PROTOCOL

Title: Mobility and Gait Markers of Disease and Disease Progression (PPMI Gait)

Sponsor: Michael J. Fox Foundation for Parkinson's Research

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Mobility and Gait Markers of Disease and Disease Progression (PPMI Gait)

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1. PURPOSE OF STUDY

The Parkinson Progression Marker Initiative (PPMI) is a broad program consisting of the primary in-clinic study (PPMI Clinical), as well as other complementary initiatives conducted under the program that will contribute to PPMI's overarching goal to identify markers of disease progression for use in clinical trials of therapies to reduce progression of PD disability.

The purpose of this study is to test the feasibility and validity of using digital mobility data for enrichment of the prodromal cohort and to test the validity of digital mobility data to monitor early phase progression in prodromal and early PD participants.

1.1 Primary Objectives

The primary objective of this study is to assess whether Digital Health Technology (DHT) can enrich the identification of individuals at risk of developing PD.

1.2 Secondary Objectives

The secondary objectives of this study are:

a. To explore whether DHT measures are sensitive to progression (prodromal and early stages of PD) and,
b. To explore clinometric parameters (sensitivity and specificity) of different measures from different applications (Roche app, Axivity, Opals) and identify the ones with greatest yield in assessing motor and non-motor features.

2. STUDY OUTCOMES

Mobility measures will be collected in both structured (in-clinic) and unstructured (home) settings with two different systems to provide a complementary view of both clinical and real-world assessments. The study outcome measures that pertain to each device are:

1. In-clinic measure will be evaluated via 4 properties of movement that are often affected in PD: amplitude, asymmetry, variability, and smoothness. We will assess these properties in arm swing, axial rotation, step length and gait (hypothesis: worse in prodromal DaT + than DaT-)
2. Home based measures relating to quantity (e.g., activity and nocturnal movements) and quality (e.g., variability of movement). Hypothesis: reduced activity, fewer transitions, more daytime sedentary bouts, more sleep interruptions, less nocturnal movements in prodromal vs controls. Measures will show deterioration in one year in prodromals and PD.

Mobility features collected in the home will be compared with measures collected with the Roche mobile application to assess sensitivity and specificity of both measures.

3. INTRODUCTION, BACKGROUND, AND RATIONALE

3.1 Introduction

The overriding goal of the PPMI study is to develop and validate biomarkers of PD progression with the aim of informing the development of new therapeutics. PPMI places great emphasis on prodromal and at risk (including genetic) cohorts. While significant progress has been made in this area, the assessment of motor symptoms still relies on clinical rating scales. Nonetheless, digital technology is rapidly entering clinical medicine

and clinical research as a technology capable of accurately capturing multiple, disparate mobility functions, while also enabling multiple repeated assessments both in controlled settings and in real-life environments. Because of the centrality of motor dysfunction in PD, the symptoms of PD are exceptionally well suited for assessment using digital technology.

3.2 Background and Rationale

Gait disturbances play a major role in the motor manifestation of Parkinson's disease (PD). Alterations in the gait pattern that are frequently observed in patients with PD include decreased velocity, small shuffling steps, reduced arm swing, shortened strides[1-3]. In recent years, quantitative, objective assessment using digital health technologies has provided more granular insight into gait and mobility impairments in PD far beyond what is possible with observational assessment[4]. Such measures include the loss of consistency in the ability to produce a steady gait rhythm which in turn produces stride-to-stride variability[1-3] and the quantification of magnitude, asymmetry and smoothness of movement[4]. Arm swing in PD diminishes in amplitude and speed and inter-limb asymmetry is observed in the early stages of the disease, reflecting the unilaterality of the early stages[5]. Over time, this asymmetry slowly decreases as the disease progresses. Using accelerometers, it is possible to quantify arm swing and changes in amplitude and asymmetry[5-7].

Another common motor feature of PD is axial rigidity. This is manifested by decreased movement of the trunk and can be seen when patients turn "en bloc". At present, axial rigidity is measured using the MDS-UPDRS-III by assessing movement of the neck. Often this may not be fully reflective or specific to PD[4]. Axial movement, specifically rotation around the vertical axis, is severely diminished in PD, but it is difficult to assess and quantify visually[8]. Here too, wearable technology can be extremely useful as it can identify even subtle changes over time that reflect disease progression or potential effects of medication.

Changes in gait can already be detected in recently diagnosed, de novo patients, even before any visible or symptomatic gait disturbances are reported and have been associated with disease progression[4]. The impetus for using digital technology in the prodromal phase stems from the notion that motor changes likely develop overtime and exist several years before diagnosis [9,10]. While the motor part of the MDS-UPDRS is widely used in studies in PD and for diagnosis purposes, it likely cannot serve as a predictive measure in pre-clinical disease[11, 12]. In a study of elderly *G2019S* carriers, baseline motor UPDRS scores did not predict conversion to PD[13]. Thus using quantitative, sensitive data capture methods may unmask indicators reflective of prominent disease which are present before the appearance of the cardinal motor signs required for diagnosis [11,14]. Several cross sectional studies have used digital technology to explore motor measures in at risk cohorts [10, 15-16]. Several studies explored gait and mobility measures. Balance stability was explored in individuals with high risk for PD (HRPD) defined by presence of hyperechogenicity in the mesencephalon on transcranial sonography and either one motor sign or two risk and prodromal markers of PD [17]. Using measures extracted from an accelerometer worn on the lower back, performance on the functional reach test showed

high specificity (85%) and sensitivity (74%) in differentiating HRPD from controls suggesting sub-threshold balance abnormalities in this cohort [17]. Arora and colleagues[10] explored the ability of 7 active tests on a smartphone to distinguish between Healthy controls, individuals with confirmed RBD and patients with PD. They showed high sensitivity and specificity in distinguishing between the groups (> 85%). Voice, tremor and gait were the most relevant measures differentiating between healthy controls and iRBD. Increased gait variability reduced axial rotation and increased arm swing asymmetry and variability were observed in non-manifesting *G2019S-LRRK2* mutation carriers as compared to non-carriers [5,15].

Another study in this population detected higher intra-individual variability of gait-associated movements in individuals with PD and non-manifesting mutation carriers but not in controls using bilateral ambulatory actigraphy[18,19]. Subtle gait abnormalities were also observed in individuals with mild parkinsonian signs as compared to controls[16]. Interestingly, these differences in gait and stability were observed under challenging conditions (e.g., balance tasks or dual tasking) and were not detected under usual walking conditions. Considering that the onset of PD appears after depletion of 70–80% of striatal dopamine[20], the lack of clinically observed gait and mobility deficits under undisturbed walking conditions (i.e., comfortable walking conditions) suggests satisfactory compensatory mechanisms in the motor system, offsetting the slowly progressing nigrostriatal dopamine depletion, both within and outside the basal ganglia. It has been suggested that dual task walking might be a valuable tool for unmasking the use of these compensatory strategies [15,19,21].

Findings from these cross-sectional studies show the potential of these technologies however they do not reflect predictive value. There are only two observational longitudinal studies that used digital technology to identify motor features in the prodromal phase or predict incidence PD. Del Din and colleagues[22] evaluated the gait of 696 healthy adults recruited in the Tubingen TREND study using a single wearable sensor worn on the lower back. Assessments were performed longitudinally 4 times at 2-year intervals. Sixteen participants were diagnosed with PD on average 4.5 years after the first visit. The analysis indicated that step length and velocity deviate from that of non-PD convertors approximately 4 years prior to diagnosis. In another cohort study[23], the motor performance of 683 ambulatory, community-dwelling older adults was annually assessed using a single sensor worn on the lower back. All participants were without Parkinsonism at baseline. During follow-up of 2.5 years, 139 individuals developed Parkinsonism. Six of 12 mobility scores were individually associated with Parkinsonism, these included gait speed and regularity, sway, transitions and turning. The sensor-derived mobility metrics improved the prediction of incident Parkinsonism in a model which included terms for chronic health conditions and clinical assessment. These findings suggest that sensor-derived mobility metrics can complement conventional clinical assessments and offer the potential for identifying older adults at risk for parkinsonism[23].

In recent years, there is much interest in wearable and digital technology for home-based assessment. This type of evaluation is indeed promising as it can enable long-term continuous monitoring of motor symptoms and provide insight into the person's functioning

in their daily living settings[24]. These data are becoming increasingly important for future clinical studies. Real-world mobility measurers could be quantified in terms of its Macrostructure (e.g., volume, quantity of movement, bouts of movement) and Microstructure (e.g., quality of movement). Both types of data properties can reveal important insight as to habitual behavior and distinct features suggesting impairments. For example, significant differences were found in discrete micro characteristics in RBD with reduced gait velocity, variability and rhythm. These characteristics significantly discriminated RBD from controls, with swing time as the single strongest discriminator. Participants with RBD also had shorter walking bouts throughout the collection period[25]. Another feature that could only be collected using continuous monitoring at home relates to sleep and nocturnal movements[26-27]. Number and type of sleep interruptions could be assessed as well as number, velocity and degree of turning in bed[26-27] reflecting non-motor symptom and patient centric features. These findings highlight the richness of this data. However, one challenge to this type of assessment is that it is collected in an unstructured environment[24]. Thus, many factors can influence data quality, the analyses, and the interpretation. One of the aims of this sub-study is to try and address these gaps[24,28,29].

This sub-study will leverage the existing digital efforts already in place in PPMI with the aim of increasing interpretability and cross validation between devices and the assessment of specificity, utility and importance of the collected measures and their relevance to disease and disease progression.

4. STUDY DESIGN

This sub-study will take place at up to 20 PPMI sites and will aim to enroll about 300 participants. Assessments will be performed during the baseline visit, the first annual visit, and, based on result of the interim analysis participants may be asked to complete a second annual follow up visit. The Prodromal cohort is estimated to include approximately 75% DaT positive and 25% DaT negative participants, which will allow us to evaluate differences in progression. The team will be blinded to the results of DAT scan.

The assessments will utilize two devices, the Opal sensors (APDM, Ltd.) for in-clinic visit and the Axivity sensor for continuous real world 24/7 monitoring. Both systems are lightweight and wireless containing 3 axial accelerometers, gyroscopes and magnetometers allowing to measure movement in 3 orthogonal axes as a function of time. During the in-clinic visit both devices will be worn in conjunction. The Opal sensors will be worn on both wrists and on the lower back (strapped with Velcro belts) and the Axivity will be attached to the lower back (lumbar area) using medical grade tape. This will enable leveraging the in-clinic 'structured' data to better understand real world patterns. After the in-clinic visit, participants will be asked to continue to wear the Axivity device on their lower back continuously for 7 days.

Participants who are also enrolled in the PPMI Digital study protocol will be asked to wear their smartphone on the belt while performing the in-clinic assessments. This will enable the comparison (and validation) of measures obtained by the devices and enable the analysis of unstructured data based on pattern recognition algorithms.

5. STUDY POPULATION

Approximately 300 participants enrolled in the PPMI Clinical will be recruited, including 200 prodromal participants, 50 participants recently diagnosed with PD, and 50 healthy controls.

6. RECRUITMENT METHODS

We will recruit a total of 300 participants, all of whom are already enrolled in the PPMI Clinical study. The clinical site staff will be responsible for recruiting participants into this sub-study. These participants will serve as reference groups for the analysis of gait in the prodromal stage.

7. PARTICIPANT ELIGIBILITY

Participants must meet the following criteria to enroll in PPMI Gait.

7.1 Inclusion Criteria

a. An enrolled PPMI Clinical participant that meets the following criteria based on cohort, as applicable:

- Healthy control participants who continue to have no current clinically significant neurological disorder (in the opinion of the Investigator) may enroll at any in person Clinical visit after Screening;
- Prodromal participants may enroll at Baseline, Year 1, Year 2, or Year 4 Clinical visit;
- PD participants may enroll at Baseline or Year 1 Clinical visit.

b. Willing to provide informed consent.

7.2 Exclusion Criteria

a. Participants with a history of stroke or other neurological pathology that causes a change in gait (e.g., Traumatic Brain Injury (TBI), neuropathic pain).

8. OBTAINING INFORMED CONSENT

The procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time, will be explained to each potential participant as part of the consent process. The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions. Consent will be obtained by the study Investigator or delegated study staff, as applicable. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization. The signed informed consent might be uploaded to a secure portal for remote monitoring.

It is the responsibility of the Investigator (or as delegated to the person obtaining consent) to make sure that the participant understands what she/he is agreeing to and that written informed consent is obtained before the participant is involved in any protocol-defined procedures. Each participant will be provided a copy of the consent form.

9. PARTICIPANT ID ASSIGNMENT

All participants will use their assigned PPMI study ID. The PPMI Participant ID number will be used to identify a participant on all study related documentation.

10. STUDY PROCEDURES

Assessments for this study will be performed as described below and in the PPMI Gait Schedule of Activities.

10.1 Baseline Visit

During the baseline visit in-clinic gait measurement assessments will be performed using two devices:

1. The Axivity AX6 Sensor: a data logger capable of recording raw data from 3-axis movement sensors measuring linear acceleration and angular velocity at high precision. The AX6 weighs 11 grams, is waterproof, and can hold up to two weeks of data without any need for charging, which makes it ideal for continuous data collection in the real world. The sensor will be taped to the participant's back prior to the gait measurement assessment and will be worn by the participant for 7 days, after which they will be asked to remove it and return it by mail to the designated site. Participants who will need to detach the device for some reason (traveling by flight) or if the device falls off, will be instructed on how to re-attach the sensor once at home.

2. Opal Sensors (Opals, APDM Ltd): lightweight, wireless wearable sensors containing 3 axial accelerometers, gyroscopes and magnetometers (Opals, APDM Ltd.). The recording units are small and are attached to the body with a custom-made Velcro-belt. 3 sensors will be used for this study.

During the in-clinic visit, the participant will be fitted with the Axivity Ax6 sensor, and also fitted with 3 lightweight wireless wearable sensors containing 3 axial accelerometers, gyroscopes and magnetometers (Opals, APDM Ltd.).

The Opal sensors will be worn on both wrists and on the lower back during all gait measurements (alongside with the Axivity sensor). The short Gait Assessment protocol will include:

1. Timed Up and Go test (TUG), a short performance-based test, which includes standing up from sitting, walking 3 meters, turning, and returning to the chair to sit down
2. Walking trials under 2 different conditions each of 1 minute
    a. participants will be asked to walk in their usual preferred walking speed for one minute (back and forth in a 12–15-meter corridor)
    b. dual task: walking in their comfortable speed while serially subtracting 3's from a predefined 3-digit number for 1 minute

The total assessment time including set-up is about 15 minutes and requires minimal expertise by the tester.

Participants who are also enrolled in the Digital study protocol will be asked to wear their smartphone on the belt while performing the above tasks. This will enable the comparison (and validation) of measures obtained by the devices and enable the analysis of unstructured data based on pattern recognition algorithms.

10.2 Annual Visits - 12 Month Visit and 24 Month Visit

During the Annual visit in-clinic gait measurements will be re-assessed using the same sensors (Axivity AX6 Sensor and the Opal Sensors).

During the in-clinic visit, the participant will be fitted with the Axivity Ax6 sensor, and fitted with 3 lightweight wireless wearable sensors containing 3 axial accelerometers, gyroscopes and magnetometers (Opals, APDM Ltd.).

The same procedure and assessment protocol that was completed at the Baseline visit (see section above) will be conducted at these annual visits. Based on the outcome of the interim analysis and Investigator decision, participants may be asked to return for a second annual follow up visit.

Participants who are also enrolled in the Digital protocol will be asked to wear their smartphone on the belt while performing the above tasks, as was done at the last visit.

11. CLINICAL ASSESSMENTS

All applicable clinical assessments will be completed under the PPMI Clinical protocol. Information collected from those assessments will be combined with any information collected for this protocol.

12. SAFETY ASSESSMENTS

All applicable safety assessments will be completed under the PPMI Clinical protocol. Information collected from those assessments will be combined with any additional information collected for this protocol.

13. RISKS TO PARTICIPANTS

- Axivity Ax6 Sensors
  Specific risk to the Axivity Ax6 Sensors is minimal and includes skin irritation from wear and adhesive used.
- Opal Sensors
  There are no risks associated with the Opal sensors.
- Gait Assessment
  Specific risk to the assessment protocol is minimal and includes loss of balance during walking activity.

14. POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct anticipated benefits to study participants in this study. However, new information may be generated by the study that will support development of better treatments for Parkinson’s disease.

15. COSTS FOR PARTICIPATION

There are no additional costs for individuals participating in this study.

16. PAYMENT FOR PARTICIPATION

Participants will not be paid for activities completed in this study.

17. PARTICPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or Sponsor's discretion at any time. Any information that has already been collected prior to the study participant's withdrawal will not be removed. Participants who withdraw from this study may continue participation in PPMI Clinical; however, if a participant withdraws from the PPMI Clinical study, the participant must also be withdrawn from this PPMI Gait study.

18. ADVERSE EVENTS

18.1 Adverse Event Reporting Requirements

Participants will be instructed to report adverse events to their PPMI study site. PPMI study site investigators and coordinators will be instructed to record adverse events reported by participants in the study adverse event log. This will include a brief description of the experience, the date of onset, the date of resolution, the severity, seriousness, and whether in the opinion of the investigator the event was related to the study application. Adverse events will be assessed at each PPMI Gait study visit and during the 2-week follow-up telephone call.

18.2 Adverse Event Definitions

Adverse Events (AE)

An AE is any undesirable experience occurring to a participant during the in-clinic Gait assessment and sensor placement visit, or within the two weeks following the in-clinic Gait assessment and sensor placement visit, whether or not considered related to the study procedure.

18.3 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE pertaining to the gait activities is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) and the study procedure should be considered:

- Unrelated - No possible relationship
  The temporal relationship between study procedure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study procedure is implausible.

- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out. While the temporal relationship between study procedure and the adverse event

onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study procedure.

- Possible - Causal relationship is uncertain
  The temporal relationship between study procedure and the adverse event onset/course is reasonable or unknown, and while other potential causes may not exist, a causal relationship to the study procedure does not appear probable.

- Probable - High degree of certainty for causal relationship
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated or are unlikely.

- Definite - Causal relationship is certain
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated.

18.4 Assessing Intensity/Severity of Adverse Events

In addition to assessing the relationship of the adverse event to the study procedure, an assessment is required of the intensity (severity) of the event. The following classifications should be used:

- *Mild:*
  A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.
- *Moderate:*
  A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.
- *Severe:*
  A severe AE is an AE that incapacitates the participant and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

19. STUDY MONITORING AND SITE MANAGEMENT

The PPMI Steering Committee has the responsibility to monitor all procedures for safety, GCP, and regulatory compliance. The study sites will be managed and overseen in an ongoing manner to verify:

a. The rights and well-being of human participants are protected.
b. The reported study data are accurate, complete, and attributable.
c. The conduct of the study follows the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement (s).

20. PRIVACY AND CONFIDENTIALITY

Privacy of participants will be protected in that each person will have the option to voluntarily choose whether to participate in this study. It is the responsibility of the site Investigator to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

The Site Investigator must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). Participants will be identified by participant ID numbers on data forms and other study materials submitted to the Site Management Core (SMC) .

The Site Investigator will permit designated SMC representative to review signed informed consent(s) and that portion of the participant's medical record that is directly related to the study (or provide certified copies of source documentation upon request). This shall include all study relevant documentation including participant medical history to verify eligibility. In addition, electronic document storage will be maintained with the Florence electronic trial master file. Identifiable participant information may be stored within this system, which has been validated and deemed compatible with 21 CFR Part 11 requirements. Only study staff requiring access to related study documentation will have permission to view identifiable information.

21. DATA COLLECTION, SHARING AND STORAGE FOR FUTURE USE

Data collected for this study will be maintained and stored indefinitely at respective study Cores on secure, password protected systems. All study information (data) will be accessed only by those who require access as pertains to the individual's role on the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

Data from the continuous monitoring and in-clinic gait assessments will be saved onto a designated computer at the site and later transferred (via a secured ftp site or drop box) to a central database at Tel-Aviv Medical Center (TLVMC) for processing.

Additional demographic information needed for processing will be extracted from the PPMI database using the unique PPMI ID.

De-identified processed data collected during the conduct of this study will be transferred to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes.

All data collected for this study will be transferred and shared across participating PPMI Cores for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, and study outcomes. All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database.

22. ANALYSIS PLAN

This is an exploratory study and therefore no formal sample size estimates are provided. Sensor-obtained data will be compared between individuals with positive and negative DAT findings and those with PD and healthy controls to evaluate differences relating to disease. Using feature selection algorithms, we will identify the most salient features with the highest discriminative power to distinguish prodromal from controls.

As a next level analysis, we will evaluate the sensitivity of mobility features to identify change over time. Based on preliminary work in this field, we expect that slower gait with greater variability in sway measures and asymmetrical inter-limb motor function observed in the in-clinic assessment will likely be sensitive to progression in the prodromal phase. We further hypothesize that prodromal participants will present with worse macro measures obtained from the real-world assessment and these measures will resemble those of patients with early-stage PD. Machine learning models will be used to identify which measures from all sensors are most sensitive for discrimination and those sensitive for progression.

An interim analysis will be conducted after the first 50 Prodromal participants complete their annual visit to evaluate signal responses, and determine if appropriate modification in sample size, and study design are required (which may include a second annual follow up visit for more longitudinal data collection). Differences between DaT positive and negative in measures obtained from both in clinic and continuous monitoring will be evaluated.

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24. APPENDIX 1: SCHEDULE OF ACTIVITIES

PPMI Gait Mobility
Schedule of Activities

Visit Number		Baseline (BL)	V01	V02*
Assessment	**Timepoint**	**0**	**Month 12 (Y1)**	**Month 24 (Y2)**
Consent Activities				
Documentation of Informed Consent		X		
Informed Consent Tracking Log		X		
General Activities				
Review Gait Inclusion/Exclusion Criteria		X		
Screen Fail Form		X[a]		
Conclusion of Study Participation			X[b]	X[b]
Sensor Placement and Gait Measurement Assessment				
Sensor Placement and Gait Measurement Assessment		X	X	X
Safety and General Health				
#Adverse Events		X	X	X
Adverse Event Telephone Assessment		X	X	X

**Window of +45 days either side of Target Visit Date within PPMI study visits
*Based on interim analysis results if additional longitudinal data collection will be required
X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a= to be completed at Baseline visit if participant does not meet eligibility criteria
b= to be completed at Visit 1 or Visit 2 once all requirements for the study have been met, unless the participant withdraws prior to Visit 1 or Visit 2
#= Adverse events collected only day of and during the 2 week follow-up telephone call per protocol.