A SINGLE-CENTER, RANDOMIZED, DOUBLE-BLINDED, DOUBLE-CROSSOVER TRIAL OF ASYMMETRIC SUBTHALAMIC DEEP BRAIN STIMULATION FOR AXIAL MOTOR DYSFUNCTION IN PARKINSON'S DISEASE

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LIST OF ABBREVIATIONS

BL	Bilateral
DBS	Deep brain stimulation
FOG	Freezing of gait
FOGQ	Freezing of gait Questionnaire
LEDD	Levodopa-equivalent daily dose
Mini-BESTest	Mini Balance Evaluation Systems Tests
PIGD	Postural instability and gait dysfunction
PD	Parkinson's disease
PDQ-39	39-item Parkinson's Disease Questionnaire
STN	Subthalamic nucleus
UL	Unilateral
UPDRS	Unified Parkinson's disease rating scale
MCID	Minimal clinically-important difference
MDS-UPDRS	Movement Disorders Society unified Parkinson's disease rating scale

PROTOCOL SUMMARY

Study Title

A single-center, randomized, double-blinded, double-crossover trial of asymmetric sub-thalamic deep brain stimulation (STN-DBS) for axial motor dysfunction in Parkinson's disease (PD).

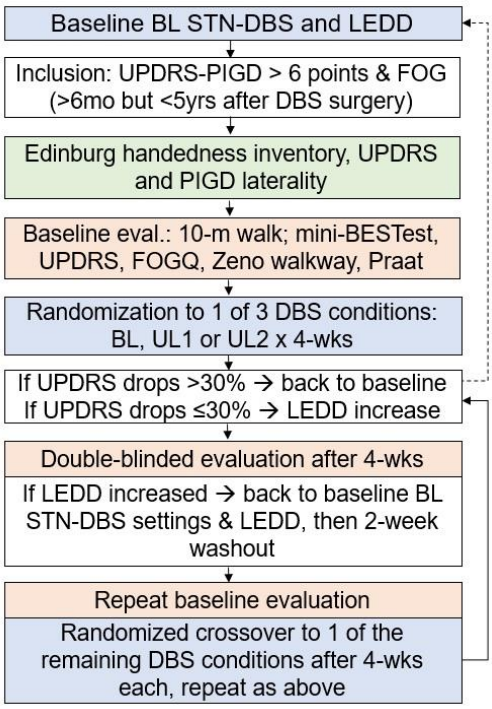
Sample Size and Study Population

- Sample Size: 27 pts.
- Study Population: Patients with PD who develop treatment-resistant postural instability gait dysfunction (PIGD) >6 months but <5 years after bilateral (BL) STN-DBS.
* Treatment-resistant PIGD is defined as freezing of gait (FOG) and >6 points in the UPDRS or MDS-UPDRS PIGD subscales despite optimization of medications and symmetric BL STN-DBS programming.

Accrual Period: 20 months

Study Design (See figure)

This single-center, randomized, double-blinded, double-crossover clinical trial will study the effects of UL 50% voltage reduction in PIGD for PD patients that develop PIGD after BL STN-DBS. The primary outcome will be the change in gait velocity as measured with the 10-m walk test. Secondary outcomes will be the changes in other PIGD, speech and motor scales as mentioned above.



Study Duration

- Start Date: October 1st 2017 (Anticipated)
- End Date: June 30th 2019 (Anticipated)
- Duration of each of the 3 DBS conditions per patient: 4 weeks.
- Additional wash-out period for each of the 3 DBS conditions if needed: 2 weeks.
- Total duration per patient: 12–18 weeks.

- During each of the 3 DBS conditions:
* If UPDRS drops >30%→ return to baseline.
* If UPDRS drops ≤30%→ increase dopaminergic medication dose, keeping track of the corresponding levodopa-equivalent daily dose (LEDD).

Return to baseline BL STN-DBS settings and LEDD after the 4-week DBS period and respective double-blinded evaluation is completed. The randomized crossover to each of the remaining DBS conditions will be performed after 2 weeks of LEDD excess washout.

Study Interventions

1. Unchanged baseline BL STN-DBS (DBS condition 1)
2. UL 50% voltage reduction (DBS condition 2)
3. Contralateral 50% voltage reduction (DBS condition 3)

Primary Objective

To compare the effects of unilateral (UL) 50% voltage reduction in gait velocity measured during the 10-m walk test for patients with PD that develop postural instability/gait dysfunction (PIGD) after bilateral (BL) STN-DBS.

Secondary Objectives

1. To explore the effects of UL 50% voltage reduction for patients with PD that develop PIGD after BL STN-DBS in:
    1) PIGD measured by the mini-BESTest,
    2) PIGD measured by the Unified PD rating scale (UPDRS),
    3) quantitative PIGD analysis as per the Zeno walkway (stride length, cadence, phase coordination index, turning time),
    4) freezing of gait (FOG) questionnaire,
    5) quantitative speech analysis as per the Praat software (intelligibility, pitch, intensity),
    6) MDS-UPDRS (total and motor scores),
    7) select cognitive tasks (verbal and semantic fluency, perception, verbal and visuospatial working memory, episodic memory), and
    8) quality of life measured by the 39-item PD Questionnaire (PDQ-39)

2. To explore whether baseline clinical evidence for hemispheric lateralization of appendicular motor control (Edinburgh handedness inventory), axial motor control (quantitative PIGD analysis) or PD severity (MDS-UPDRS laterality index) correlates with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS.

3. To explore whether intraoperative electrophysiological evidence for STN asymmetry is associated with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS. Intraoperative electrophysiological data obtained from chart review will be analyzed for 1) order of DBS lead placement (right STN first vs. left STN first), 2) number of STN trajectories per side, 3) STN trajectory lengths in millimeters, 4) STN mean firing rates in Hertz (local field potentials) and 5) STN burst indices.

4. To explore whether the differences in volume of tissue activation (VTA) between the 3 DBS conditions are associated with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS. Comparative imaging analysis will be performed by estimating the VTA for each DBS condition per patient and overlapping the VTAs with the corresponding post-operative magnetic resonance images.

Primary Endpoint of the Study

Gait velocity measured during the 10-m walk test for patients with PD that develop PIGD after BL STN-DBS.

1. GENERAL INFORMATION

1.1. Protocol title:

"A single-center, randomized, double-blinded, double-crossover trial of asymmetric subthalamic deep brain stimulation for axial motor dysfunction in Parkinson's disease."

1.2. Investigators and contact information:

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2. BACKGROUND INFORMATION

2.1. Rationale:

Axial motor dysfunction remains a significant source of disability, morbidity and mortality in patients with PD. Axial symptoms in PD include dysarthria and PIGD (including FOG). These symptoms do not necessarily improve with dopaminergic therapy, might not respond and could even worsen with BL STN-DBS.[1]
Whereas left hemispheric dominance for appendicular motor control is well-established in humans, evidence for right hemispheric dominance for axial motor control in healthy individuals and PD patients is still growing.[2-4] For instance, PD patients with right-greater-than-left nigrostriatal degeneration and subsequent left-sided appendicular symptom predominance are at higher risk for developing FOG.[4] In this context, symmetric BL DBS programing might be contributing with the observed axial worsening after STN-DBS. Moreover, cognitive abilities that lateralize to one hemisphere (such as verbal fluency) can also decline after BL STN-DBS. Since BL STN-DBS is an established treatment modality in PD, asymmetric programming is a feasible and unexplored alternative that could have a large beneficial impact for these patients. In fact, previous studies already suggest potential benefits of asymmetric programing for axial dysfunction in PD.[5,6]

2.2. Supporting Data:

Functional asymmetries have been observed in human cognition and locomotion. For example, verbal memory lateralizes to the left hemisphere and normal stride length appears to be longer with the right foot. A possible explanation for the latter is that the right leg has greater muscle power and dominates gait propulsion, whereas the left leg has greater power absorption and dominates postural stabilization.[7] Normal gait asymmetry in hu-

mans might therefore be associated with the posited hemispheric asymmetries for axial (right hemisphere/left leg) and appendicular (left hemisphere/right leg) motor control. The specific impairment of baseline gait coordination might be important for the development of FOG in PD.[8] In fact, the interference of BL STN-DBS with potentially asymmetric circuits underlying normal asymmetric interlimb coordination during gait has been suggested as a cause of FOG.[5] In that study, FOG in patients with PD and BL STN-DBS improved more with UL 50% voltage reduction contralateral to the side with the longer stride length when compared with BL and UL 50% voltage reduction contralateral to the side with the shorter stride length.[5] Given that normal stride length appears to be longer with the right foot, left-sided predominant PD might exaggerate this asymmetry by reducing stride length with the left foot, which could potentially explain the higher risk for FOG in these patients.[4]

The differential effects of right-sided, left-sided and BL STN-DBS in the context of potentially lateralized axial motor circuits have not been systematically studied. In a recent pilot study of 22 PD patients that developed PIGD after BL STN-DBS, stride length improved 5 cm. more with right-sided ON/left-sided OFF versus left-sided ON/right-sided OFF, and 7 cm. more with BL-ON versus left-sided ON/right-sided OFF. The 2 cm. difference in favor of BL versus right-sided ON/left-sided OFF was not statistically significant. Other gait parameters such as stride velocity and turning time were similar between BL and both UL STN-DBS conditions; however, motor and gait UPDRS scores improved more with BL versus UL STN-DBS.[6] In that study, the potential benefits of asymmetric stimulation on axial symptoms were limited by the worsening of appendicular symptoms. Moreover, patients were evaluated for the 3 DBS conditions 45-60 minutes after changing DBS parameters during the same day.

In this trial, we will evaluate patients 1 month after each DBS condition change to decrease the risk for carry-over effects and to allow for the full motor benefits of DBS to be established. Additionally, we hope to maintain the benefits of BL STN-DBS on appendicular symptoms by reducing DBS voltage unilaterally by 50% instead of turning OFF the stimulation.

2.3. Potential Risks and Benefits:

As mentioned above, the potential benefits of asymmetric BL STN-DBS are improvement in axial motor function for patients with PD. In previous studies of asymmetric BL STN-DBS, these potential benefits were limited by worsening of appendicular symptoms. Nevertheless, the stimulation was completely turned OFF during each of the DBS conditions. In this trial, we will not turn OFF stimulation but we will decrease voltage by 50%. With this settings, we hope to maintain appendicular symptom control while assessing the potential benefits on axial symptoms. As mentioned later, we will attempt to manage symptom worsening with dopaminergic medications.

2.4. Study Population:

The study population will encompass patients with PD who develop treatment-resistant postural instability gait dysfunction (PIGD) >6 months but <5 years after bilateral (BL)

STN-DBS. Treatment-resistant PIGD is defined as freezing of gait (FOG) and >6 points in the UPDRS or MDS-UPDRS PIGD subscales despite optimization of medications and symmetric BL STN-DBS programming.

3. STUDY OBJECTIVES AND HYPOTHESIS

3.1. Objectives and Purpose:

3.1.1. Primary Objective:

The primary objective is to compare the effects of UL 50% voltage reduction in gait velocity measured during the 10-m walk test for patients with PD that develop PIGD after BL STN-DBS.

3.1.2. Secondary Objectives:

1) To explore the effects of UL 50% voltage reduction for patients with PD that develop PIGD after BL STN-DBS in:

1. PIGD measured by the mini-BESTest
2. PIGD measured by the Unified PD rating scale (UPDRS)
3. MDS-UPDRS (Total and motor subscales)
4. FOG as per the FOG questionnaire
5. Quantitative PIGD analysis as per the Zeno walkway (stride length, cadence, phase coordination index, turning time)
6. Quantitative speech analysis as per the Praat software (intelligibility, pitch, intensity)
7. 39-item PD questionnaire (PDQ-39)

2) To explore whether baseline clinical evidence for hemispheric lateralization of appendicular motor control (Edinburgh handedness inventory), axial motor control (quantitative PIGD analysis) or PD severity (MDS-UPDRS laterality index) correlates with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS.

3) To explore whether intraoperative electrophysiological evidence for STN asymmetry is associated with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS. Intraoperative electrophysiological data obtained from chart review will be analyzed for 1) order of DBS lead placement (right STN first vs. left STN first), 2) number of STN trajectories per side, 3) STN trajectory lengths in millimeters, 4) STN mean firing rates in Hertz (local field potentials) and 5) STN burst indices.

4) To explore whether the differences in volume of tissue activation (VTA) between the 3 DBS conditions are associated with the motor responses to UL 50% reduction in voltage of STN-DBS in patients with PD who develop PIGD after BL STN-DBS. Comparative

imaging analysis will be performed by estimating the VTA for each DBS condition per patient and overlapping the VTAs with the corresponding post-operative magnetic resonance images.

3.2. Study Hypothesis:

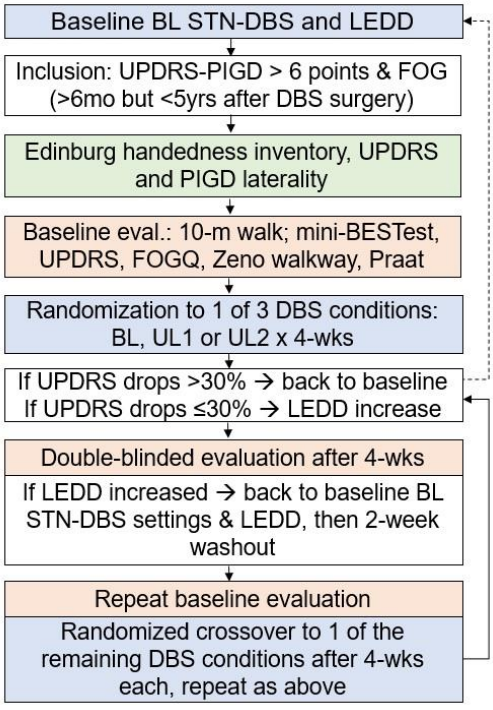
The study hypothesis is that UL 50% voltage reduction results in an improvement of at least 0.10–0.16 m/s* in gait velocity when compared to baseline BL STN-DBS (Alternative hypothesis).
*Minimum clinically-important difference in gait velocity for non-PD patients.[9]

Null hypothesis: UL 50% voltage reduction does not result in an improvement of at least 0.10–0.16 m/s in gait velocity when compared to baseline.

4. STUDY DESIGN

This single center, randomized, double-blinded, double-crossover clinical trial will study the effects of UL 50% voltage reduction in PIGD for PD patients that develop PIGD after BL STN-DBS.
The primary endpoint will be the change in gait velocity as measured with the 10-m walk test. Secondary endpoints will be the changes in other PIGD, speech, motor scales, select cognitive tasks and quality of life as mentioned above.

After informed consent, PD patients that develop treatment-resistant PIGD more than 6 months but less than 5 years after BL STN-DBS surgery will be enrolled. Treatment-resistant PIGD will be defined as the presence of FOG and a score of >6 points in the UPDRS-PIGD subscale despite optimization of dopaminergic medications as measured by the levodopa-equivalent daily dose (LEDD) and symmetric BL STN-DBS programming. Enrolled patients will have an initial assessment of motor lateralization with the Edinburgh handedness inventory, as well as lateralization scores from the UPDRS, quantitative PIGD analysis and select cognitive tasks. After a baseline evaluation for primary and secondary outcome measures is performed, the patients will be randomized to 1 of 3 conditions: BL (maintaining baseline symmetric programming), UL1 or UL2 (50% voltage reduction on either the left or right side). In a



double-blinded fashion, primary and secondary outcome measures will be evaluated 4-weeks after the first DBS condition began, followed by randomized cross-over to each the remaining 2 DBS conditions after the corresponding 4-week periods and repeated outcome evaluations.
During the 4-week duration of each of the 3 DBS conditions, increases in LEDD will be allowed if the UPDRS drops ≤30%. After the 4-week DBS period and the respective double-blinded evaluation is completed, the patient will return to baseline BL STN-DBS settings and LEDD. The randomized crossover to each of the remaining DBS conditions will be performed after 2 weeks of LEDD excess washout.
If the UPDRS drops >30% at any moment, the patient will return to the baseline BL STN-DBS settings and LEDD. After 2 weeks of LEDD excess washout, the patient will be given the option to: 1) be randomly crossed over to either of the remaining DBS conditions or 2) to drop out from the study and return to standard of care. Expected duration of subject participation will therefore be between 12–18 weeks. All efforts will be done for patients to complete the study as the primary analysis will be intention-to-treat.

5. SELECTION OF SUBJECTS

5.1. Subject Inclusion Criteria:

1. Patients with PD (previously diagnosed according to the UK brain bank criteria) who develop treatment-resistant PIGD >6 months but <5 years after BL STN-DBS.

2. Treatment-resistant PIGD will be defined as FOG and UPDRS or MDS-UPDRS PIGD subscales >6 points despite optimization of medications (measured by LEDD) and symmetric BL STN-DBS programming.

3. Prior therapy: Dopaminergic medications will be documented by their respective LEDD. Changes in medication doses will be allowed as previously specified. Other therapies aimed at improving PIGD (e.g. amantadine, cholinergic agents, physical therapy) will not be allowed during this study.

5.2. Subject Exclusion Criteria:

1. Development of PIGD <6 months or >5 years after BL STN-DBS surgery.

2. Development of PIGD responsive to optimization of LEDD or symmetric BL STN-DBS programming.

3. Patients with cognitive impairment or psychiatric comorbidities (including substance abuse) that would interfere with the informed consent process, study adherence or outcome assessments.

4. Patients with advanced PD or any other neurological, cardiovascular or musculoskeletal co-morbidities that would preclude or require assistance to complete the 10-m walking test.

5. Patients not able to comply with 4-week interval evaluations following their potential enrollment due to personal reasons.

6. Serious illness (requiring systemic treatment and/or hospitalization) until subject either completes therapy or is clinically-stable on therapy, in the opinion of the site investigator, for at least 30 days prior to study entry.

7. Inability or unwillingness of subject or legal guardian/representative to give written informed consent.

5.3. Study Enrollment Procedures:

1. Potential study patients will be screened at the DBS clinics at the University of Toronto Movement Disorders Center, where they undergo routine UPDRS and/or MDS-UPDRS testing at each 3-month visit as per protocol. This will facilitate recognition of PD patients with treatment-resistant PIGD after BL STN-DBS.

2. Once a patient that meets the eligibility criteria is identified. Initial contact will be made by one of the members of the circle of care and the patient will be offered participation in this study. The corresponding informed consent process will be started by one of the members of the study team as applicable.

3. After the appropriate informed consent is obtained, a baseline assessment of primary and secondary outcome measures will be performed. Afterwards, the patient will be randomized and evaluated at 1-month intervals as described above, for a total study duration of 3 months per patient.

6. STUDY INTERVENTION

6.1. Interventions, Administration, and Duration:

After the baseline outcome assessment, enrolled patients will be randomized to 1 of 3 conditions: BL (maintaining the baseline symmetric STN-DBS), UL1 (50% voltage reduction in side 1 [either left or right]) or UL2 (50% voltage reduction in side 2 [either right or left]). The primary and secondary outcome measures will be assessed in a double-blinded fashion 4-weeks after the initial randomization. Enrolled patients will then be randomly crossed over to 1 of the 2 remaining conditions and then same blinded evaluation will be performed 4-weeks later. Patients will finally be crossed over to the remaining condition and the same blinded evaluations will be performed 4-weeks later. Total study duration will therefore be a minimum of 12-weeks for each patient.
In addition to the 3 evaluations after completing each of the 4-week DBS periods, patients will be called the day after and 2 weeks after each DBS condition change to ensure

tolerability. Patients will be instructed to call the DBS clinic at any time for any issues. The study team will be available 24/7 to answer any questions related to the study. If there is worsening of PD symptoms at any time during the study, increases in LEDD will be allowed as long as the UPDRS drop is ≤30%. The increase in LEDD will be performed as per the DBS clinic protocols by a physician un-blinded to study arm allocation. This same physician will keep record of the specific DBS parameters and will be in charge of the DBS condition changes, as well as the return to baseline BL STN-DBS and LEDD in case medication optimization is not sufficient to address symptom worsening. The rate and moment of PD symptom worsening and LEDD changes will be recorded, as it could represent a proxy of UL STN-DBS effects.
After the 4-week DBS period and the respective double-blinded evaluation is completed, the patient will return to baseline BL STN-DBS settings and LEDD. The randomized crossover to each of the remaining DBS conditions will be performed after 2 weeks of LEDD excess washout. Maximum study duration will therefore be 18 weeks per patient. If the worsening of PD symptoms is reflected in a UPDRS drop of >30% at any moment during the study, the patient will return to the baseline BL STN-DBS settings and LEDD. After 2 weeks of LEDD excess washout, the patient will be given the option to: 1) be randomly crossed over to either of the remaining DBS conditions or 2) to drop out from the study and return to standard of care. A 20% patient drop-out is anticipated but all efforts will be done for patients to complete the study as the primary analysis will be intention-to-treat.

6.2. Medications during the study:

As mentioned above, a movement disorders specialist with expertise in DBS programming will be un-blinded to study arm allocation and will be in charge of programming the patients every 4–6 weeks to 1 of the 3 DBS conditions as per randomization. Optimization of dopaminergic medications will be allowed in case PD symptoms deteriorate during this study, as specified above. Dopaminergic medication changes will be tracked by the corresponding LEDD. Starting other medications specifically to address motor symptoms will not be allowed during this study. These medications include amantadine, cholinergic agents, norepinephrine and serotoninergic modulators. These medications will be continued as long as they are at a stable dose for at least 30 days before enrollment. Changes in their dosing during the study will not be allowed.

6.3. Procedures for monitoring subject compliance:
Compliance will be ensured by revision of previous DBS parameters during all the DBS programming visits (at least every 4 weeks) by the un-blinded physician as mentioned before.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy Parameters:

The efficacy of UL 50% voltage reduction in BL STN-DBS as treatment for axial dysfunction in PD will be primarily assessed by the changes in gait speed measured during the 10-m walk test. The 10-m walk test is a simple, widely used test that has been vali-

dated in patients with PD. Gait speed measurements provided by the 10-m walk test are reliable with good internal and external validity, as well as excellent clinimetric properties.[10] As presented below, normal ranges for gait speed in different age groups are established and they correlate with different functional parameters. In addition, the minimal clinically important difference (MCID) has been established for patients with several neurologic conditions, but not for PD.[10]
Other secondary efficacy parameters will be the changes in other scores that measure axial symptoms, including the mini-BESTest, the PIGD score of the UPDRS, the FOG questionnaire, quantitative gait analysis performed with the Zeno walkway (which is available in the movement disorders center) and quantitative speech analysis performed with the Praat software (freely available). Finally, patients will also complete the PDQ-39 and a brief (<60min) cognitive assessment at baseline and at the end of each cross-over period.

7.2. Assessment of Efficacy Parameters:

The primary and secondary efficacy parameters mentioned above will be assessed for each patient at the time of study entry (baseline), and then more 3 times after completing the 4-weeks of each of the 3 DBS conditions (BL, UL1 or UL2). If needed, 2 additional assessments will be performed after the 2-week LEDD excess washout periods and before changing the DBS setting to either of the 2 remaining DBS conditions. Therefore, efficacy assessments will be performed a minimum of 4 times and a maximum of 6 times.

The 10-m walk test will be performed in the movement disorders clinic as per standard protocol. For this test, the patients will be asked to walk first at a comfortable pace and then at a fast pace. A 10-m length of will be marked in the floor, which will be used for the patient to walk. Gait speed will be measured by measuring the time it takes for the patient to walk through the middle 6 meters of the 10-meter path. The mini-BESTest will also be performed in the movement disorders clinic as per standard protocol (See appendix). The Zeno Walkway is located inside of one of the movement disorders clinic rooms. One of the computers in this room will also have installed the Praat software for speech analysis. The UPDRS, FOG questionnaire, brief cognitive assessment and PDQ-39 will also be performed in the movement disorders clinic (See appendix).

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters:

As seen in previous studies including our previous pilot data, the main safety concern with asymmetric STN-DBS is the worsening of appendicular PD symptoms contralateral to the side of reduced stimulation (tremor, bradykinesia, rigidity). As opposed to those studies, we will not turn OFF stimulation completely. Therefore, we hope to maintain the benefits of BL DBS on appendicular symptoms. This possible symptom deterioration will be assessed through phone calls, focused examination and the UPDRS scale.

8.2. Assessment of Safety Parameters:

The patients will be called on the day after and 2-weeks after each of the DBS changes. In addition, patients will be instructed to call the movement disorders clinic for any symptom change and the study team will be available 24/7 to assess these symptom changes. If symptom deterioration is clinically relevant on the opinion of the patients and/or clinician and/or investigator, the patient will be instructed to return to the movement disorders clinic. At that time, a focused examination that includes the UPDRS will be performed. As previously specified, if symptom deterioration is associated with a drop in the UPDRS of ≤30%, we will allow for dopaminergic medication adjustments. If the symptoms deterioration is >30%, the patient will return to baseline BL STN-DBS and LEDD and will continue to be followed in the study protocol.

9. STATISTICS

9.1. General Design Issues:

- Null hypothesis: UL 50% voltage reduction does not result in an improvement of at least 0.10–0.16 m/s* in gait velocity when compared to baseline.
- Alternative hypothesis: UL 50% voltage reduction results in an improvement of at least 0.10–0.16 m/s* in gait velocity when compared to baseline.
  *Minimum clinically-important difference in gait velocity for non-PD patients.[9]

- Primary outcome measure: Gait velocity during the 10-m walk test. The 10-m walk test has been validated in PD patients by independent groups, displaying good clinimetric properties. This test is easy to administer and might be useful for identifying changes in gait speed over time in mild to moderate PD. A possible limitation is that the presence of FOG may affect gait speed.
- Secondary outcome measures: (Other qualitative and quantitative measures of PIGD)
  - PIGD measured by the mini-BESTest. The mini-BESTest has been validated in PD patients and displays good clinimetric properties. It is a short test that can be administered in 10-15 min. A limitation is that its responsiveness has not yet been examined in a pure PD population.
  - PIGD measured by the UPDRS. The PIGD scores of the UPDRS has been extensively and independently used in PD populations. A limitation is its possible floor effect making it less suitable for patients with mild disease.
  - FOG as per the FOG questionnaire: The FOG questionnaire is a short, reliable instrument that is easy to use and validated in PD. A limitation is that it includes 2 gait items, implying that it is not a pure measure of FOG. In addition, it relies on self-report as opposed to objective ratings.
  - MDS-UPDRS. The total and motor scores of the MDS-UPDRS have been extensively and independently validated in PD populations. Given its more recent development, the PIGD score of the MDS-UPDRS is still not recommended over the PIGD score of the UPDRS.
  - Quantitative PIGD analysis as per the Zeno walkway (stride length, cadence, phase coordination index, turning time). The Zeno walkway by Protokinetics (http://www.protokinetics.com/zenowalkway.html) is a floor mat equipped with electronic

sensors that are able to reliably measure spatiotemporal parameters of gait including stride length and velocity, cadence, turning time. This has not yet been validated in PD patients.
  - Quantitative speech analysis as per the Praat software (intelligibility, pitch, intensity). The Praat software is a freely available program that allows for the recording and quantitative analysis of speech including pitch, intensity and intelligibility. This has not yet been validated in PD patients.
  - Brief cognitive assessment (<60 min): Select cognitive abilities that have been shown to decline after STN-DBS or that show a lateralization effect in the PD literature will be assessed. To assess left hemispheric function, tasks of verbal fluency, verbal working memory and verbal episodic memory will be administered. To assess right hemispheric function, tasks of visuospatial working memory, visual episodic memory, and spatial perception will be administered.
  - The PDQ-39 is a self-completion patient related outcome designed to address aspects of functioning and well-being for individuals affected by PD. Substantial evidence suggests that the PDQ is reliable, valid, responsive and feasible for the assessment of quality of life in PD patients. The PDQ-39 encompasses 39 questions with 8 discrete scales in mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items) and bodily discomfort (3 items).
  - Intraoperative electrophysiological evidence for STN asymmetry will be analyzed by comparing intraoperative electrophysiological recordings of the left and right STN per patient for 1) order of DBS lead placement (right STN first vs. left STN first), 2) number of STN trajectories per side, 3) STN trajectory lengths in millimeters, 4) STN mean firing rates in Hertz (local field potentials) and 5) STN burst indices.
  - Comparative imaging analysis will be performed by estimating the VTA for each DBS condition per patient and overlapping the VTAs with the corresponding postoperative magnetic resonance images.
- Outcome assessment will be performed in a blinded fashion by research assistants (including students and other movement disorders fellows). Outcome adjudication will be performed in a blinded fashion by a movement disorders specialist not involved with the design of this study.
- The choice of a randomized, double-blinded, double-crossover design will allow us to have baseline assessments for each patient, which will serve as his/her own control for comparison of changes that occur after each study intervention. As opposed to previous similar studies that employed a same-day crossover design, this study will have 1-month periods in between assessments in order to allow for the full motor effects of STN-DBS to develop, and will also serve as wash-out periods from the previous DBS condition and decrease the risk for any carry-over effect.

9.2. Outcomes:

Primary outcome: Gait velocity measured during the 10-m walk test. In this test, subjects will be asked to walk at either their self-selected most comfortable speed over a

10-m course. Timing will be performed over the middle 6-m to account for acceleration and deceleration in the initial or final 2-m of the course.
The patients will walk over the Zeno Walkway during this test in order to record and store the quantitative data as a back-up.

Secondary outcomes:

- PIGD measured by the mini-BESTest
- PIGD measured by the UPDRS
- MDS-UPDRS (Total and motor scores)
- FOG as per the FOG questionnaire
- Quantitative PIGD analysis as per the Zeno walkway (stride length, cadence, phase coordination index, turning time)
- Quantitative speech analysis as per the Praat software (intelligibility, pitch, intensity)
- Select cognitive abilities (verbal fluency, verbal working and episodic memory, visuospatial working memory, visual episodic memory and spatial perception)
- Quality of life measured by the PDQ-39

9.3. Sample Size and Accrual:

A minimum sample size of 27 patients was calculated taking into account a 20% drop-out rate added to the actual sample size of 22 patients. The actual sample size of 22 patients was obtained using the sample size formula for paired t-test with an alpha of 0.025 (two-tailed with Bonferroni correction for multiple comparisons), 80% power and anticipated gait velocity means in m/s (primary endpoint) from the following sources:
1) From pilot study in 22 PD pts. with PIGD after BL STN-DBS:[6]
(mean ± standard deviation)
- BL STN-DBS OFF = 0.84 ± 0.07
- Right STN-DBS ON = 0.92 ± 0.05, Left STN-DBS ON = 0.90 ± 0.05
- BL STN-DBS ON = 0.95 ± 0.05 → anticipated mean for group 2 (BL STN-DBS) (The standard deviation of 0.05 was increased to 0.1 given the reduced variability and small sample size in this pilot study)

2) From the literature:
- Minimum clinically-important difference for non-PD = 0.10–0.16 [10]→ anticipated mean for group 1 (UL STN-DBS) = (0.95 ± 0.05) + 0.10–0.16 = 1.0–1.16 (1.08 ± 0.08)
* Minimum clinically-important difference for PD = Unknown [10]
Given the reported frequency of up to 20% patients with PD who develop PIGD in the first year after BL STN-DBS implantation [1,11], the number of PD patients that undergo BL STN-DBS surgery (4 new patients per month) and are followed at the Movement Disorders Center of the University of Toronto, we estimate that we will be able to enroll the minimum of 27 patients in the 1.5 years of planned study duration. The minimum accrual would be of 1-2 patients per month.

9.4. Data Monitoring:

An interim data analysis will be performed one year after randomization of the first subject and when/if the drop-out rate exceeds the anticipated 20% despite all efforts. An independent data safety monitoring board that will include 2 movement disorders physicians not involved in this study will analyze the data at this time and will recommend if the study should be stopped for safety or futility. Given the sample size of <30 patients and its relative short duration, this study will not be stopped for efficacy until completion. If patient recruitment slows down to <2-3 patients/month, all movement disorders physicians in the DBS clinics will be reminded of the study protocol and enrollment criteria.

9.5. Data Analyses:

Intention-to-treat will be the primary analysis method and per-protocol will be the secondary analysis method if/as needed. Missing data, outliers, noncompliance and losses to follow-up will be reduced as much as possible with the close follow-up as mentioned above. In addition, gait speed will also be measured on the Zeno Walkway as explained above, which will allow for back-up data and further quantitative analysis. Finally, we expect patients to be highly motivated to comply with this study given the treatment-resistant axial dysfunction that triggered their interest and participation.
Covariance analysis using mixed models will be performed to evaluate the differences in least square means of gait speed changes (primary outcome) between the 3 STN-DBS conditions compared to baseline. The effects of UL STN-DBS preferentially targeting the body side most or least affected by PD, as well as dominant or non-dominant hemispheres for appendicular and/or axial motor control will be compared.
Covariance analysis using mixed models will also be performed to evaluate the differences in least square means of secondary outcomes between the 3 STN-DBS conditions.
After these comparisons have been completed, we will determine if UL1 and UL2 corresponded to 50% voltage reduction targeting: 1) the left or right hemisphere, 2) the dominant or non-dominant hemispheres for appendicular and/or axial motor control and 3) the hemisphere ipsilateral or contralateral to the side most affected by PD.
We will then perform multivariate linear regression to determine if any feature of motor control lateralization is associated with the change in gait velocity observed during the 3 STN-DBS conditions: BL, left or right.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Investigators will have direct access to the study documentation. The un-blinded physician will have additional access to the source data documentation (patient's charts), for standard of care and appropriate symptom management as previously specified. All study related, source data and chart documentation will be available for monitoring, review or audits as deemed necessary by the institutional REB or any other regulatory agency.

11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Throughout the duration of this study, each participant will receive phone calls in a bi-weekly fashion to ensure tolerability and to encourage compliance with the study protocol. In addition, adherence assessments will be performed during each of the study visits

as previously specified. Study investigators assigned to perform the blinded outcome evaluations will first receive extensive training on the appropriate performance of the 10-m walk test, the mini-BESTest, rating scales (UPDRS, MDS-UPDRS), FOG questionnaire, Zeno Walkway and Praat software. The use of the Zeno Walkway for quantitative gait analysis will allow for back-up data on gait speed, in addition to the one obtained with the 10-m walk test. The study team will meet to review all study documentation weekly. Data will be entered in the REDCap database after the consistency and quality of collected data is assured. The database will be available only in one of the computers of the movement disorders clinic, which will be password protected and locked when not in use by the study investigators.

12. ETHICS

12.1. Informed Consent Process:

Patients will be screened for eligibility during their regular visits to the DBS clinic of the movement disorders center. All physicians in charge of providing standard of care during these visits will be aware of this study and will be able to identify potential study participants. Once a patient is deemed eligible for the study, one of the investigators will contact them regarding the study. The patient will be extensively educated on the nature and purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent form will describe in English and French each of these topics in lay terms for the patient and/or legal guarding to be able to understand these points. The patient will be given the opportunity to ask questions regarding the study, which will be fully addressed by one of the investigators. A copy of the consent form will be given to the subject or legal guardian, and this fact will be documented in the subject's record. A signed consent form will be obtained from the subject by one of the investigators, after the appropriate informed consent process and before enrollment in this study. A period of up to 30 days will be allowed from the time of screening for the patient to review the consent and make a decision regarding participation. The patient and/or legal guardian will be able to finish his/her participation in this study at any time without having repercussions in the standard of care offered at the DBS clinic. An institutional translator will be available for subjects whose primary language is not English or French. For subjects who cannot consent for themselves, a legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study.

12.2. Research Ethics Board:

This protocol, the informed consent document and any subsequent amendments will be reviewed and approved by the REB before any study related procedures or implemented changes begin.

13. DATA HANDLING AND RECORD KEEPING

Study data will be initially recorded in a Case Report Form (CRF) designed for each of the study visits for each participant (See appendix). The completed CRFs will be reviewed by the study team (including the P.I.) every week to ensure accuracy, complete-

ness, legibility and timeliness. Afterwards, data will be transferred to the REDcap database as mentioned above. All CRFs and other study documentation will be identified only by the Study Identification Number (SIN) to maintain subject confidentiality. All records will be kept in a password-protected computer kept in a locked room in the movement disorders clinic at Toronto Western Hospital. All database entry will be done using SINs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the institutional REB or other regulatory agencies. All records and documents pertaining to the study will be retained by the movement disorders clinic for at least 25 years from the completion of the study, and will be available for inspection by regulatory agencies. The study may be modified or discontinued at any time by the institutional REB or other regulatory agencies as part of their duties to ensure that research subjects are protected.

14. FINANCING

This study will be funded by internal resources from the movement disorders clinic.

15. PUBLICATION POLICY

This clinical trial will be registered at clinicaltrials.gov. Publication of partial or final results of this trial will be governed by the policies and procedures of the University of Toronto Movement Disorders Center in the context of REB approval, and following all requirements by the corresponding authorities.

16. SUPPLEMENTS

SCHEDULE OF EVALUATIONS

Evaluation	Screening (<30 days)	Pre-Entry (<15 days)	Entry (Baseline)	2 wk.	4±2 wk.	6±2 wk.	8±2 wk.	10±2 wk.	12±2 wk.	14±2 wk.	Worsening at anytime
Informed consent process	X	X	X								
Documentation of disease	X	X	X								
Medical/Treatment history	X	X	X		X		X		X		X
Targeted physical exam (including UPDRS or MDS-UPDRS)	X		X	*	X	*	X	*	X		X
Schedule study follow-up visits and review with patient	X	X	X	X	X	X	X	X	X		X
Phone calls to assess tolerability				X	X	X	X	X	X	X	X
Edinburgh handedness inventory			X								
MDS-UPDRS laterality index			X		X		X		X		
Randomization / crossover			X		X		X				
Primary outcome assessment: Gait velocity / 10-m walk test			X	*	X	*	X	*	X		
Secondary outcome assessments:			X	*	X	*	X	*	X		
Mini-BESTest for PIGD			X	*	X	*	X	*	X		
Quantitative gait analysis (Zeno)			X	*	X	*	X	*	X		
FOGQ, cognitive tasks, PDQ-39			X	*	X	*	X	*	X		
Quantitative speech analysis			X	*	X	*	X	*	X		
Medication adjustment (LEDD increase if UPDRS drops ≤30%)				*	*	*	*	*	*		* If UPDRS drops ≤30%
LEDD excess washout (+2 wks. if LEED increased)					X		X		X		X
Return to baseline if UPDRS drops >30%				**	**	**	**	**	**	X	** If UPDRS drops >30%
Adherence Assessments					X		X		X		

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title:
A single-center, randomized, double-blinded, double-crossover trial of asymmetric subthalamic deep brain stimulation for axial motor dysfunction in Parkinson's disease.

Investigators/Study Doctors:
Alfonso Fasano, M.D., Ph.D. (Principal Investigator); Karlo J. Lizarraga, M.D., M.S.; Renato Munhoz, M.D.; Connie Marras, M.D., Ph.D.; Melanie Cohn, Ph.D., C.Psych.

Contact Information:
Movement Disorders Clinic, Toronto Western Hospital
399 Bathurst Street, McL 7th Floor, Toronto, Ontario M5T 2S8
Phone: 416-603-6422
24-hour study pager: 416-714-7942 (will page the study team directly)

Introduction:
You are being asked to take part in a research study. Please read the information about the study presented in this form. The form includes details on study's risks and benefits that you should know before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Background/Purpose:
Parkinson's disease affects motor and non-motor aspects of daily living. Motor symptoms such as tremor, rigidity and slowness of movement can initially respond to medications. With time, motor complications (dyskinesias, fluctuations) can develop. When these complications appear, deep brain stimulation is an effective treatment modality that allows for better motor symptom control.
With disease progression, patients with Parkinson's disease also develop other symptoms called axial motor symptoms (postural instability, gait difficulties including freezing of gait, speech problems). For unknown reasons, the development of axial motor symptoms in these patients can be faster and/or more severe after deep brain stimulation. Currently, the standard of care for this axial deterioration is to try to optimize Parkinson's disease medications and/or deep brain stimulation parameters; however, in many cases there is unfortunately no improvement.
There is growing scientific evidence that one side of the brain could be more important than the other for gait control. If this were the case, bilateral deep brain stimulation might be unnecessary for all patients and could be contributing with worse axial symptoms due to excessive stimulation. Moreover, previous studies suggest that these axial symptoms could improve with different stimulation parameters for each side of the brain.

A minimum of 27 patients will participate in this study that will take approximately 2 years to complete.

Study Design:

In this study, we are comparing the effects of 3 different types of deep brain stimulation in the motor symptoms of patients with Parkinson's disease who develop worsening axial symptoms despite of treatment, more than 6 months but less than 5 years after deep brain stimulation surgery. The 3 stimulation parameters being compared are 1) bilateral, 2) unilateral #1 (right more than left-sided stimulation) and 3) unilateral #2 (left more than right-sided stimulation).

This is a randomized double blinded study. If you decide to participate you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by change. It is like flipping a coin. Neither you nor your doctor can choose what group you will be in, but at the end of the study you will have received the 3 types of deep brain stimulation described.

The first time you are randomized, you will have a 1 in 3 chance of being placed in one of the 3 types of stimulation. The second time you are randomized, you will have a 1 in 2 chance of being placed in one of the other 2 types of stimulation. The last type of stimulation you receive will be the remaining one. Neither you nor your doctor will know which group you are in. In an emergency, if the type of deep brain stimulation needs to be identified, the doctor can get this information.

Study Visits and Procedures:

All enrolled patients will undergo a baseline evaluation of motor and non-motor symptoms. After completion of this baseline evaluation, enrolled patients will be randomly assigned to one of the 3 types of stimulation. This initial stimulation parameter will be maintained for 4 weeks. Patients will undergo a second evaluation of motor and non-motor symptoms after completion of these first 4 weeks. After this second evaluation is completed, enrolled patients will be randomly assigned to one of the 2 remaining types of stimulation. This second stimulation parameter will be maintained for another 4-week period. Patients will undergo a third evaluation of motor and non-motor symptoms after completion of this second 4-week period. After this third evaluation is completed, stimulation will be changed to the remaining type. This third type of stimulation will be maintained for additional 4 weeks. Patients will undergo a fourth and last evaluation of motor and non-motor symptoms after completion of this third 4-week period. The study investigators and enrolled patients will not know which of the 3 types of stimulation is being evaluated at any particular moment.

In summary, all enrolled patients will undergo a minimum of 4 evaluations in the movement disorders clinic: 1 baseline evaluation and a minimum of 3 additional evaluations after completing 3 different types of stimulation for 4 weeks each. The minimum study duration will thus be 12 weeks per patient.

If there is worsening of your Parkinson's disease symptoms, please contact the movement disorders clinic and we will call you back as soon as possible to evaluate the worsening with you. After discussing the worsening over the phone, you might need to come to the movement disorders clinic to be examined. We will have two options if your symptoms worsen during the study: 1) optimize the doses of your Parkinson's disease

medications or 2) return to the type of stimulation that you were on before entering the study. You will continue being closely followed with either of these options.
If we needed to increase the Parkinson's disease medications at any time, there will be an additional period of 2 weeks once you complete the corresponding 4-week period. Specifically, the type of stimulation and doses of your Parkinson's disease medications will be returned to what they were before entering the study, and we will wait 2 weeks to ensure the additional amount of medication is out of your system. In addition, you would be evaluated for motor and non-motor symptoms again before you continue with the rest of the study. Therefore, the study duration could increase to a maximum of 18 weeks and the evaluations could increase to a maximum of 7 evaluations (1 baseline, 3 scheduled and 3 additional if needed).

Risks:
Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.
The risks we know of are possible worsening of some of the motor symptoms of Parkinson's disease (tremor, rigidity, slowness of movement). The exact frequency and severity of this risk is unknown and we expect that this will vary depending on every patient's different baseline symptoms and tolerance. In addition to being available for you anytime, we will call you the day after and 2 weeks after changing the type of stimulation to ensure you are tolerating the new settings.

Benefits:
You may directly benefit from being in this study. Your gait, balance and/or speech could significantly improve during the study. After the study is completed, you will be given the opportunity to return to the type of stimulation that you were on before entering the study, or to be changed to any of the other types that helped your symptoms the most during the study. Information learned from this study may also help other patients with Parkinson's disease that have similar problems.

Reminders and Responsibilities:
Your main responsibility would be compliance with the study visits and evaluations to the best of your abilities. As mentioned above, the minimum study duration would be 12 weeks including evaluations of your symptoms every 4 weeks. The maximum study duration would be 18 weeks including evaluations of your symptoms every 4 weeks and additional evaluations 2 weeks after medication changes.
We will remind you of the scheduled study visits to the Movement Disorders Clinic during the phone calls mentioned previously: the day after and 2 weeks after each stimulation parameter change.

Alternatives to Being in the Study:
You do not have to join this study to receive treatment for your condition. If you decide not to participate in this study, you will continue receiving the standard of care at the Toronto Western Hospital movement disorders clinic. Nevertheless, your condition might

not improve even after optimization of your Parkinson's disease medications and/or deep brain stimulation.

Confidentiality:

Your data will be shared as described in this consent form or as required by law. All personal information such as your name, address, phone number, OHIP number, and family physician's name will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept by the study doctor in a secure place, separate from your file.

Personal Health Information

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could identify you and includes your:

- name,
- address,
- full date of birth,
- new or existing medical records including types, dates and results of medical tests or procedures.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines:

- Representatives of the University Health Network (UHN) including the UHN Research Ethics Board
- Representatives of Health Canada or other regulatory bodies (groups of people who oversee research studies)

The study doctor will keep any personal health information about you in a secure and confidential location for 25 years as required.

Your participation in this study will also be recorded in your medical record at this hospital. This is for clinical safety purposes.

Research Information in Shared Clinical Records

If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. The study team can tell you what information about you will be stored electronically and may be shared outside the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

Voluntary Participation:
Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later. You may leave the study at any time without any repercussion in the standard of care you will receive at the Toronto Western Hospital movement disorders clinic. We will give you any new information that is learned during the study that might affect your decision to stay in the study.

Withdrawal from the Study:
You might be withdrawn from this study if 1) your condition becomes so severe that you need assistance to walk, become wheelchair or bedbound; 2) you develop cognitive or psychiatric problems that preclude you from understanding the risks and benefits of this study at any time; 3) you develop a severe illness that precludes you from completing the planned or additional study visits.
If you are withdrawn from the study, the standard of care you receive at the Toronto Western Hospital movement disorders clinic will not be affected.

Costs and Reimbursement:
We will reimburse you up to 30.00 CAD of the costs of each of the 4–7 study visits to the Toronto Western Hospital.

Rights as a Participant:
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.
By signing this form, you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Conflict of Interest:
Researchers have an interest in completing their studies and those interests should not influence your decision to participate in this study. The study doctors do not have any other perceived conflict of interest related to this study.

Questions about the Study:
If you have any questions, concerns or would like to speak to the study team for any reason, please call the Toronto Western Hospital Movement Disorders Clinic at 416-603-6422. If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential. You will be given a signed copy of this consent form.

Consent:

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

Print Study Participant's Name	Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person ing Consent	Signature	Date Obtain-

Was the participant assisted during the consent process? ☐ YES ☐ NO
If **YES**, please check the relevant box and complete the signature space below:

☐ The person signing below acted as an interpreter, and attests that the study as set out in the consent form was accurately sight translated and/or interpreted, and that interpretation was provided on questions, responses and additional discussion arising from this process.

Print Name of Interpreter	Signature	Date

Relationship to Participant	Language

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Print Name of Witness	Signature	Date

Relationship to Participant

CASE REPORT FORM FOR STUDY ENTRY

Study identification number: _____ Visit Date (MMM/YY): _____/_____

1) Date of Parkinson's disease (PD) motor symptom onset (MMM/YY): _____/_____

2) Predominant motor symptom at onset: tremor / rigidity / slowness / PIGD / FOG

3) Side of the body most affected by motor symptoms at PD onset: L / R / Both equal

4) Date of bilateral STN-DBS surgery (MMM/YY): _____/_____

5) Predominant symptom just before surgery: tremor / rigidity / slowness / PIGD / FOG

6) Side of the body most affected by motor symptoms just before surgery: L / R / Both equal

7) Date of axial motor symptom development (MMM/YY): _____/_____

8) Predominant axial motor symptom: PIGD / FOG / speech changes

9) Side of the body most affected by motor symptoms now: L / R / Both equal

10) Current STN-DBS settings (baseline):

	Left-STN	Right-STN
Voltage		
Frequency		
Pulse width		

11) Current dopaminergic medication(s) and dose(s):

Medication	Dose (mg/day)	Levodopa-equivalent dose (mg/day)

12) Total levodopa-equivalent daily dose (mg/day): _____

CASE REPORT FORM FOR BASELINE STUDY EVALUATION

Study identification number: _____ Visit Date (MMM/YY): _____/_____

1) From the 20 acts in the Edinburgh handedness inventory, calculate the laterality index as 100 x [(R – L) / (R + L)], where R is the number of acts performed with the right, and L is the number performed with the left:

_____

2) 10-metter walk test:

* Calculated gait speed (Normal): _____ m/s
* Calculated gait speed (Fast): _____ m/s

3) Mini-BESTest:

* Anticipatory: _____/ 6 points
* Reactive postural control: _____/ 6 points
* Sensory orientation: _____/ 6 points
* Dynamic gait: _____/ 10 points

* Total score: _____/ 28 points

4) UPDRS-PIGD sub score:

* Activities of daily living
  * Falling: _____/ 4 points
  * FOG: _____/ 4 points
  * Walking: _____/ 4 points
* Examination
  * Gait: _____/ 4 points
  * Postural stability: _____/ 4 points

* Total score: _____/ 20 points

5) MDS-UPDRS:

* MDS-UPDRS motor score (Part III) _____
* MDS-UPDRS total score _____

6) FOG questionnaire _____/ 24 points

7) 39-PDQ _____

CASE REPORT FORM FOR FOLLOW-UP STUDY EVALUATIONS

Study identification number: _____ Visit Date (MMM/YY): _____/_____

Visit type: Scheduled #1 / #2 / #3 Additional #1 / #2 / #3

1) Current dopaminergic medication(s) and dose(s):

Medication	Dose (mg/day)	Levodopa-equivalent dose (mg/day)

2) Total levodopa-equivalent daily dose (mg/day): _____

3) 10-metter walk test:
* Calculated gait speed (Normal): _____ m/s
* Calculated gait speed (Fast): _____ m/s

4) Mini-BESTest:
* Anticipatory: _____/ 6 points
* Reactive postural control: _____/ 6 points
* Sensory orientation: _____/ 6 points
* Dynamic gait: _____/ 10 points
* Total score: _____/ 28 points

5) UPDRS-PIGD sub score:
* Activities of daily living
    * Falling: _____/ 4 points
    * FOG: _____/ 4 points
    * Walking: _____/ 4 points
* Examination
    * Gait: _____/ 4 points
    * Postural stability: _____/ 4 points
* Total score: _____/ 20 points

6) MDS-UPDRS:
* MDS-UPDRS motor score (Part III) _____
* MDS-UPDRS total score _____

7) FOG questionnaire _____/ 24 points
8) PDQ-39 _____

EDINBURGH HANDEDNESS INVENTORY

Study Identification Number: _____ Date (MMM/YY): _____/_____

1) Have you ever had any tendency to left-handedness? YES / NO

2) Please indicate your preferences in the use of hands in the following activities by putting a + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. If in any case you are really indifferent put + in both columns. Some of the activities require both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in brackets. Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

	Activity	Right	Left
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Comb		
6	Toothbrush		
7	Knife (without fork)		
8	Spoon		
9	Hammer		
10	Screwdriver		
11	Tennis Racket		
12	Knife (with fork)		

13	Cricket bat (lower hand)		
14	Golf Club (lower hand)		
15	Broom (upper hand)		
16	Rake (upper hand)		
17	Striking Match (match)		
18	Opening box (lid)		
19	Dealing cards (card being dealt)		
20	Threading needle (needle or thread according to which is moved)		
40	Which foot do you prefer to kick with?		
41	Which eye do you use when using only one?		

10 METER WALK TEST (GAIT SPEED)

Study Identification Number: _____ Date (MMM/YY): _____/_____

TEST PROTOCOL: Measure and mark a 10-meter (32.8 feet) distance. Then measure and mark 2 meters (6.6 feet) from the start and 2 meters from the finish. The central 6 meters are timed, the 2 meters on either side are not timed and are intended for acceleration and deceleration. Patient may use an assistive device, but this should be kept consistent and documented. If assistance is required, this test should not be performed. This tests may be performed for preferred gait speed or fast speed.

Walking direction → (10 meters / 34.8 feet) →		
2 meters	6 meters	2 meters
6.6 feet	19.7 feet	6.6 feet
← Starting line	← START TIMING STOP TIMING →	Finish line →

INSTRUCTIONS:

- Start timing when the toes of the leading foot cross the first 2-meter mark.
- Stop timing when the toes of the leading foot cross the second 2-meter mark (8 meters from the starting line, 6 meters from the first 2-meter mark)
- Collect 3 trials and calculate the average of the three trials.

NORMAL: “I will say ready, set, go. When I say go, walk at your normal comfortable speed until I say stop.”
FAST: “I will say ready, set, go. When I say go, walk as fast as you safely can until I say stop.”

GAIT SPEED = 6 METERS / TIME TO COMPLETE
(For example, the person takes 9 seconds to walk 6 meters → 6/9 = 0.67 m/s)

Patient’s performance (Normal): _____ seconds

Calculated gait speed (Normal): _____ meters/second (m/s) (round to 2 decimal places)

Patient’s performance (Fast): _____ seconds

Calculated gait speed (Fast): _____ meters/second (m/s) (round to 2 decimal places)

Mini-BESTest: Balance Evaluation Systems Test

Study Identification Number: _____ Date (MMM/YY): _____/_____

ANTICIPATORY *SUB SCORE:* /6

1. SIT TO STAND
Instruction: "Cross your arms across your chest. Try not to use your hands unless you must. Do not let your legs lean against the back of the chair when you stand. Please stand up now."
(2) Normal: Comes to stand without use of hands and stabilizes independently.
(1) Moderate: Comes to stand WITH use of hands on first attempt.
(0) Severe: Unable to stand up from chair without assistance, OR needs several attempts with use of hands.

2. RISE TO TOES
Instruction: "Place your feet shoulder-width apart. Place your hands on your hips. Try to rise as high as you can onto your toes. I will count out loud to 3 seconds. Try to hold this pose for at least 3 seconds. Look straight ahead. Rise now."
(2) Normal: Stable for 3 s with maximum height.
(1) Moderate: Heels up, but not full range (smaller than when holding hands), OR noticeable instability for 3 s.
(0) Severe: ≤ 3 s.

3. STAND ON ONE LEG
Instruction: "Look straight ahead. Keep your hands on your hips. Lift your leg off of the ground behind you without touching or resting your raised leg upon your other standing leg. Stay standing on one leg as long as you can. Look straight ahead. Lift now."

Left: Time in Seconds Trial 1:____ Trial 2: ____	*Right: Time in Seconds Trial 1:____ Trial 2:___*
(2) Normal: 20 s.	(2) Normal: 20 s.
(1) Moderate: < 20 s.	(1) Moderate: < 20 s.
(0) Severe: Unable	(0) Severe: Unable

*To score each side separately use the trial with the longest time. To calculate the sub-score and total score use the side [left or right] with the lowest numerical score [i.e. the worse side].

REACTIVE POSTURAL CONTOL *SUB SCORE:* /6

4. COMPENSATORY STEPPING CORRECTION- FORWARD
Instruction: "Stand with your feet shoulder-width apart, arms at your sides. Lean forward against my hands beyond your forward limits. When I let go, do whatever is necessary, including taking a step, to avoid a fall."
(2) Normal: Recovers independently with a single, large step (second realignment step is allowed).
(1) Moderate: More than one step used to recover equilibrium.
(0) Severe: No step, OR would fall if not caught, OR falls spontaneously.

5. COMPENSATORY STEPPING CORRECTION- BACKWARD
Instruction: "Stand with your feet shoulder-width apart, arms at your sides. Lean backward against my hands beyond your backward limits. When I let go, do whatever is necessary, including taking a step, to avoid a fall."
(2) Normal: Recovers independently with a single, large step.

(1) Moderate: More than one step used to recover equilibrium.
(0) Severe: No step, OR would fall if not caught, OR falls spontaneously.

6. COMPENSATORY STEPPING CORRECTION- LATERAL

Instruction: "Stand with your feet together, arms down at your sides. Lean into my hand beyond your sideways limit. When I let go, do whatever is necessary, including taking a step, to avoid a fall."

Left:	*Right:*
(2) Normal: Recovers independently with 1 step (crossover or lateral OK)	(2) Normal: Recovers independently with 1 step (crossover or lateral OK)
(1) Moderate: Several steps to recover equilibrium.	(1) Moderate: Several steps to recover.
(0) Severe: Falls, or cannot step.	(0) Severe: Falls, or cannot step.

*Use the side with the lowest score to calculate sub-score and total score.

SENSORY ORIENTATION *SUB SCORE:* /6

7. STANCE (FEET TOGETHER); EYES OPEN, FIRM SURFACE

Instruction: "Place your hands on your hips. Place your feet together until almost touching. Look straight ahead. Be as stable and still as possible, until I say stop."
Time in seconds: _____
(2) Normal: 30 s.
(1) Moderate: < 30 s.
(0) Severe: Unable.

8. STANCE (FEET TOGETHER); EYES CLOSED, FOAM SURFACE

Instruction: "Step onto the foam. Place your hands on your hips. Place your feet together until almost touching. Be as stable and still as possible, until I say stop. I will start timing when you close your eyes."
Time in seconds: _____
(2) Normal: 30 s.
(1) Moderate: < 30 s.
(0) Severe: Unable.

9. INCLINE- EYES CLOSED

Instruction: "Step onto the incline ramp. Please stand on the incline ramp with your toes toward the top. Place your feet shoulder-width apart and have your arms down at your sides. I will start timing when you close your eyes."
Time in seconds: _____
(2) Normal: Stands independently 30 s and aligns with gravity.
(1) Moderate: Stands independently < 30 s OR aligns with surface.
(0) Severe: Unable.

DYNAMIC GAIT *SUB SCORE:* /10

10. CHANGE IN GAIT SPEED

Instruction: "Begin walking at your normal speed, when I tell you 'fast', walk as fast as you can. When I say 'slow', walk very slowly."
(2) Normal: Significantly changes walking speed without imbalance.
(1) Moderate: Unable to change walking speed or signs of imbalance.
(0) Severe: Unable to achieve significant change in walking speed AND signs of imbalance.

11. WALK WITH HEAD TURNS – HORIZONTAL

Instruction: "Begin walking at your normal speed, when I say 'right', turn your head and look to the right. When I say 'left', turn your head and look to the left. Try to keep yourself walking in a straight line."

(2) Normal: Performs head turns with no change in gait speed and good balance.
(1) Moderate: Performs head turns with reduction in gait speed.
(0) Severe: Performs head turns with imbalance.

12. WALK WITH PIVOT TURNS

Instruction: "Begin walking at your normal speed. When I tell you to 'turn and stop', turn as quickly as you can, face then opposite direction, and stop. After the turn, your feet should be close together."

(2) Normal: Turns with feet close FAST (≤ 3 steps) with good balance.
(1) Moderate: Turns with feet close SLOW (≥ 4 steps) with good balance.
(0) Severe: Cannot turn with feet close at any speed without imbalance.

13. STEP OVER OBSTACLES

Instruction: "Begin walking at your normal speed. When you get to the box, step over it, not around it and keep walking."

(2) Normal: Able to step over box with minimal change of gait speed and with good balance.
(1) Moderate: Steps over box but touches box OR displays cautious behavior by slowing gait.
(0) Severe: Unable to step over box OR steps around box.

14. TIMED UP & GO WITH DUAL TASK [3 METER WALK]

Instruction TUG: "When I say 'Go', stand up from chair, walk at your normal speed across the tape on the floor, turn around, and come back to sit in the chair."
Instruction TUG with Dual Task: "Count backwards by threes starting at ____. When I say 'Go', stand up from chair, walk at your normal speed across the tape on the floor, turn around, and come back to sit in the chair. Continue counting backwards the entire time."

TUG: _____ seconds; Dual Task TUG: _____ seconds.

(2) Normal: No noticeable change in sitting, standing or walking while backward counting when compared to TUG without Dual Task.
(1) Moderate: Dual Task affects either counting OR walking (>10%) when compared to the TUG without Dual Task.
(0) Severe: Stops counting while walking OR stops walking while counting.
*When scoring item 14, if subject's gait speed slows more than 10% between the TUG without and with a Dual Task the score should be decreased by 1 point.

*TOTAL SCORE:*_____/28

UPDRS-PIGD SUBSCALE

Study Identification Number: _____ Date (MMM/YY): _____/_____

ACTIVITIES OF DAILY LIVING (QUESTIONNAIRE)

FALLING
0 = None
1 = Rare
2 = Occasional (< 1/day)
3 = Approximately once/day
4 = More than once/day

FREEZING OF GAIT
0 = None
1 = Rare, may have "start hesitation"
2 = Occasional
3 = Frequent with occasional falls
4 = Frequently falls from freezing of gait

WALKING
0 = Normal
1 = Mild difficulties. May not swing arms or may tend to drag leg
2 = Moderate difficulties but requires little or no assistance
3 = Severe disturbance, requiring assistance
4 = Cannot walk even with assistance

EXAMINATION

GAIT
0 = Normal
1 = Walks slowly, may shuffle with short steps, but no festination or propulsion
2 = Walks with difficulty, but requires little or no assistance. May have some festination, short steps, or propulsion
3 = Severe disturbance requiring assistance
4 = Cannot walk at all

POSTURAL STABILITY
0 = Normal
1 = Retropulsion, but recovers unaided
2 = Absence of postural response; would fall if not caught by examiner
3 = Very unstable, tends to lose balance spontaneously
4 = Unable to stand without assistance

TOTAL UPDRS-PIGD SCORE: _____ points

FREEZING OF GAIT QUESTIONNAIRE

Study Identification Number: _____ Date (MMM/YY): _____/_____

1. During your WORST state – Do you walk: _____
   0 Normally
   1 Almost normally – somewhat slow
   2 Slow but fully independent
   3 Need assistance or walking aid
   4 Unable to walk

2. Are your gait difficulties affecting your daily activities and independence? _____
   0 Not at all
   1 Mildly
   2 Moderately
   3 Severely
   4 Unable to walk

3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)? _____
   0 Never
   1 Very rarely – about once a month
   2 Rarely – about once a week
   3 Often – about once a day
   4 Always – whenever walking

4. How long is your LONGEST freezing episode? _____
   0 Never happened
   1 1–2 seconds
   2 3–10 seconds
   3 11–30 seconds
   4 Unable to walk for more than 30 seconds

5. How long is your TYPICAL start hesitation episode (freezing when initiating the first step)?
   0 None _____
   1 Takes longer than 1 second to start walking
   2 Takes longer than 3 seconds to start walking
   3 Takes longer than 10 seconds to start walking
   4 Takes longer than 30 seconds to start walking

6. How long is your TYPICAL turning hesitation (freezing when turning)? _____
   0 None
   1 Resume turning in 1–2 seconds
   2 Resume turning in 3–10 seconds
   3 Resume turning in 11–30 seconds
   4 Unable to resume turning for more than 30 seconds

PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (PDQ-39)

Due to having Parkinson's disease,
how often during the last month have you…

*Please **circle one answer** for each question*

1. Had difficulty doing the leisure activities which you would like to do?

Never Occasionally Sometimes Often Always

2. Had difficulty looking after your home, e.g. housework, cooking?

Never Occasionally Sometimes Often Always

3. Had difficulty carrying bags of shopping?

Never Occasionally Sometimes Often Always

4. Had problems walking half a mile?

Never Occasionally Sometimes Often Always

5. Had problems walking 100 yards?

Never Occasionally Sometimes Often Always

6. Had problems getting around the house as easily as you would like?

Never Occasionally Sometimes Often Always

7. Had difficulty getting around in public?

Never Occasionally Sometimes Often Always

8. Needed someone else to accompany you when you went out?

Never Occasionally Sometimes Often Always

9. Felt frightened or worried about falling over in public?

Never Occasionally Sometimes Often Always

10. Been confined to the house more than you would like?

Never Occasionally Sometimes Often Always

Please check that you have ***circled one answer for each question*** before going onto the next page

Due to having Parkinson's disease,
how often during the last month have you…

*Please **circle one answer** for each question*

11. Had difficulty washing yourself?

Never Occasionally Sometimes Often Always

12. Had difficulty dressing yourself?

Never Occasionally Sometimes Often Always

13. Had problems doing up buttons or shoe laces?

Never Occasionally Sometimes Often Always

14. Had problems writing clearly?

Never Occasionally Sometimes Often Always

15. Had difficulty cutting up your food?

Never Occasionally Sometimes Often Always

16. Had difficulty holding a drink without spilling it?

Never Occasionally Sometimes Often Always

17. Felt depressed?

Never Occasionally Sometimes Often Always

18. Felt isolated and lonely?

Never Occasionally Sometimes Often Always

19. Felt weepy or tearful?

Never Occasionally Sometimes Often Always

20. Felt angry or bitter?

Never Occasionally Sometimes Often Always

Please check that you have ***circled one answer for each question*** before going onto the next page

Due to having Parkinson's disease,
how often during the last month have you…

*Please **circle one answer** for each question*

21. Felt anxious?

Never Occasionally Sometimes Often Always

22. Felt worried about your future?

Never Occasionally Sometimes Often Always

23. Felt you had to conceal your Parkinson's from people?

Never Occasionally Sometimes Often Always

24. Avoided situations which involve eating or drinking in public?

Never Occasionally Sometimes Often Always

25. Felt embarrassed in public due to having Parkinson's disease?

Never Occasionally Sometimes Often Always

26. Felt worried by other people's reaction to you?

Never Occasionally Sometimes Often Always

27. Had problems with your close personal relationships?

Never Occasionally Sometimes Often Always

28. Lacked support in the ways you need from your spouse or partner?

Never Occasionally Sometimes Often Always

I do not have a spouse or partner

29. Lacked support in the ways you need from your family or close friends?

Never Occasionally Sometimes Often Always

30. Unexpectedly fallen asleep during the day?

Never Occasionally Sometimes Often Always

Please check that you have ***circled one answer for each question*** before going onto the next page

Due to having Parkinson's disease,
how often during the last month have you…

*Please **circle one answer** for each question*

31. Had problems with your concentration, e.g. when reading or watching TV?

Never Occasionally Sometimes Often Always

32. Felt your memory was bad?

Never Occasionally Sometimes Often Always

33. Had distressing dreams or hallucinations?

Never Occasionally Sometimes Often Always

34. Had difficulty with your speech?

Never Occasionally Sometimes Often Always

35. Felt unable to communicate with people properly?

Never Occasionally Sometimes Often Always

36. Felt ignored by people?

Never Occasionally Sometimes Often Always

37. Had painful muscle cramps or spasms?

Never Occasionally Sometimes Often Always

38. Had aches and pains in your joints or body?

Never Occasionally Sometimes Often Always

39. Felt unpleasantly hot or cold?

Never Occasionally Sometimes Often Always

Please check that you have ***circled one answer for each question.***

Thank you for completing the questionnaire.

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