H., *Repetitive stepping in place identifies and measures freezing episodes in subjects with Parkinson's disease*. Gait & Posture, 2011. **34**(3): 329-333.
6. Bronte-Stewart, H., Louie, S., Batya, S., Henderson, J.M., *Clinical motor outcome of bilateral subthalamic nucleus deep-brain stimulation for Parkinson's disease using image-guided frameless stereotaxy*. Neurosurgery, 2010. **67**(4): 1088-93.

5. MANUFACTURING INFORMATION

Please reference [redacted] Master File # [redacted].

6. INVESTIGATOR AGREEMENT

Please see **Appendix I**.

7. IRB INFORMATION

Research Compliance Office, Stanford University
3000 El Camino Real
Five Palo Alto Square, 4th Floor
Palo Alto, CA 94306

Please see **Appendix J** for roster**.**

8. . ENVIRONMENTAL ASSESSMENT

This study releases no toxic substances into the environment, nor does it generate any radioactive material. Extracranial electrical fields produced by stimulation are negligible. The sponsor requests categorical exclusion for this study protocol under 21 CFR 25.34 (g).

9. LABELING

Upon receipt of the Activa PC+S, Nexus-D and Nexus-E devices, each individual box will be labeled "INVESTIGATIONAL USE ONLY" and will be kept in locked storage accessible to only the investigator and/or coordinator.

Other device labeling can be found in the [redacted] Master File # [redacted].

10. INFORMED CONSENT

Study 2
Please see **Appendix N** for informed consent forms. There are two versions of the consent form.

1. Informed Consent for those already implanted with Activa PC+S in or completed study 1 and/or study 2.

2. Informed Consent for those who have not been implanted with the Activa PC+S.

Adaptive Closed Loop Neuromodulation and Neural Signatures of Parkinson's Disease -Nexus E Update

Are you participating in any other research studies? _____ Yes _____No

You are invited to participate in a study of your movements for the treatment of your movement disorder (such as Parkinson's disease, Parkinsonism, Essential Tremor, Dystonia, or other). You have been asked to participate because you are being evaluated for Deep Brain Stimulation (DBS) surgery to treat your movement disorder. This research is separate from the DBS, but you can only be in the study if you receive DBS. Up to 15 people who qualify for DBS surgery and up to 15 people who have already had the Activa PC+S implanted will be enrolled into this study (up to 30 Participants total).

Kinematic analysis (computerized movement measurements) will be done in addition to standard clinical examinations. The information gathered from these measurements will be used for the clinical evaluation. Some of it may also be used for clinical outcomes and research projects.

Neural activity will be recorded using the implantable Activa PC+S Neurostimulator System, (Medtronic INC). Data will be retrieved after and during each kinematic testing using a Clinician Sensing Programmer and the Nexus-E System (Medtronic INC).

PURPOSE

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 track how these change over time. The secondary purpose is to use brain and movement signals to automatically 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 demand-based therapy in the future.

This study is being conducted to understand more about brain signals that are involved in movement and not to test the non-FDA approved components of the device.

Your participation in this study is entirely voluntary and your decision not to participate will not have any negative effect on you or your medical care. You can 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. If you decide to terminate your participation in this study, you should notify Dr. Bronte-Stewart by writing to the following address: Dr Helen Bronte Stewart, 300 Pasteur Drive, [redacted], Stanford, CA 94305.

This research study is looking for up to 30 participants with movement disorder (such as Parkinson's disease, Parkinsonism, Essential Tremor, Dystonia, or other).

[redacted]

DURATION OF STUDY INVOLVEMENT
Research in this study will occur at each of your already scheduled clinic visits.

PROCEDURES DURING RESEARCH TESTING
You will have been implanted with the Activa PC+S Neurostimulator System. The device you have received is an investigational device, which is similar to the FDA approved commercial device but has some new components associated with sending information from the stimulator to an external computer. The study will begin after the device has been implanted.

Kinematic analysis during your clinical evaluation: Your doctor will ask for your medical history, and you will have a full physical and neurological examination. This will also reevaluate whether it is appropriate for you to continue participation in this study once enrolled. 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 OFF your medications and again ON your medications. As most patients are taking little or no medication once on DBS, this does not usually cause difficulty in your mobility.

You will undergo computerized assessment of your motor function in the Stanford Human Motor Control and Balance Laboratory. Depending on your condition, this could include repetitive alternating finger tapping (**RAFT),** repetitive wrist flexion-extension (**rWFE**) with simultaneous monitoring of muscle activity (**EMGs**), **tremorography**, and a stepping in place (**SIP**) task. The tests that you undergo will depend on your symptoms, for instance if you do not have tremor, we shall not do the tremorography test. The length of time for each test (range 10-160 seconds) will depend on the assessment point in the study.

RAFT is a computerized objective measure of fine motor control using an engineered quantitative digitography (QDG) keyboard. This test will involve you performing alternating finger tapping movements (trill) on adjacent keys on the keyboard for each hand for either 10, 30, or 80 seconds depending on the test condition. During this test, you will wear a pair of headphones playing white noise at an adjustable, tolerable volume.

RWFE is an objective measure of the speed at which you can move your hand in a repetitive backwards and forwards motion. Motus motion analysis sensors that fit like a glove will be placed on your hands.

EMGs (sensors that record the electrical activity of your muscles) may be placed on the skin above the wrist flexor and extensor muscles that move the hand. Measurements will be taken using the Delsys Surface EMG System while you move your hand from side to

side while holding the rest of your arm stationary for 10, 30, or 80 seconds for each hand depending on the test condition.

Tremorography may be performed using the same glove-like sensors and surface EMG sensors. Using these sensors on your hands/arms and feet/legs, we can record the presence of tremor. During the task, your hands and feet should be in a relaxed position and your hands and feet are extended out in front of your body. This test will last for 10, 30, or 70 seconds for both the hands and the feet depending on the test condition.

Gait Analysis: You will wear sensors on your hands, arms, chest, trunk, feet and legs (APDM System). These tasks will quantify measures such as gait asymmetry, gait rhythmicity and left-right step coordination during your normal walking. You may be asked to do regular forward walking, step in place, turn in place, and/or walk around obstacles such as small room dividers. These obstacles will be used in order to elicit freezing, which can often occur in constrained spaces. You will be monitored carefully by the research team in order to ensure your safety and comfort. All quantitative tests are non-invasive.

The stepping in place (**SIP**) task is an objective measure of your ability to walk. While wearing a harness and the APDM sensors on your body, you will be asked to step in place repetitively on two adjacent force platforms (Bertec Balance Advantage – Dynamic CDP by Bertec Corporation, Columbus OH) with one foot on each force platform. You will be asked to perform this stepping motion at your normal walking speed for 60, 100, or 160 seconds depending on the test condition.

Vibrotactile Stimulation: You may be asked to perform some or all of the gait tasks above while wearing the VibroGait device on your wrists or other extremities. The VibroGait was developed by our collaborators at Oregon Health & Sciences University, who may also be present during testing with this device. The VibroGait produces an intermittent vibrotactile (i.e., vibration) stimulation. The vibration feels similar to a cell phone on vibration mode.

During or before the above tasks, you may also be asked to wear google glasses and watch a series of videos of an individual walking to a predetermined cadence. Videos are developed by Moving Through Glass, a project created by the Mark Morris Dance Company. There are videos that address typical Parkinson's disease symptoms such as balance, smooth movement, walking, and freezing of gait. You will be watched carefully to be sure you can handle the walking while wearing the glasses.

Cognitive Testing

A certified administrator will administer the Montreal Cognitive Assessment (MoCA) to assess overall cognitive function. During kinematic tasks, subjects may be asked to perform cognitive tasks that include but are not limited to reciting the months of the year backwards and serial 7s.

[redacted]

Columbia-Suicide Severity Rating Scale (C-SSRS)
The C-SSRS questionnaire is used for suicide assessment developed by multiple university institutions. The purpose of this risk assessment is to help establish a person's immediate risk of suicide. At your initial research visit, the baseline version of the C-SSRS will be administered; at every subsequent visit, the "Since last visit" version will be used.

Speech Assessment
While wearing a voice-recording headset, subject will perform speech tasks that include reading sentences and phonation.

At your study visits an investigational research tool (Nexus D and E Systems) will be used. The Nexus D/E systems establish a connection between your implanted neurostimulator (Activa PC+S) and an external computer or your sensing device (implanted in your chest). This will allow for recording of your brain activity in real time and adjustment of stimulation within clinically safe limits using a program that responds to real time recordings of your movement and brain.

Nexus E Firmware Update: You will undergo a Nexus E Firmware update at one of your study visits. The Nexus E Firmware update allows the researchers to record signals from your brain in real time with better resolution when using the Nexus D research tool. The Nexus E firmware update will take approximately 30 minutes to perform. During the firmware update you will not receive any stimulation therapy. Once the firmware update is complete your clinician can turn your clinical stimulation settings back on.

Video recording
All the kinematic testing will be video recorded. The video content will be used at a later time only by the research staff to review what happened during the experiment. The video content will be stored on encrypted hard drives in a locked office room.

Participant Responsibilities
As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Ask questions as they come to mind.
- Tell the Protocol Director or research staff if you change your mind about participating in the study.

[redacted]

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Bronte-Stewart in writing (Dr. Helen Bronte-Stewart 300 Pasteur Drive, [redacted], Stanford, CA 94305.) You can also reach Dr. Bronte-Stewart by calling (650) 723-2116.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and/or study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- You need treatment not permitted in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

Battery life of the Activa PC+S (research device) and the Activa PC (non-research device, used in standard DBS surgeries) is estimated to last approximately 3-5 years. Once the battery of your Activa PC+S runs out, you will need to get a replacement device, and at that point, Dr. Bronte-Stewart will reevaluate whether you are a good candidate for future experiments. If you are a good candidate for future experiments, you may be given the option of receiving a replacement Activa PC+S device and continuing in the study. If you are not a good candidate for future experiments, you will be treated with the standard implantation of the non-research device.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

The tools used for kinematic analysis are non-invasive (do not enter your body). Physical sensors will be applied to the surface of your body. Besides potential removal of adhesive tape holding the sensors on the skin, the tests are at all not physically painful. The risk of participating in the study is that the DBS device (Activa PC+S) implanted in study participants is not yet FDA approved. This device is the same as the currently FDA approved PC neurostimulator but contains additional sensing components. Potential changes that could occur with the new sensing components may include sensing malfunction or premature battery drainage. Risks associated with vibrotactile stimulation are discomfort or pain. Preliminary testing by the researchers has not indicated any discomfort or worsening of symptoms, but you will be able to stop using stimulation if you notice any of these events occurring. Risks

[redacted]

associated with using Google Glasses during forward walking tasks are minimal but may include losing balance while watching videos on display.

The Nexus-D and Nexus E investigational research tools have not received FDA approval, are not commercially available, and can only be used in studies such as this one. For your safety the Nexus D and Nexus E System will only be used during study visits. Before testing, your clinician will set safety limits for the amount of stimulation you can comfortably tolerate. Your clinician and the Nexus-D and Nexus-E systems will only be able to make changes to your stimulation within these preset safety constraints. Potential issues that could occur while using the Nexus-D/Nexus-E system may include device malfunction or premature battery drainage of your DBS device. Closed-loop experiments using the Nexus-D/Nexus-E system may require over multiple hours of continuous streaming. For the Activa PC+S device, for every 1 hour of sensing, there is approximately a 12-hour loss in battery longevity. For example, an 8-hour session of streaming will result in a 2-day loss in battery longevity.

General Risks of Deep Brain Stimulation

The potential complications associated with deep brain stimulation include tingling, numbness, muscle contractions, double vision, eye deviation, cognitive problems, speech difficulties, mania, depression, suicidal ideation or others that we might not anticipate, as well as the risk of infection or device malfunction which could necessitate removal of the system.

These potential complications will be monitored throughout the study by evaluation with your physician and completion of questionnaires. Suicidal ideation over the course of the study will be monitored by the C-SSRS questionnaire.

If you notice any of the above symptoms between visits please call the Stanford Movement Disorders Center at (650) 736-0514. If you are having a suicidal thoughts or a psychiatric emergency please call the National Suicide Hotline 1-800-273-8255.

Medication Withdrawal Risk

If you are taking medications for Parkinson's disease you will be asked to stop these up to 72 hours before testing. There is a chance your symptoms of slowness, stiffness, and walking difficulty will temporarily worsen OFF of these medications. You can restart your medications as soon as the testing is complete.

While participating in this study, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing and x-rays, interaction of research drugs, or similar hazards.

[redacted]

BENEFITS
We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES
The alternative is to get the standard DBS device implanted and not participate in the study.

PARTICIPANT'S RIGHTS
You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will still receive care for your disease and will not lose any benefits to which you would otherwise be entitled. You will be told of any important new information that is learned during the course of this research study, which may affect your condition or your willingness to continue participation in this study.

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

CONFIDENTIALITYThe 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.

Some deidentified data related to vibrotactile stimulation may be shared with collaborators at the Oregon Health and Sciences University.

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.

CERTIFICATE OF CONFIDENTIALITY
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 NIH 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 of child abuse, neglect, or harm to self or others. It will also not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as the inclusion of research related data to your medical record.

[redacted]

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

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 research is to provide objective measurements of abnormal movements of the body and abnormal neural activity in the brain and to track changes in both over time. This may allow for the development of objective measures of abnormal movements and abnormal nerve cell activity and may lead to new types of deep brain stimulators which can sense abnormal nerve cell activity that is related to abnormal movement.

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.

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

[redacted]

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 at the following address: 300 Pasteur Drive, Room H3160, Stanford, CA 94305.

What Personal Information Will Be 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, kinematic analysis data, 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:

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

Who May Receive / 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
- The Stanford Movement Disorders Center

[redacted]

- All **de-identified data** (your identity will not be disclosed) will be shared with Medtronic, Inc.
- All **de-identified data** (your identity will not be disclosed) will be shared with the Michael J. Fox Foundation for Parkinson's Research and the NIH (the study funders) This data may be kept for storage at a central repository either hosted by the Michael J Fox Foundation, its collaborators, or consultants and will be kept indefinitely. In order to advance scientific discoveries, your de-identified data will be made publically available (with no personal identifying information) for the intended use of research in Parkinson's disease as well as other biomedical research studies that may not be related to Parkinson's disease.
- FDA (Food and Drug Administration) and other regulatory agencies as required by Law.

Your information may be re-disclosed if the recipients described above 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 expire on January 1, 2055 or when the research project ends, whichever is earlier.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

[redacted]

FINANCIAL CONSIDERATIONS

PAYMENT
You will not be paid to participate in this research study.

COSTS
If you participate in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. The Michael J. Fox foundation and the National Institute of Health (NIH) is providing funding but no materials to Stanford Medical Center for this study. Medtronic is providing materials but no financial support to Stanford Medical Center for this study.

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.

STUDY FUNDING
This Study is funded by the National Institute of Health (NIH) and the Parkinson's Disease Foundation.

Consultative or Financial Relationships
Dr. Bronte-Stewart is a paid advisor to Medtronic, the company sponsoring this study.

CONTACT INFORMATION
- Appointment Contact: If you need to change your appointment, please contact our research assistant at [redacted].
- Questions, Concerns, or Complaints: 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. You may contact her now or later at Dr. Bronte-Stewart: [redacted]. You should also contact her at any time if you feel you have been hurt by being a part of this study.
- Alternate Contact: If you cannot reach the Protocol Director, please contact [redacted], the study coordinator, 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

[redacted]

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.

COMPENSATION

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.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a human subject you have the following rights. These rights include but are not limited to the subject'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.

[redacted]

VIDEO RECORDING CONSENT

I give consent to be videotaped during this study:
Please initial: ___Yes ___No

I give consent for tapes resulting from this study to be used by researcher to review the experiment session when data will be analyzed:
Please initial: ___Yes ___No

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

_____ _____
Signature of Adult Participant Date

_____
Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Name of Person Obtaining Consent