NCT04184791

Computational Modeling of 60 Hz Subthalamic Nucleus Deep Brain Stimulation for Gait Disorder in Parkinson's Disease

Protocol

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Computational Modeling of 60 Hz Subthalamic Nucleus Deep Brain Stimulation for Gait Disorder in Parkinson's disease

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.2	Removal of non-English speaking exclusion criterion	Study can successfully be carried out with proper translation in place

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Computational Modeling of 60 Hz Subthalamic Nucleus Deep Brain Stimulation for Gait Disorder in Parkinson's disease

Study Description: The goal of this research is to further our understanding and application of deep brain stimulation in Parkinson's patients with gait disorder.

We will assess the degree to which stimulation parameters affect gait parameters. We will test the hypothesis that the addition of levodopa in combination with stimulation produces a synergistic improvement in certain gait domains. In addition, we test the hypothesis that a subject's gait on stimulation can be predicted with statistically significant accuracy using gait measurements on high frequency stimulation. Finally, we will test the hypothesis that the best stimulation frequency, which yields improvement among various gait parameters, can be predicted using objective sensor data collected at baseline

Objectives:

Aim 1: To determine the impact of 60Hz subthalamic deep brain stimulation on gait kinematics using wearable sensors

- Aim 1.1: To determine whether 60Hz STN-DBS elicits a differential response in gait kinematics compared to high frequency
- Aim 1.2: To determine the influence of 60Hz STN-DBS and levodopa on gait kinematics

Aim 2: To develop machine learning models to predict optimal subthalamic deep brain stimulation frequency based on wearable sensor profiles of baseline Parkinson's motor symptoms

- Aim 2.1: To develop machine learning models to predict gait response to 60Hz stimulation without additional testing
- Aim 2.2: To develop machine learning models to predict best stimulation frequency (60Hz vs. high frequency).

Endpoints:

Primary Endpoints:
Gait parameters:

- Postural sway – root mean square (RMS) sway in antero-posterior (AP) and medio-lateral (ML) planes;
- Gait – cycle duration (seconds), speed (m/s), stance (%), swing (%), heel strike angle (degrees), toe off angle (degrees), stride length (cm), cadence (steps/min), step duration (seconds), elevation at midswing (cm) (foot clearance), double support (%), arm swing velocity (deg/s), and range of motion (degrees);

	• Circumduction – turn angle (degrees), turn duration (seconds), and turn velocity (deg/s). Machine learning models to: 1) predict gait kinematics on 60Hz STN-DBS; 2) predict best stimulation frequency using wearable sensor data collected at baseline. Secondary Endpoints: Tremor (rest, kinetic, postural) Bradykinesia (finger taps, hand grasps, wrist rotation, toe taps and leg lifts) MDS-UPDRS III
Study Population:	We will recruit 30 patients (male and female; ages 21-80) who have Parkinson's disease and who will be undergoing STN-DBS implantation or who have chronic bilateral STN-DBS.
Description of Sites/Facilities Enrolling Participants:	This study will take place at Northwell Health: North Shore University Hospital, Feinstein Institutes for Medical Research, and Physician Partner locations.
Description of Study Intervention:	Assess gait kinematics using wearable sensors in subjects whose STN-DBS is changed from low frequency (60 Hz) to high frequency (130-85 Hz) in both the medicated and unmedicated states.
Study Duration:	2 years
Participant Duration:	Chronic DBS patients: 1-4 weeks Preoperative DBS patients: 12-15weeks

1.2 SCHEMA

Overview of the study design: **Figure 1:** For subjects undergoing STN–DBS implantation, Phase I will be preoperative (study visit 1), and Phase II will be 12-15 weeks post initial programming (study visit 2). For chronic DBS patients, Phase II will commence during study visit 1.

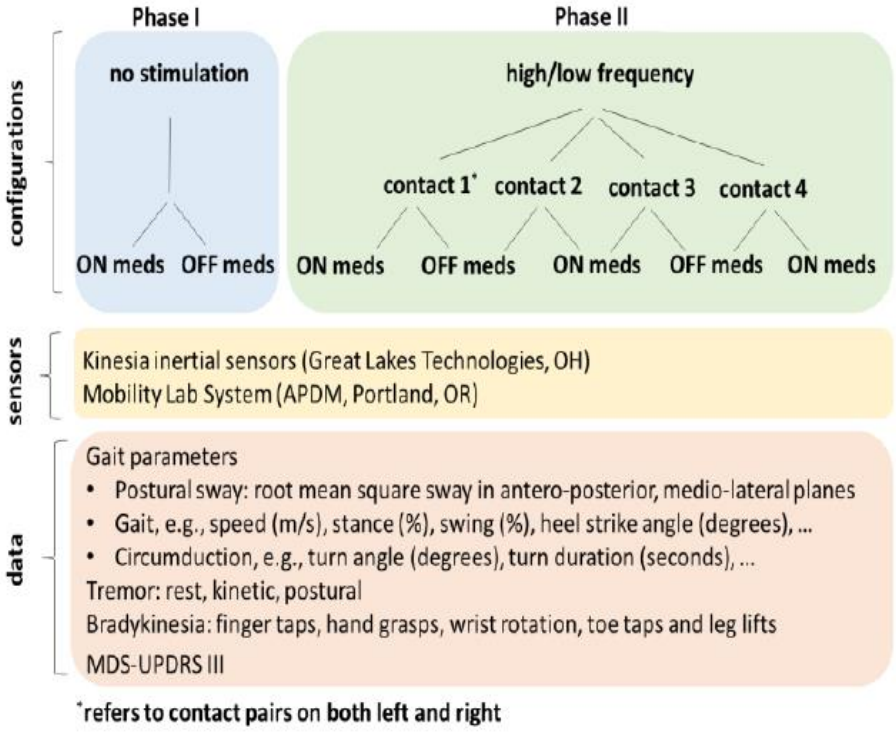
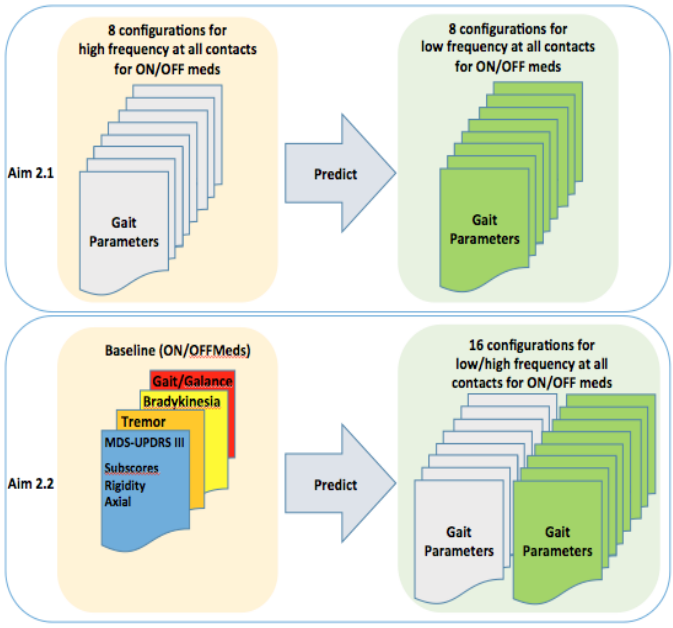


Figure 2. Overview of Aim 2 and the analysis to be performed.


Aim 2.1
8 configurations for high frequency at all contacts for ON/OFF meds
Gait Parameters
Predict
8 configurations for low frequency at all contacts for ON/OFF meds
Gait Parameters
Aim 2.2
Baseline (ON/OFFMeds)
Gait/Galance
Bradykinesia
Tremor
MDS-UPDRS III
Subscores
Rigidity
Axial
Predict
16 configurations for low/high frequency at all contacts for ON/OFF meds
Gait Parameters
Gait Parameters

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Visit 1	Visit 2[1]
Informed consent	X	
Demographics (age, gender, height, and weight and disease duration)	X	
LED[2]	X	
MMSE	X	
MDS-UPDRS III[3]	X	X
DBS Adjustments		X
Bradykinesia Sensor assessment[4]	X	X
Tremor Sensor assessment[5]	X	X
Full body Opal Sensors for Gait Assessment	X	X

[1] For chronic DBS patients, phase II will commence during study visit 1. For preoperative subjects, phase II will be conducted on a separate visit (study visit #2) that will take place 12-15 weeks after initial programming of bilateral STN deep brain stimulation implantation. If fatigue develops in either cohort, the study will be completed at a third visit.
[2] Daily levodopa equivalent dose (LED) will be calculated based on published conversion factors for PD medications (41)
[3] Items 3.1, 3.3(a-e), 3.9, 3.11, 3.12, 3.13
[4]The following tasks will be performed to assess bradykinesia: finger taps, hand grasps, wrist rotation, toe taps and leg lifts.
[5]The tremor assessments will be determined from the following tasks: arms resting (resting tremor), arms extended (postural tremor), and finger to nose (action tremor).

For chronic DBS patients, evaluation of electrode contact pairs conducted in the off medication state (initial step of Phase II) may be completed in conjunction with a scheduled clinical visit when the subject is under the clinical care of the PI. This evaluation will be considered SV1 and the remaining study procedures will be conducted as part of SV2 and SV3 (if needed). This may alter the SOA and extend the study duration, but will have no effect on the goals of the study. SV2 will commence within six months as the side effect threshold established during the evaluation is not expected to change during this timeframe. SV2 and SV3 (if needed) will be conducted within a 1-4 week period.

2 INTRODUCTION

2.1 STUDY RATIONALE

The goal of this proposal is to further our understanding and application of 60Hz subthalamic deep brain stimulation (STN-DBS) in Parkinson's patients with gait disorder. It is well established that deep brain stimulation ameliorates the cardinal symptoms of Parkinson's disease (PD) (e.g., tremor, bradykinesia, and rigidity) along with attenuating levodopa induced motor complications such as dyskinesia and motor fluctuations (1-3). It has been the prevailing notion that high frequency stimulation (130-185Hz) is the driving force of this clinical benefit; however, gait disorder, including freezing of gait, which may arise later in the disease course, can be recalcitrant to both STN-DBS and pharmacological therapy, resulting

in a decline in quality of life and increased risk for falls (2, 4-6). Indeed, frequencies <60Hz have been thought to worsen akinesia and increase tremor, but this supposition has been challenged, as studies have suggested that low frequency STN stimulation (60-80Hz) in chronic DBS patients may alleviate freezing and improve gait in chronic DBS patients (7-11). Furthermore, 60Hz STN-DBS has been shown to be beneficial in treating gait disorder in patients within the first year of implantation (12).

The nature of 60Hz STN-DBS response has relied on clinical rating scales, which lack continuous, granular and objective measurements of gait. Therefore, by using wearable body motion sensors, we seek to address the following questions: 1) What specific aspects of gait and balance (e.g., gait speed, stride length, circumduction, postural sway) are impacted by 60hz STN-DBS? 2) Is there interplay between 60Hz STN-DBS, dopaminergic medications, and electrode polarity with respect to changes in gait? 3) Are there 60Hz STN-DBS responsive PD subtype(s) and could they be elucidated from sensor based motor measurements? 4) Can sensor measurements of baseline motor symptoms be directly used to confidently estimate response of STN-DBS patient symptomatology at both high frequency and 60Hz? This information could reshape the manner by which Parkinson's patients are considered for DBS as well as managed postoperatively, potentially improving the efficiency and time to clinical optimization. The following proposed studies and analyses would strive to fill the aforementioned knowledge gaps through two primary aims.

- **Aim 1: To determine the impact of 60Hz subthalamic deep brain stimulation on gait kinematics using wearable sensors**
    - Aim 1.1: To determine whether 60Hz STN-DBS elicits a differential response in gait kinematics compared to high frequency
    - Aim 1.2: To determine the influence of 60Hz STN-DBS and levodopa on gait kinematics
- **Aim 2: To develop machine learning models to predict optimal subthalamic deep brain stimulation frequency based on wearable sensor profiles of baseline Parkinson's motor symptoms**
    - Aim 2.1: To develop machine learning models to predict gait response to 60Hz stimulation without additional testing
    - Aim 2.2: To develop machine learning models to predict best stimulation frequency (60Hz vs. high frequency).

This study will set the stage for developing a randomized trial that would assess a new paradigm for selecting DBS patients for 60Hz stimulation prior to surgery, conducting initial programming and other elaborate programming approaches under this stimulation mode, and achieving programming optimization using sensors, through a data-driven approach. In addition, the results may indicate that certain PD phenotypic subtypes are most suitable for 60Hz DBS.

2.2 BACKGROUND

Parkinson's disease (PD) is characterized by four cardinal motor features, namely, bradykinesia, rigidity, rest tremor and postural instability/gait disorder. Some of these cardinal clinical features often segregate together so that clinical subtypes of PD have been described, such as "tremor predominant" and "postural instability gait disorder" types (13). These subtypes have clinical significance in that they

may provide prognostic information (e.g., tremor predominant PD often progresses more slowly over time) and likelihood of response to Deep Brain Stimulation (DBS). That is, DBS is an effective therapy for PD patients suffering from medication refractory tremor, motor complications and/or troublesome dyskinesia (1-3). However, gait disorder including freezing of gait, can be recalcitrant to subthalamic DBS (and pharmacological therapy) leading to a decline in quality of life.

The subthalamic nucleus has emerged as one of the preferred anatomic substrates implanted with DBS electrodes for PD (14). High frequency stimulation (130-185Hz) of the STN enables reduction in dopaminergic medications by an average of 40-60% (15-17). Following implantation, DBS programming involves determining appropriate contact configuration, amplitude, pulse width (PW) and frequency in order to effectively alleviate the cardinal symptoms. Though there are some conventional principles to programming Parkinson's patients, such as utilizing high frequencies and using shorter PW, the process is based largely on trial and error. As a result, programming sessions can be long and tiresome for patients while putting a major constraint on physician time.

Gait disorder, which manifests as shuffling, reduction in speed, multistep turning, and/or freezing of gait (FOG), can arise later in the disease course and cause significant disability. Ultimately, patients are at risk for falls (18) and can become socially isolated due to their mobility limitations. These axial symptoms tend not to respond to high frequency STN-DBS (4-6). In fact, high frequency DBS has been reported in some instances to worsen gait (19, 20). Several studies have shown the efficacy of lower frequency stimulation (60-80Hz) of the STN in treating gait disorder and/or freezing of gait (7-12). The sustainability of this benefit is variable and little is known as to which patient will show a clinical response. Additionally, the lack of understanding of the interaction between dopaminergic medication and low frequency stimulation and the nature of programming the stimulator in 60Hz frequency has thwarted widespread use of it.

There has been growing evidence that stimulation frequencies influence motor circuitry via modulation of neuronal oscillations. In the unmedicated PD resting state, STN neuronal oscillations in the alpha (8-12Hz) and beta (13-30Hz) bands are present (21-23). High frequency stimulation reduces the entire beta band and decouples synchrony in the cortico-STN hyperdirect pathway (24, 25). These changes have been associated with clinical improvement of bradykinesia and rigidity (24, 26-28). Low frequency stimulation has been shown to improve limb bradykinesia (29, 30) while being inadequate for controlling tremor (31). Underscoring these clinical findings, 60Hz-DBS attenuates the high sub-band (19-27Hz) of the beta range while amplifying alpha and low beta sub-bands (11-15Hz) (30, 32). Furthermore, there is evidence that patients with FOG have lower beta power and greater beta unpredictability in the STN when stepping without freezing compared to non-freezers, suggesting that high frequency stimulation suppression of the entire band may risk worsening gait in such patients (33). The neurophysiological understanding of the interactions of various neuronal oscillations in the basal ganglia and their relationship to axial PD symptoms underscores the idea that frequency modulation may differentially influence various motor networks and symptoms (34-37).

Therefore, it is timely to further our understanding of the impact of 60Hz subthalamic deep brain stimulation on gait kinematics, both with and without the presence of levodopa (Aim 1). In addition, the development of a computational model that implements a data-driven approach for stimulation parameter estimates can stand to enhance the manner by which DBS candidates and surgical targets are selected, as well as increase the efficiency of achieving programming optimization (Aim 2).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Patients will be withdrawn from their PD medications the night before the study visit(s) in order to be assessed in practically defined OFF state. Subjects will experience more of their parkinsonian motor symptoms including possible worsening of their gait which could increase their risk of falling.

When carbidopa/levodopa 25-100 tablet(s) are administered orally, subjects may experience lightheadedness, nausea, hypotension, and/or fatigue.

During the DBS adjustments, transient stimulation induced sensory (e.g., paresthesia) or motor symptoms (e.g. muscle contractions or pulling sensations) may occur as amplitudes are incrementally raised for each electrode contact during Phase II.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may not benefit from this study, but could derive a sense of well-being from having their gait comprehensively assessed.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential Benefits:

Expected Outcomes: Aim 1. We would have extensively investigated the impact of 60Hz stimulation on several gait spatiotemporal domains (e.g., pace, turning, postural sway) and relate it to other stimulation features (e.g., activated electrode contacts, therapeutic amplitudes) using wearable sensors. We will also determine the influence that levodopa has on 60Hz stimulation in the context of kinematic gait changes. These results can help facilitate the application of this stimulation to certain PD-DBS subpopulations. *Aim 2.* Our results will allow for instantaneous recommendations by artificial intelligence on which stimulation frequency is best suitable for a subject based on *a priori* sensor measurements of motor symptoms. The ranking provided can guide clinical evaluations and potentially reduce the amount of time needed for programming by changing the “trial and error” paradigm to a sensor guided paradigm with either 60Hz or HFS initiated from the outset.

Potential Risks:
Subjects will be closely monitored following administration of carbidopa/levodopa 25/100mg tablet(s) to ensure any side effects are minimized and addressed immediately.

Any stimulation side effect will immediately be alleviated with reduction in DBS amplitude. All assessments will be done at amplitudes below the side effect threshold. Furthermore, all sensor assessments will be conducted in a control setting with the research coordinator and Principal investigator present at all times to minimize risk any risk of falling during the gait assessment.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: To determine the impact of 60Hz subthalamic deep brain stimulation on gait kinematics using wearable sensors Aim 1.1: To determine whether 60Hz STN-DBS elicits a differential response in gait kinematics compared to high frequency Aim 1.2: To determine the influence of 60Hz STN-DBS and levodopa on gait kinematics	Postural sway – root mean square (RMS) sway in antero-posterior (AP) and medio-lateral (ML) planes; • Gait – cycle duration (seconds), speed (m/s), stance (%), swing (%), heel strike angle (degrees), toe off angle (degrees), stride length (cm), cadence (steps/min), step duration (seconds), elevation at midswing (cm) (foot clearance), double support (%), arm swing velocity (deg/s), and range of motion (degrees); • Circumduction – turn angle (degrees), turn duration (seconds), and turn velocity (deg/s). Acquired from Opal sensors (APDM, Opal, and Portland, OR)	Based on normative spatial-temporal gait analysis in healthy young and elderly adults (44-46), we selected the following measurements to be assessed during this instrumented walk
Aim 2: To develop machine learning models to predict optimal subthalamic deep brain stimulation frequency based on wearable sensor profiles of baseline Parkinson's motor symptoms Aim 2.1: To develop machine learning models to predict gait response to 60Hz stimulation without additional testing	The goal of this sub-Aim is to predict the gait parameters for patients on low frequency by using the gait sensor measurements obtained on high frequency. We will utilize the raw data collected during Phase II to develop regression models, under both ON and OFF medication states for all contact pairs. We will also build models under both ON and OFF medications.	Random Forest (RF)is based on an ensemble of decision trees, referred to as a 'forest,' where predictions for any new observation are obtained from averaging the predictions of individual trees (56). To develop the regression models, we use non-linear regression analysis based on random forest (RF) classifier. However, to assure that the RF based models are the best performing models, we also develop models based on some of the other machine learning techniques, such as neural networks (56), and use them as benchmarks

Aim 2.2: To develop machine learning models to predict best stimulation frequency (60Hz vs. high frequency).	In this sub-Aim, gait parameters are predicted on low and high frequency in the context of ON and OFF medication conditions using baseline bradykinesia, tremor, and gait sensor measurements, plus MDS-UPDRS III rigidity and axial sub scores.	Models will be based on RF classifier, where other modeling techniques, such as neural networks, will be used as benchmarks.
Secondary		
Tremor **Bradykinesia** **MDS-UPDRS III**	Tremor (rest, postural, kinetics) measurements captured from Kinesia inertial sensors (Great Lakes Technologies, OH) Bradykinesia measurements (finger taps, hand grasps, wrist rotation, toe taps and leg lifts) captured from Kinesia inertial sensors (Great Lakes Technologies, OH) Items 3.1, 3.3(a-e), 3.9, 3.11, 3.12, 3.13 of MDS-UPDRS III.	To establish a baseline kinematic profile of subjects in terms of tremor, bradykinesia, along with gait using objective sensor measurements that will be used for developing regression models for Aim 2 MDS-UPDRS assessment are for facial masking, speech, rigidity, freezing of gait, postural and postural instability -- symptoms that are not measured by sensors in this study, but important for the machine learning analysis that will be conducted.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will be conducted in two phases: **Phase I.** The primary goal of Phase I is to establish a baseline kinematic profile of subjects in terms of their tremor, bradykinesia, and gait using objective sensor measurements. After being consented, participant's demographic data (age, gender, height, and weight) and disease duration (years) will be collected. Daily levodopa equivalent dose (LED) will be calculated based on published conversion factors for PD medications (41). Each subject will then be evaluated during an in-laboratory session under two conditions: 1) the practically defined OFF state following overnight withdrawal of their dopaminergic medications; and 2) levodopa ON State. Participants will be given 1.5 times their usual levodopa dose (up to 300mg) to ensure transition to the ON state in-

laboratory, and experimenters will repeat assessments 1 hour afterwards (or sooner based on patient report and visual confirmation by physician). Cognitive function in the ON state will be captured via the Mini Mental Status Exam (MMSE) by a study coordinator or physician. Phase I for preoperative subjects will be integrated into their standard of care core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD) (42). For those subjects with chronic DBS, their stimulators will be turned off for at least 50 minutes to ensure adequate “wash-out” of stimulation effects (43) prior to the assessment in each condition. For subjects that experience intolerable symptoms during this time, the assessment may take place sooner (<50 minutes after stimulators are turned off).

During each condition, a movement disorder’s specialist will conduct an assessment of items 3.1, 3.3(a-e), 3.9, 3.11, 3.12, 3.13 of MDS-UPDRS III. Afterwards, each participant will be outfitted with full body Opal sensors (APDM, Opal, and Portland, OR) affixed to the wrists, feet, sternum and lumbar spine (L5 level). A trained research coordinator will instruct each participant to conduct the Stand and Walk (SAW) test. During this test, subjects will stand for 30 seconds quietly, then walk 7 meters at their comfortable speed, turn 180 degrees, and walk back. Walking aides will be permissible, if needed. Unless the participant is unable to do so, the SAW test will be conducted twice for each trial in order to capture a sufficient number of gait cycles. Based on normative spatial-temporal gait analysis in healthy young and elderly adults (44-46), we selected the following measurements to be assessed during this instrumented walk: 1) Postural sway – root mean square (RMS) sway in antero-posterior (AP) and medio-lateral (ML) planes; 2) Gait – cycle duration (seconds), speed (m/s), stance (%), swing (%), heel strike angle (degrees), toe off angle (degrees), stride length (cm), cadence (steps/min), step duration (seconds), elevation at midswing (cm) (foot clearance), double support (%), arm swing velocity (deg/s), and range of motion (degrees); 3) Circumduction – turn angle (degrees), turn duration (seconds), and turn velocity (deg/s).

Following the gait testing, participants will undergo tremor and bradykinesia analysis with the Kinesia inertial sensors (Great Lakes Technologies, OH) that will be affixed to their finger and ankle. While seated, subjects will be guided through a series of movement tasks by interacting with the ONE tablet from Kinesia. Each motor test will appear on the touch screen interface that will instruct the participant on the motor task. The following tasks will be performed to assess bradykinesia: finger taps, hand grasps, wrist rotation, toe taps and leg lifts. The tremor assessments will be determined from the following tasks: arms resting (resting tremor), arms extended (postural tremor), and finger to nose (action tremor). Each motor task will last 15 seconds.

Phase II. The primary goal of Phase II is to investigate the impact of stimulation frequencies (low and high), stimulation spatial characteristics and levodopa on gait kinematic domains. Participants will be evaluated in two conditions: 1) OFF medication/ON stimulation; 2) ON medication/ON stimulation. Patient’s weight will be collected prior to this assessment. For chronic DBS patients, phase II will commence during study visit 1. For preoperative subjects, phase II will be conducted on a separate visit (study visit #2) that will take place 12-15 weeks after initial programming of bilateral STN deep brain stimulation implantation. This visit will also be conducted in a laboratory setting. The impact of the lesion effect from the surgery would also be avoided with this timeframe.

During condition (1), patients will be evaluated following overnight withdrawal of dopaminergic medications. Afterwards, each electrode contact will be reprogrammed by the Lead Principal Investigator in both low frequency and HFS. For each of the 4 contacts on both electrodes, the amplitude will be slowly increased by 0.1-V increment until sustained sensory or motor side effects are produced in HFS. The amplitude below the side effect threshold will be used along with a standard pulse width of 60µs. For low frequency stimulation (LFS) programming, milliamps will be adjusted to keep the

total electrical energy delivered (TEED) between both LFS and HFS conditions equivalent for each respective contact. The TEED is calculated as milliamp^2 x frequency x pulse width/impedance (47).

The opal body sensors (APDM, Opal, Portland, OR) will be fixed to each subject's wrists, ankles, sternum and lumbar spine and the SAW task will be carried out by the research coordinator for each combination of low and high frequency stimulation for the four contact pairs (total of 8 trials with each contact pair being either LFS or HFS, exclusively; refer to Figure 1). The gait measurements will be the same as in Phase I. Bradykinesia and tremor assessments will be conducted for each combination of stimulation and contact pairs using the Kinesia inertial sensors (Great Lakes Technologies, OH) as well. Ratings of items 3.1, 3.3 (a-e), 3.9, 3.11, 3.12, 3.13 of MDS-UPDRS III will also be conducted for each stimulation-contact pairing. Following each stimulation parameter change, there will be a 10-minute latency before the gait task is conducted. The participants will be blinded to each stimulation change.

During condition (2), the stimulators will be turned off and subjects will be given 1.5 times their usual levodopa dose (up to 300mg) to ensure transition to the medication ON state. Retesting will be done 1 hour after the levodopa challenge (or sooner based on patient report and visual confirmation by physician). Gait, bradykinesia and tremor sensor assessments as well as MDS-UPDRS III rigidity and axial subscore ratings will be conducted in the same manner as condition (1). The participants will be blinded to stimulation changes. At the completion of Visit 2, participants will return to their initial programming settings and resume their medication regimen as per their standard of care. If participant fatigue develops, he/she will have the option to complete condition (2) on another visit within a 4 week time period.

Beginning September 2020, and until the COVID-19 pandemic has passed, all subjects who are not fully vaccinated against COVID-19 will be tested for COVID-19 prior to participation (as outlined in Section 10.2). As a result, remote consent will be employed during the COVID-19 pandemic (see Section 8.2). COVID-19 tests will be performed by nasopharyngeal swab at a Northwell facility, the cost of which will be billed to the study fund.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN AND JUSTIFICATION FOR DOSE

Several studies have shown the efficacy of lower frequency stimulation, defined anywhere from 60-80Hz of the STN, in treating gait dysfunction and freezing that develop years later among chronic DBS patients (7-12). We reported that 60Hz stimulation could be utilized and beneficial within the first year of implantation for a small number of patients with significant gait disorder (12). We also showed that stimulation through the ventral contacts was utilized in all patients with relatively modest changes achieved in levodopa equivalent daily dose. Building upon this result, we performed a systemic analysis to determine whether a clinical pattern exists among subjects that benefited most from certain stimulation frequencies (38). The team analyzed preoperative MDS-UPDRS III scores (32 indicators) collected from 20 PD patients implanted with STN-DBS on either 60 Hz stimulation (ten patients) or HFS (130–185 Hz) (ten patients) for an average of 12 months. The goal was to apply machine learning to accurately "classify" patients into their corresponding optimal stimulation frequency group using a subset or all of the patient-specific indicators collected preoperatively. Machine learning algorithms are of two main types, namely, supervised and unsupervised algorithms. Supervised learning algorithms require ground truth (e.g., direct measurements or observations) for the data used in training and testing, whereas unsupervised learning algorithms do not require ground truth and are typically used to

group the data into clusters with respect to their similarities. In supervised learning, the task of estimating the ground truth for a new observation is generally referred to as making a "prediction." Predicting ground truths of categorical type is typically referred to as "classification," and predicting ground truths of continuous type is generally referred to as "regression." In our prior work, we developed a novel supervised machine learning model based on random forest method that was able to classify patients into subgroups with 95% accuracy and determined that gait and rest tremor of the right hand were consistently the most important factors to the classification.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 21-80
4. Patients diagnosed with Parkinson's disease (PD) (Hughes 1992)
5. PD subjects who have bilateral STN-DBS (greater than 3 months) or in the preoperative stage of being implanted with bilateral STN-DBS
6. Have underlying gait disorder defined as a score of 2 or more on the gait sub-score of the MDS-UPDRS III in the levodopa-OFF state
7. Currently treated with oral levodopa therapy

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Cognitive deficits based on historical record that limit participant compliance with study protocol
2. Vestibular disorder or musculoskeletal problems affecting gait or balance

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of decompensation of their Parkinson's disease due to other medical issues or acute musculoskeletal problems may be rescreened after they have returned to their baseline physical state. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from *the Neurology Parkinson's and Movement Disorders Division at Northwell Health* and from local physicians within and outside of Northwell Health. Outreach will include recruitment databases such as [but not limited to] Fox Trial Finder, CenterWatch, The Parkinson Alliance, Northwell E-news bulletin and the Northwell Health Clinical Trials webpage. For participants recruited outside of Northwell Health, medical records will be required to confirm eligibility. Participant screening and recruitment will then be conducted by the Lead Principal Investigator and research coordinator. Retention of participants will be maintained through thoroughness by the lead principal investigator and research coordinator.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Deep Brain Stimulation Programming
Parkinson's patients who will be undergoing STN-DBS implantation or who have chronic bilateral STN-DBS will be eligible to participate. Each electrode contact will be reprogrammed by the Lead Principal Investigator in both low frequency and HFS. For each of the 4 contacts on both electrodes, the amplitude will be slowly increased by 0.1-V increment until sustained sensory or motor side effects are produced in HFS. The amplitude below the side effect threshold will be used along with a standard pulse width of 60µs.

Inertial Sensors:
Participants will also be outfitted with the full body Opal sensors (APDM, Opal, and Portland, OR) affixed to the wrists, feet, sternum and lumbar spine (L5 level) and the Kinesia inertial sensors (Great Lakes Technologies, OH) that will be affixed to their finger and ankle. For the gait analysis, the Mobility Lab System (APDM, Portland, OR) will be used. It includes both ambulatory PD monitoring as well as expansive analytical software that measures outcomes from watch size sensors that are tethered to various body regions by Velcro bands. Each sensor acquires 3-D linear acceleration, angular velocity and magnetic field information for directional orientation from accelerometers, gyroscopes, and magnetometers, respectively (48). The sensor data is wirelessly streamed to a laptop where Mobility Lab software will generate the gait and balance metrics. iSway and iTUG are two of the modules within the software system. iTUG's gait calculations, including stride length, velocity, cadence, trunk movements, turning, and turn to sit, were deemed to be most reliable and correlated well to the UPDRS III (49). iSWAY has also been validated to measure dynamics of postural control (50).

The Kinesia One (Great Lake Neurotechnologies, Cleveland, OH) sensor incorporates both triaxial accelerometers and gyroscopes in a small compact sensor device worn on a finger and ankle and will be used for the tremor and bradykinesia analysis. Subjects will follow motor tasks displayed on Kinesia's

touch screen tablet as the sensor data is captured and accessed from Kinesia's web application, which is a HIPAA-compliant online interface.

The Kinesia and Mobility Lab devices are FDA approved medical devices and are both commercially available.

During both study phases, participants will be assessed in the OFF medication state following overnight withdrawal of dopaminergic medications. They will be given 1.5 times their usual levodopa dose (up to 300mg) using Carbidopa/levodopa 25/100 tablet to ensure transition to the ON medication state. Carbidopa/levodopa 25/100 is widely used in treating PD and virtually all PD patients have taken it at some point in their treatment course. In addition, it is the drug of choice for the CAPSIT-PD, used for the preoperative assessment for deep brain stimulation.

Patients will return to the original DBS settings and medication regimen at the conclusion of each study visit.

6.1.2 DOSING AND ADMINISTRATION

During Phase I, participants will receive no stimulation. For those subjects with chronic DBS, their stimulators will be turned off for at least 50 minutes to ensure adequate "wash-out" of stimulation effects prior to the assessment in each condition. If symptoms become intolerable, the wash out period may be shortened. This will be determined by the PI on a case by case basis. During Phase II, the Lead Principal Investigator will reprogram each electrode contract pair in both 60Hz frequency and high frequency stimulation (HFS). For each of the 4 contacts on both electrodes, the amplitude will be slowly increased by 0.1-V/mA increment until sustained sensory or motor side effects are produced in HFS. The amplitude below the side effect threshold will be used along with a standard pulse width of 60μs.

In both Phases, participants will assessed in the practically defined levodopa OFF condition--whereby they will have their overnight dopaminergic medications withdrawn--and the Levodopa ON condition, in which participants will be given 1.5 times their usual levodopa dose (up to 300mg) using carbidopa/levodopa 25/100 tablets with water.

SINEMET tablets are available in a 1:4 ratio of carbidopa to levodopa (SINEMET 25-100) as well as 1:10 ratio (SINEMET 25-250 and SINEMET 10-100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage. Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. The optimum daily dosage of Sinemet must be determined by careful titration in each patient.

- This dosage schedule provides 75 mg of carbidopa per day.
- The patient should be informed that Sinemet is an immediate-release formulation of carbidopa levodopa that is designed to begin release of ingredients within 30 minutes.
- All study participants will be on a levodopa regimen. They will be given 1.5 times their usual dopaminergic dose in the form of the study drug with 3 tabs being the maximum dosage. This is in line with the standard of care in assessing the transition of a Parkinson's patient from the OFF levodopa state to the ON state in a controlled setting.
- Study drug will be taken at the research site by mouth with water.

- Participants will be instructed to discontinue dopaminergic medications the night before each study visit, but they will remain on all other prescription medications. A drug-drug interaction is not anticipated during study participation with carbidopa/levodopa, as PD subjects, especially those with gait disorder, remain on some formulation of levodopa.
- Additional tablets will be administered (up to 1.5 times their usual dopaminergic dose) if wearing off is observed prior to the completion of study assessments.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The devices and drug identified as study interventions in this protocol will not be implanted or administered as investigational. Chronic DBS patients or patients planning to undergo DBS implantation are eligible for this study. Similarly, patients eligible for this study will already be taking levodopa as a part of their standard care for their Parkinson's disease. While this protocol does not intend to investigate the effects of Sinemet, this drug will be provided from an investigational supply. Carbidopa/levodopa (brand name: Sinemet) 25/100 oral tablets will be acquired in bulk (100 count single dose blister packs) from the North Shore University Hospital Pharmacy via email order to Elizabeth Mathew, Rph or another NSUH pharmacist in Dr. Mathew's absence; the cost of which will be paid by study funds. Patient-specific prescriptions will *not* be utilized. Study drug will be acquired by a study coordinator and administered by Dr. Ramdhani. The Northwell Drug Accountability Record Form template will be utilized to document lot#, expiration, administrations, disposal, etc. Unused drug will be disposed of via the North Shore University Hospital Pharmacy at the end of the study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Carbidopa/levodopa (brand name: Sinemet) 25/100 oral tablets. Tablets are yellow, oval, uncoated, that are scored and coded "650" on one side and "Sinemet" on the other side. Supplied in single dose blister packs, total count of 100. Sinemet is an FDA approved drug. No special preparation, randomization, packing, or other requests are required for this protocol.

6.2.3 PRODUCT STORAGE AND STABILITY

The kinesia and APDM mobility lab sensors will be stored in the Principal Investigators office in a locked cabinet. Carbidopa/levodopa (brand name: Sinemet) oral tablets will be stored at room temperature, protected from light, in the Principal Investigator's office in a locked cabinet and will be maintained in accordance with applicable investigational drug guidance.

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be blinded to the stimulation changes in Phase II, conditions (1) & (2) as described in the study design. Any blinded ratings of the MDS-UPDRS Part III will be done at the discretion of the PI.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be assessed via completed study tasks during each of the study phases and conditions.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. If a subject is not taking carbidopa/levodopa 25/100 as part of their routine treatment, the principal investigator will prescribe the number of tablets needed for Phase I and II. Subject's dopaminergic medications will be withdrawn the night before each study visit, but they will remain on all other prescription medications. A drug-drug interaction is not anticipated during the study visit with carbidopa/levodopa, as PD subjects, especially those with gait disorder, remain on some formulation of levodopa.

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

This study does not require continuous follow-up. All assessments and interventions will be conducted during the study visits and subjects will return to their default DBS settings and medication regimen after each visit. There will be no change to their standard of care PD management.

If a subject is unable to complete the study visit due to occurrence of any of the aforementioned potential risks, they will offered the opportunity to complete the remainder of the study at another study visit within 4 weeks.

The data to be collected at the time of study intervention discontinuation will include the following:

- Any demographic and clinical data
- Sensor based data

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (eCRF). Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits if they are undergoing DBS implantation or at most 2 study visits if they are considered chronic DBS subjects and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Description of the Study Phases. This study will be conducted in two phases: **Phase I.** Each subject will then be evaluated during an in-laboratory session under two conditions: 1) the practically defined OFF state following overnight withdrawal of their dopaminergic medications; and 2) levodopa ON State. Participants will be given 1.5 times their usual levodopa dose (up to 300mg) to ensure transition to the ON state in-laboratory, and experimenters will repeat assessments 1 hour afterwards (or sooner based on patient report and visual confirmation by physician). Cognitive function in the ON state will be captured via the Mini Mental Status Exam (MMSE) by a study coordinator or physician. Phase I for preoperative subjects will be integrated into their standard of care core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD) (42). For those subjects with chronic DBS, their stimulators will be turned off for at least 50 minutes to ensure adequate "wash-out" of stimulation effects (43) prior to the assessment in each condition. If symptoms become intolerable, the wash out period may be shortened. This will be determined by the PI on a case by case basis.

During each condition, a movement disorder's specialist will conduct an assessment of items 3.1, 3.3(a-e), 3.9, 3.11, 3.12, 3.13 of MDS-UPDRS III. Afterwards, each participant will be outfitted with full body Opal sensors (APDM, Opal, and Portland, OR) affixed to the wrists, feet, sternum and lumbar spine (L5 level). A trained research coordinator will instruct each participant to conduct the Stand and Walk (SAW)

test. During this test, subjects will stand for 30 seconds quietly, then walk 7 meters at their comfortable speed, turn 180 degrees, and walk back. Walking aides will be permissible, if needed. Unless the participant is unable to do so, the SAW test will be conducted twice for each trial in order to capture a sufficient number of gait cycles. Based on normative spatial-temporal gait analysis in healthy young and elderly adults (44-46), we selected the following measurements to be assessed during this instrumented walk: 1) Postural sway – root mean square (RMS) sway in antero-posterior (AP) and medio-lateral (ML) planes; 2) Gait – cycle duration (seconds), speed (m/s), stance (%), swing (%), heel strike angle (degrees), toe off angle (degrees), stride length (cm), cadence (steps/min), step duration (seconds), elevation at midswing (cm) (foot clearance), double support (%), arm swing velocity (deg/s), and range of motion (degrees); 3) Circumduction – turn angle (degrees), turn duration (seconds), and turn velocity (deg/s).

Following the gait testing, participants will undergo tremor and bradykinesia analysis with the Kinesia inertial sensors (Great Lakes Technologies, OH) that will be affixed to their finger and ankle. While seated, subjects will be guided through a series of movement tasks by interacting with the ONE tablet from Kinesia. Each motor test will appear on the touch screen interface that will instruct the participant on the motor task. The following tasks will be performed to assess bradykinesia: finger taps, hand grasps, wrist rotation, toe taps and leg lifts. The tremor assessments will be determined from the following tasks: arms resting (resting tremor), arms extended (postural tremor), and finger to nose (action tremor). Each motor task will last 15 seconds.

Phase II. Participants will be evaluated in two conditions: 1) OFF medication/ON stimulation; 2) ON medication/ON stimulation.

During condition (1), patients will be evaluated following overnight withdrawal of dopaminergic medications. Afterwards, each electrode contact will be reprogrammed by the Lead Principal Investigator in both low frequency and HFS. For each of the 4 contacts on both electrodes, the amplitude will be slowly increased by 0.1-V increment until sustained sensory or motor side effects are produced in HFS. The amplitude below the side effect threshold will be used along with a standard pulse width of 60μs. For low frequency stimulation (LFS) programming, milliamps will be adjusted to keep the total electrical energy delivered (TEED) between both LFS and HFS conditions equivalent for each respective contact. The TEED is calculated as milliamp2 x frequency x pulse width/impedance (47).

The opal body sensors (APDM, Opal, Portland, OR) will be fixed to each subject's wrists, ankles, sternum and lumbar spine and the SAW task will be carried out by the research coordinator for each combination of low and high frequency stimulation for the four contact pairs (total of 8 trials with each contact pair being either LFS or HFS, exclusively; refer to Figure 1). The gait measurements will be the same as in Phase I. Bradykinesia and tremor assessments will be conducted for each combination of stimulation and contact pairs using the Kinesia inertial sensors (Great Lakes Technologies, OH) as well. To minimize participant fatigue, the following bradykinesia and tremor assessments will be conducted during this phase: Hand grasps, leg lifts, rest tremor and postural tremor. Ratings of items 3.1, 3.3 (a-e), 3.9, 3.11, 3.12, 3.13 of MDS-UPDRS III will also be conducted for each stimulation contact pairing. Following each stimulation parameter change, there will be a 10-minute latency before the gait task is conducted. The participants will be blinded to each stimulation change.

During condition (2), the stimulators will be turned off and subjects will be given 1.5 times their usual levodopa dose (up to 300mg) to ensure transition to the medication ON state. Retesting will be done 1 hour after the levodopa challenge (or sooner based on patient report and visual confirmation by physician). Gait, bradykinesia and tremor sensor assessments as well as MDS-UPDRS III rigidity and axial

subscore ratings will be conducted in the same manner as condition (1). The participants will be blinded to stimulation changes. At the completion of Visit 2, participants will return to their initial programming settings and resume their medication regimen as per their standard of care. If participant fatigue develops, he/she will have the option to complete condition (2) on another visit within a 4 week time period.

8.2 SAFETY AND OTHER ASSESSMENTS

Description of Consent and Procedure for Obtaining Informed Consent

Participants will be consented by the Lead Principal Investigator in person at the Parkinson's and Movement Disorders Center. All potential participants will be asked to review a copy of the informed consent form, regardless of diagnosis, unless there is evidence of serious mental disability that would impair judgment or reasoning. Patients will not be approached regarding study participation by anyone not directly involved in their treatment, unless the patient has given permission for this interaction or has self-referred. The patient will then be contacted by the Principal Investigator and will be offered written information about the study. Informed written consent will be obtained prior to any study assessment. Subsequent clinical evaluation may result in an exclusion from the study. The PI and research coordinator will review the informed consent form with potential participants and address any questions or concerns prior to obtaining written informed consent for participation. The research members will also address any future questions or concerns of participants. A copy of the consent will be provided to the participant after it has been signed and witnessed.

Remote consent will be employed during the COVID-19 pandemic through a combination of telephone and email contact by the investigator and coordinator per Northwell HRPP Policies and Procedures. Initial and/or interim discussions with the PI may also take place in-person during clinical visits. The coordinator will provide potential participants with a brief summary of the study and a copy of the consent document for review. If the subject is interested in participation, the PI will discuss the study and answer any questions. If the subject agrees to participate in research, he/she will be directed by the PI to sign the consent form and return it by mail or email (scanned consent form as a PDF) to the study coordinator. Alternative methods such as facsimile will be utilized depending on the subject's access. An enrollment note will be generated for each subject to document this process. Once the signed consent document is received by the coordinator, it will be forwarded to the PI for signature. The study team will note the date discrepancies of the signatures on both the consent document and enrollment note. The study coordinator will send a copy of the fully signed consent document to the subject for his/her files. When in-person consent is possible (e.g., during a clinical visit), traditional consent methods will be employed.

Study Visit 1 will be scheduled within 30 days of subject consent.

All study visits will be conducted by the PI and research coordinator in a controlled setting. Each subject will be closely monitored during each motor assessment to reduce risk of falls and will be queried regularly during the visit to assess for fatigue.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

AEs will be reported to the study sponsor and the IRB within X 7 days of the study staff learning of the event.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to IRB any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported

in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the IRB.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <1 week > of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <2 weeks> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <2 weeks > of the IRB's receipt of the report of the problem from the investigator.]

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1. Our preliminary study established that gait and rest tremor are important factors to determine whether patients benefit from 60Hz stimulation or high frequency stimulation (38). However, the degree to which stimulation parameters affect gait parameters is not well established. In Aim 1, we will test the *hypothesis* that certain gait parameters are differentially affected between 60Hz and high frequency STN-DBS at various electrode contact configurations. In addition, in our preliminary analysis, we observed a modest reduction in dopaminergic medications in patients on 60Hz stimulation (12). Hence, we will also test the *hypothesis* that for some patients, the addition of levodopa in combination with 60Hz stimulation produces a synergistic improvement in certain gait domains.

Aim 2. Our preliminary data suggested that there is a link between the patient's baseline motor symptomatology measured by the MDS-UPDRS III ratings and the best stimulation frequency (60 Hz or HFS) chosen for the patient based on intensive clinical evaluations, which remained unchanged for an average of 12 months. In Aim 2, we test the *hypothesis* that a subject's gait kinematics on 60Hz stimulation can be predicted with statistically significant accuracy using gait measurements on high frequency stimulation. In addition, we will test the *hypothesis* that the best stimulation frequency (60Hz or HFS stimulation), which yields improvement among various gait parameters, can be predicted using objective sensor data collected at baseline. We define baseline motor performance as the severity of motor symptoms in the levodopa OFF and ON state without stimulation. In the remainder of this proposal, for simplicity we refer to 60 Hz stimulation and high frequency stimulation (130-180Hz) as low frequency (LFS) and high frequency (HFS), respectively.

9.2 SAMPLE SIZE DETERMINATION

To determine the sample size, we averaged the gait parameters (across all age groups) along with pooled variance captured on the APDM inertial sensors for healthy subjects (53) and PD patients with gait disorder (54) and computed a reasonable sample size of 24 (which equates to a Cohen's d= 0.8) with a power of 0.80 and level of significance of 0.05. Assuming a 20% attrition rate, we will attempt to recruit 30 patients.

Sample Size estimation

$(\alpha) = 0.05$, $Z_\alpha = 1.96$
$(\beta) = 0.80$

$$n = \frac{2\left(Z_a + Z_{1-\beta}\right)^{2_\sigma 2,}}{\Delta^2}$$

Reference Gait values for healthy individuals using APDM sensors

Age Groups	n	mean normalized speed	STD	Variance
20-29	41	1.14	0.12	0.0144
30-39	41	1.16	0.14	0.0196
40-49	42	1.14	0.16	0.0256
50-59	45	1.21	0.14	0.0196
60-69	51	1.13	0.12	0.0144
70-89	72	0.86	0.23	0.0529

Ages 50-89: **Mean Velocity - 1.06**

Calculated Pooled Variance for Ages 50-89- 0.03

Calculated Pooled Variance for All ages – 0.03

Fang X, Liu C, Jiang Z. Reference values of gait using APDM movement monitoring inertial sensor system. R Soc Open Sci. 2018;5(1):170818

Gait Parameters for PD patients with gait disorder (FOG- & FOG +) using APDM sensors

Walking Measure		Single Task Mean ± STD
Stride Length (m)	FoG−	1.06 ± 0.15
	FoG+	0.92 ± 0.22
Stride Velocity (m/s)	FoG−	0.99 ± 0.18
	FoG+	0.86 ± 0.21

Average age 68 STD 8.4 (FOG -)

Average Age 69 STD 7.9 (FOG+)

Mean Velocity – 0.925 (FOG- & FOG+)

de Souza Fortaleza AC, Mancini M, Carlson-Kuhta P, King LA, Nutt JG, Chagas EF, Freitas IFJ, Horak FB. Dual task interference on postural sway, postural transitions and gait in people with Parkinson's disease and freezing of gait. Gait Posture. 2017;56:76-81.

Effect Size 1.06-0.925 = .14

N = 15.79 (.03)/ $(.14)^2$ = 24 + 20% attrition = total study recruitment 29 subjects.

Final Study N= 30 subjects

9.3 POPULATIONS FOR ANALYSES

Not applicable

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will perform descriptive statistics—i.e., mean (standard deviation) on all demographic, LED, MDS-UPDRS III (Total score), baseline DBS parameters and gait kinematic parameters. In order to eliminate body height as a confounder, we will normalize (N), according to gender, the following parameters: speed (S), stride length (L), cadence (C) according to Schwesig et al.(55).

$$D = \text{sqrt (body height/mean body height)}$$

$$S_N = S / D^2$$

$$L_N = L / D^2$$

$$C_N = C \times D^2$$

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Aim 1.1.
Using the analytical software of APDM, the SWAY and TUG algorithms included in the SAW test will calculate asymmetry and variability for: postural sway (RMS AP & ML planes), cadence (CN), gait cycle duration, gait speed (SN), swing, double support, elevation at midswing, foot strike angle, toe off angle, stance, step duration, stride length (LN), arm swing velocity, arm range of motion, turn angle, turn duration, and turn velocity. All data will be tested for normality with Shapiro-Wilk test. Linear mixed models with repeated measures (LMMRM) will be used to compare high and low frequency over all contact pairs in the levodopa-OFF state. Parameter estimation will be based on restricted maximum likelihood and the form of the covariance matrix will be chosen based on Akaike's Information Criteria and Schwarz' Bayesian Criterion. The Holm-Bonferroni method will be used to adjust for multiple comparisons for the 20 outcome measures.

Aim 1.2. To investigate levodopa's effects on the gait domains, we will include the data for levodopa-ON and add a binary variable for levodopa (on or off) to the LMMRM from Aim1.1.

Aim 2.1. We will utilize the raw data collected during Phase II to develop regression models, under both ON and OFF medication states for all contact pairs. The top panel in Figure 2 presents the overview of Aim 2.1; the goal of this sub-Aim is to predict the gait parameters for patients on low frequency by using the gait sensor measurements obtained on high frequency. Additional independent variables/regressors include general patient/disease characteristics such as age, gender, and disease duration. We will also build models under both ON and OFF medications. To develop the regression models, we use non-linear regression analysis based on random forest (RF) classifier. RF is based on an ensemble of decision trees, referred to as a 'forest,' where predictions for any new observation are obtained from averaging the predictions of individual trees (56). Generally, RF models are not prone to overfitting and are robust against noisy or high-dimensional datasets (57). In addition, they are generally interpretable, allowing for further examination of results and easier subject subtyping with respect to symptomology. However, to assure that the RF based models are the best performing models, we also develop models based on some of the other machine learning techniques, such as neural networks (56), and use them as benchmarks. If needed, to improve model performance we will perform model building in RF models to identify and include the most important parameters (38). We will use techniques such as cross-validation (e.g., leave-one-out) and bootstrapping to examine the generalizability of the models and acquire confidence intervals for the predicted values. Lastly, we will compare the best performing models obtained for both ON and OFF medications and their most important contributing parameters to further investigate the interaction of medications and stimulation frequency.

Aim 2.2. Similar to Aim 2.1, in this sub-Aim we conduct regression analysis to predict gait parameters. However, in this sub-Aim, gait parameters are predicted on low and high frequency in the context of ON and OFF medication conditions using baseline bradykinesia, tremor, and gait sensor measurements, plus MDS-UPDRS III rigidity and axial sub scores. Patient and disease characteristics will be used as regressors. Again, models will be based on RF classifier, where other modeling techniques, such as neura networks, will be used as benchmarks. The best performing parameters identified in Aim 2.1 will be used to guide the model building in this sub-Aim. Also, aforementioned performance enhancing techniques will be used, if possible, and confidence intervals will be generated using bootstrapping. These models will be able to predict the best stimulation frequency and contact pairs for the patient immediately after baseline evaluations and provide a confidence level. Similar to Aim 2.1, we will

develop these models with and without accounting for PD medications to further quantify their impact and provide additional options for patients.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be factored into the regression modeling for AIM 2.

9.4.4 SAFETY ANALYSES

Not applicable

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Refer to section 9.4.1

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

The subgroup analyses will be analyzed based on age, gender, and disease duration for both primary and secondary endpoints.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A consent form describing in detail the study intervention, study procedures, and risks is given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

In the event that consent is obtained during Study Visit 1, we request a waiver of written documentation of consent for the dopaminergic medication withdrawal to take place 12 hrs prior to this visit. This waiver will not affect data validity, subject safety, or one's willingness to participate.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in a private and controlled setting.

The collected data will include self-reported demographic information as well as clinical and sensor based measurements. A REDCap (Research Electronic Data Capture) database will be created for the purposes of this project at Northwell Health. This is a secure web based research data management application in which demographic data, baseline DBS parameters, and daily levodopa equivalent dose will be stored. Data will be de-identified and stored securely in a HIPAA compliant manner. A unique study identification number will identify individual participants and their research data. The clinical research coordinator will input data into this database within 24 hours of acquiring clinical data for each subject.

All sensor based data will be stored on secured research laptop and backed up to an encrypted external hard-drive regularly. Paper copies of all research materials as well as backup copies of sensor data and the database will be stored on encrypted portal storage devices that will be kept securely in the PI's office. All research and data storage equipment will be stored in the PI's office in a locked cabinet.

Each subject will have a unique identification number that will be used for all assessments. The PI and Research coordinator will conduct routine monitoring and cleaning of the data to ensure accuracy. The dataset will be de-identified and shared with the research team at the University of Tennessee Knoxville in adherence to the resource-sharing plan.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in a REDCap Database at Northwell and an encrypted external hard-drive. De-identified, archived data will be transmitted securely to the University of Tennessee for use by other researchers on this project to conduct Aim 2. Permission to transmit data to the UTK will be included in the informed consent. This transference of data will occur in parallel following completion of each subject's study visits for Aim 1.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Ritesh Ramdhani, MD Director, Deep Brain Stimulation Program	N/A

Associate Director, Parkinson's and Movement Disorders	
Northwell Health	Institution Name
611 Northern Boulevard Great Neck, NY 11021	Address
516-325-7000	Phone Number
rramdhani@northwell.edu	Email

10.1.6 SAFETY OVERSIGHT

The PI will review aggregate safety data every six months and provide the outcomes of these reviews to the IRB for acknowledgement.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Study PI with each study visit. Random review of study data will be done by PT to ensure accuracy of data input and cataloging.
- Independent audits will be conducted by Northwell IRB to ensure monitoring practices are performed consistently across all participating sites if needed

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the study PI will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

Data (including demographics, medical history, DBS surgical history, results of sensor and clinical rating scale assessments, adverse events (AEs), and any clinical observations) will be entered into <Redcap Database at Northwell Health>, a 21 CFR Part 11-compliant data capture system provided by the <Northwell Health>. Clinical data will be entered directly from the source documents. Sensor based data will be stored on an encrypted research laptop that will be backed up to an encrypted external HD.

The clinical and sensor dataset will be de-identified and shared with the research team at the University of Tennessee Knoxville in adherence to the resource-sharing plan.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within no more than 7 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to National Institute of Neurological Disorders and Stroke (NINDS) Program Official and <Northwell Health's IRB>. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for

knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Dr. Ritesh Ramdhani.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Study visits were suspended in March 2020 due to the COVID-19 pandemic. We plan to resume study visits in the fall of 2020 according to institutional and state guidelines. This timeline is subject to change based on the status of COVID-19 in New York; future suspensions may be required if there is a spike in the number of infections. Due to current facility restrictions and limited space availability, SVs will be conducted between our offices at the Neuroscience Institute (Great Neck, NY) and the Feinstein Institutes for Medical Research (Manhasset, NY).

The following safety measures will be taken.

1. All study subjects will undergo a telephone preappointment COVID Screen
    a. Those without symptoms will get a COVID test 48-72hrs prior to their first study visit (SV).
    b. If the COVID test is positive, they will have their SV postponed for 2 weeks and will be retested prior to SV1.

   c. Those with reported symptoms on telephone prescreening will have their SV postponed for 14 days followed by a COVID test 48-72 hrs prior to their first SV.
2. Fully vaccinated subjects will be exempt from COVID-19 testing prior to SV1. Testing may be warranted at any time if the subject reports symptoms of COVID-19 during telephone preappointment screening.
3. Any subject with an initial positive COVID test must have a negative result upon retest, prior to participation.
4. Preappointment screening will be repeated prior to each SV. Postponement of SV or repeat COVID-19 testing may be warranted.
5. Prior to each study visit, subjects will be instructed when to enter the building, don a mask, and have their temperature checked. If a fever is present, their SV will be postponed for 14 days or more and they will be (re)tested for COVID-19.
6. Attempt will be made to conduct all SVs on consecutive research days (within 2 weeks). COVID-19 testing may be repeated if participation exceeds 14 days.
7. All research staff will follow site specific COVID-19 safety and hygiene policies including wearing an N95 mask
8. When possible, a plexiglass barrier will be placed on the table between research coordinator/PI and subject for additional safety.
9. Social distancing will be practiced whenever possible.

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	4/15/19	Original	N/A
1.1	10/29/19	Updated eligibility criteria, editorial clarification, LD dose maximum 300mg, shortened off period for chronic DBS subject experiencing intolerable symptoms, additional of external referral sources and on-line outreach	Clarity, patient comfort, to meet recruitment goals
1.2	1/8/20	Addition of second SAW test for every trial, change source of LD tablets from patient to NSUH pharmacy.	Ensure enough gait cycles are captured, remove drug supply/cost burden on participants.
1.3	1/22/20	IP supply changed from bottle to single dose blister packs; Removal of finger taps, touch nose, wrist rotation, and toe taps sensor assessments from Phase II	Availability through NSUH pharmacy; participant fatigue
1.4	3/2/20	Completion of one SAW test if participant is unable to do both; chronic DBS eligibility revised from one year to 6 months; administration of additional levodopa in event of wearing off	Subject safety and comfort, facilitate recruitment, maintain levodopa ON state during assessments
1.5	8/4/20	Add Visit 3 to Schedule of Activities; Addition of COVID-19 safety measures including preappointment screening, COVID-19 testing and remote consent.	Clarity; COVID-19 pandemic
1.6	12/22/20	Chronic DBS patient eligibility revised from 6 months to 3 months	Facilitate recruitment
1.7	3/11/21	Fully vaccinated subjects exempt from COVID-19 testing prior to SV1; updated remote consent procedures; modified SOA to include optional use of clinical visit to complete electrode contact pair evaluation.	CDC guidance, subject convenience
1.8	4/15/21	Removal of blinding requirement for MDS-UPDRS Part III assessments	Blinded assessments are not factored into primary study analysis; not shown to be

			significant features on interim computational modeling (n=10)
1.9	8/12/21	Removal of non-English speaking criterion	Translation is sufficient to carryout study

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