Trial No.:	001
Title:	The Parkinson's Progression Markers Initiative (PPMI)
Clinical Phase:	Observational Study
Sponsor:	Michael J. Fox Foundation
Principal Investigator:	Kenneth Marek, MD
Date of Protocol:	April 20, 2010
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PROTOCOL APPROVAL

The Parkinson's Progression Markers Initiative (PPMI)

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INVESTIGATOR AGREEMENT

I have carefully read this protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and International Conference on Harmonization (ICH) guidelines, and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to this project, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the conduct of the study.

I agree to keep records on all subject information (case report forms, informed consent statements and all other information collected during the study) in accordance with the current GCP, ICH, local, national and European regulations.

_____ _____
Site Number Printed Site Name

_____
Printed Site Investigator Name

_____ _____
Site Investigator Signature Date

List of Abbreviations and Definitions

AD	Alzheimer disease
ADL	activities of daily living
ADNI	Alzheimer Disease Neuroimaging Initiative
AMADEUS	American and European Union SPECT Imaging Consortium
β-CIT	2β-carboxymethoxy-3β-(4-iodophenyl) tropane
CFR	Code of Federal Regulations
β-CFT	2β-carboxymethoxy-3β-(4-fluorophenyl) tropane
Beta-HCG	beta-human chorionic gonadotropin
CFR	Code of Federal Regulations
CRF	Case Report Form
CSF	cerebral spinal fluid
CSOC	Clinical Study Oversight Committee
CTCC	Clinical Trials Coordination Center
DAT	dopamine transporter
DaTSCAN	dopamine transporter scan
DNA	Deoxyribonucleic acid
DTI	diffusion tensor imaging
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ELLDOPA	Earlier versus Later Levodopa Therapy in Parkinson Disease
ESS	Epworth Sleepiness Scale
F-Dopa	fluorodopa
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HC	Healthy Control
HIPAA	Health Insurance Portability and Accountability Act
HSPP	Human Subject Protection Program
HVLT-R	Hopkins Verbal Learning Test - Revised
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LONI	Laboratory of Neuro Imaging
MAO-B	Monoamine Oxidase-B
MDS-UPDRS	Movement Disorder Society Unified Parkinson Disease Rating Scale
MJFF	Michael J. Fox Foundation
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
OTC	over-the-counter
PARS	Parkinson Associated Risk Study
PD	Parkinson disease
PET	positron emission tomography
PPMI	Parkinson's Progression Markers Initiative

List of Abbreviations and Definitions (continued)

PW	premature withdrawal
QA	quality assurance
QC	quality control
QUIP-S	Questionnaire for Impulsive-Compulsive Disorders
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
REM	rapid eye movement
SAB	Scientific Advisory Board
SAE	serious adverse event
SC	Steering Committee
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease
SDMT	Symbol Digit Modalities Test
SPECT	single-photon emission computed tomography
ST	symptomatic therapy
STAI	State-Trait Anxiety Inventory
SWEDD	Scans Without Evidence of Dopaminergic Degeneration
UPSIT	University of Pennsylvania Smell Identification Test
VMAT2	Vesicular Monoamine Transporter 2

PPMI
PROTOCOL SYNOPSIS

Protocol Number	Study 001
Protocol Title	The Parkinson's Progression Markers Initiative (PPMI)
Sponsor	Michael J Fox Foundation
Clinical Phase	Observational
Investigators	Multi-center trial
Study Centers	About 20 centers in United States and Europe
Study Period	3-5 Years
Study Objective and Specific Aims	The primary objective of this study is to identify clinical, imaging and biologic markers of PD progression for use in clinical trials of disease-modifying therapies. The specific aims to accomplish the primary objective are: a. Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biomic data that can be used by the PD research community. b. Develop a comprehensive and uniformly acquired clinical and imaging dataset and biological samples that can be used to estimate the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients. c. Investigate existing and identify novel clinical, imaging, and biomic Parkinson disease progression markers to identify quantitative individual measures or combination of measures that demonstrate optimum interval change in PD patients in comparison to healthy controls or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging, or biomic change. d. Conduct preliminary verification studies on promising biological markers using stored collected samples.
Study Design	Observational, multi-center study to assess progression of clinical features, imaging and biologic markers in Parkinson disease patients and healthy controls.
Number of Subjects	600 Subjects Enrolled o 400 Parkinson disease (PD) o 200 Healthy controls (HC)
Main Eligibility Criteria	**Parkinson Disease (PD) Subjects:** Inclusion: • Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia. • A diagnosis of Parkinson disease for 2 years or less at Screening. • Hoehn and Yahr stage I or II. • Confirmation from imaging core that screening DAT scan is consistent with dopamine transporter deficit.

	• Not expected to require PD medication with at least 6 months from Baseline. • Male or female age 30 years or older at time of PD diagnosis. Exclusion: • Currently taking levodopa, dopamine agonists, MAO-B inhibitors, amantadine or other PD medication. • Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline. • Has taken levodopa or dopamine agonists prior to Baseline for more than a total of 60 days. • Received any of the following drugs that might interfere with DAT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening. • Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture. • Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia. • Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10). **Healthy Control (HC) Subjects:** Inclusion: • Male or female age 30 years or older at Screening. • Confirmation from imaging core that screening DAT scan is consistent with no dopamine transporter deficit. Exclusion: • Current or active neurological disorder. • First degree relative with idiopathic PD (parent, sibling, child). • MoCA score $\leq$ 26. • Received any of the following drugs that might interfere with DAT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening. • Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture. • Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia. • Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).

Primary Outcome	The primary study outcome is: The mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients, and where appropriate the comparison of these rates between PD patient subsets and between PD and healthy subjects at study intervals from 3 months to 36 months. Specific examples of outcomes include MDS-UPDRS, DAT striatal uptake, and serum and CSF alpha-synuclein**.** PD patient subsets may be defined by baseline assessments, progression milestones and/or rate of clinical, imaging, or biomic change.
Secondary Outcome	The secondary outcomes are: • Correlations between the rates of change in the mean of clinical, imaging and biomic outcomes in early PD patient subsets and between PD and healthy subjects at study intervals from 3 months to 36 months. • Prevalence of measures of clinical, imaging and biomic outcomes in early PD patients and healthy subjects at study intervals from baseline to 36 months. • To establish the predictive value of early clinical non-motor features, baseline imaging and biomic outcomes for future course of disease.
Safety Assessments	Incidence of adverse events, proportion of withdrawals due to adverse events, vital signs and clinical laboratory assessment changes from baseline.
Statistical Methods	Changes from baseline to the one year, two year and three year evaluations will be calculated and summarized descriptively. We will calculate 95% confidence intervals for the mean rate of change and between subject variability, For this purpose the between subject variability will be estimated by fitting mixed models to all available data. Correlations will be calculated between the different measures, for example between change in total MDS-UPDRS and change in DAT uptake or alpha-synuclein levels.
Data Access	Data will be securely stored at central data coordinating facilities and will have all personally identifiable information removed before it is shared outside the study. All organizations responsible for data storage will observe the highest precautions to ensure data integrity and security. It is the goal of PPMI to enable timely access to the data by the PD research community.

Schedule of Activities – Parkinson Disease (PD) Subjects

Visit Number	SC	BL	V01	V02	V03	V04[b]	V05[b]	V06[b]	V07[b]	V08[b]	V09[b]	V10[b]	V11[b]	V12 / PW	ST	Unsch Visit
Visit Description Months (±30 days)	**-1**	**0**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**---**	**---**
Written Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical and Family History/Demographics	X															
Physical Examination	X															
Neurological Examination/Diagnosis	X					X		X		X		X		X		X[g]
Vital Signs	X	X[c]	X	X	X	X[c]	X	X[c]	X	X[c]	X	X[c]	X	X[c]	X	X
Blood Sample for DNA	X															
Clinical Laboratory Assessments	X					X		X		X		X		X		X[g]
Biomic blood sample		X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	*X[f]	X[f]	
MDS-UPDRS (including Hoehn & Yahr)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Modified Schwab & England ADL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
MDS-UPDRS Part III / Hoehn & Yahr[h]						X		X		X		X		X		
Olfactory Testing (UPSIT)		X														
Hopkins Verbal Learning Test – Revised		X				X		X		X		X		X		
Benton Judgment of Line Orientation		X				X		X		X		X		X		
Semantic Fluency		X				X		X		X		X		X		
Letter Number Sequencing		X				X		X		X		X		X		
Symbol Digit Modalities Test		X				X		X		X		X		X		
Montreal Cognitive Assessment (MoCA)	X					X		X		X		X		X		
Epworth Sleepiness Scale		X		X		X		X		X		X		X	X	
REM Sleep Behavior Questionnaire		X		X		X		X		X		X		X	X	
Geriatric Depression Scale (GDS-15)		X		X		X		X		X		X		X	X	
State-Trait Anxiety Inventory for Adults		X		X		X		X		X		X		X	X	
QUIP		X		X		X		X		X		X		X	X	
SCOPA-AUT		X		X		X		X		X		X		X	X	
MRI (structural)		X														
MRI (DTI)[e]		X				X		X				X		^X		
DAT imaging	X[d]					X		X				X		^X		
Lumbar puncture (CSF collection)		X		X[i]		X		X		X		X		*X	X	
Adverse Events	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	X[a]	
Current Medical Conditions Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Adverse events assessed at the visit and by phone 7 (± 3) days following the visit.
[b] Telephone visit will occur at Months 15, 21, 27, 33, 39, 45, 51 and 57.
[c] Height and weight also collected.
[d] Screening DAT image may be conducted up to 7 days prior to BL visit.
[e] Diffusion tensor MRI scan will be conducted at selected sites.
[f] Biomic urine sample also collected.
[g] Conduct as clinically indicated – see protocol Unscheduled Visits.
[h] Conduct in practically defined off, then 1hr post treatment for subjects on levodopa or dopamine agonist.
[i] LP not repeated if ST visit completed prior to V02.
ST = Symptomatic Therapy visit
PW = Premature Withdrawal (*if not done in last 3 mths; ^ PW visit only, if not done in last 12 mths)

Schedule of Activities – Healthy Control (HC) Subjects

Visit Number	SC	BL	V01	V02	V03	V04[b]	V05[b]	V06[b]	V07[b]	V08[b]	V09[b]	V10[b]	V11[b]	V12	PW	Unsch Visit
Visit Description Months (±30 days)	**-1**	**0**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**---**	**---**
Written Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical and Family History/Demographics	X															
Physical Examination	X															
Neurological Examination/Diagnosis	X					X		X		X		X		X	X	X[g]
Vital Signs	X	X[c]	X	X	X	X[c]	X	X[c]	X	X[c]	X	X[c]	X	X[c]	X[c]	X
Blood Sample for DNA	X															
Clinical Laboratory Assessments	X					X		X		X		X		X	X	X[g]
Biomic blood sample		X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	*X[f]	
MDS-UPDRS (including Hoehn & Yahr)		X				X		X		X		X		X	X	X[g]
Olfactory Testing (UPSIT)		X														
Hopkins Verbal Learning Test – Revised		X				X		X		X		X		X	X	
Benton Judgment of Line Orientation		X				X		X		X		X		X	X	
Semantic Fluency		X				X		X		X		X		X	X	
Letter Number Sequencing		X				X		X		X		X		X	X	
Symbol Digit Modalities Test		X				X		X		X		X		X	X	
Montreal Cognitive Assessment (MoCA)	X					X		X		X		X		X	X	
Epworth Sleepiness Scale		X				X		X		X		X		X	X	
REM Sleep Behavior Questionnaire		X				X		X		X		X		X	X	
Geriatric Depression Scale (GDS-15)		X				X		X		X		X		X	X	
State-Trait Anxiety Inventory for Adults		X				X		X		X		X		X	X	
QUIP		X				X		X		X		X		X	X	
SCOPA-AUT		X				X		X		X		X		X	X	
DAT imaging	X[d]															
MRI (structural)		X														
MRI (DTI)[e]		X				X									^X	
Lumbar puncture (CSF collection)		X		X		X		X		X		X		X	*X	
Adverse Events	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	X[a]	
Current Medical Conditions Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Adverse events will be assessed at the visit and by phone 7 days ± 3 days following the visit.
[b] Telephone visit will occur at Months 15, 21, 27, 33, 39, 45, 51 and 57.
[c] Height and weight also collected.
[d] Screening DAT image may be conducted up to 7 days prior to BL visit.
[e] Diffusion tensor MRI scan will be conducted at selected sites.
[f] Biomic urine sample also collected.
[g] Conduct as clinically indicated – see protocol Unscheduled Visits.
PW = Premature Withdrawal (*if not done in last 3 mths; ^ only if PW done within first 12 mths and MRI DTI not done in last 6 mths)

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1. Introduction

1.1. Background

The defining motor features of Parkinson disease (PD) are characterized by their insidious onset and inexorable but variable progression. Reliable and well-validated biomarkers to monitor PD progression would dramatically improve patient care and accelerate research into both PD etiology and therapeutics. During the past two decades much progress has been made in identifying and assessing PD biomarkers, but as yet no fully validated biomarker for PD is currently available. Nonetheless there is increasing evidence that assessment of blood and CSF, and advanced in vivo brain imaging will provide critical tools for PD drug development and ultimately to assist in the medical management of PD patients.

While it is important to acknowledge that a true surrogate marker for PD does not exist, it is even more critical to note that existing and developing biomarkers for PD are and may be extremely useful for disease monitoring and for drug development. In considering biomarkers for PD three crucial issues must be addressed. First, to identify whether the marker is meaningful or relevant to the disease process. Second, to identify the performance characteristics of the marker in the relevant subject population under study (examination of markers for PD progression in early untreated PD patients). Third, to identify how the biomarker may be generalized to the PD population – the effect of stage of disease, age, gender, medications or environment on the biomarker must be carefully assessed.

Biomarkers offer the potential to complement the clinical assessments used as a primary study outcome in clinical studies of PD. Biomarkers are generally objective measures of disease and therefore are more easily standardized and identically measured repeatedly during the trial. Standardization of biomarker collection and analysis requires clear and detailed procedures to enable objective data to be pooled at multiple study sites. Most often biomarkers are assessed at a core lab with expertise in analytical methodology. Specific procedures for transfer of biological samples and/or imaging data must be in place. The AMADEUS imaging network, a SPECT imaging consortium for PD, and the Alzheimer Disease Neuroimaging Initiative (ADNI) for AD have demonstrated that both biological and imaging samples can be collected and analyzed in studies of disease progression. (1) Given the multiple genetic etiologies for PD already identified, the marked variability in the loss of dopaminergic markers measured by imaging at motor symptom onset, and the clear heterogeneity of clinical symptoms in PD onset and clinical progression, it is clear that many biomarkers with a focus ranging from clinical symptoms to PD pathobiology to molecular genetic mechanisms will be necessary to fully map PD progression. (2) (3-4)

In clinical studies multiple biomarkers may be assessed in the same subjects. This strategy may enable comparison and correlation of biomarkers such as imaging markers, biomic markers and/or markers that target multiple neuronal systems. When multiple biomarkers are evaluated concurrently, the power of the study may be substantially increased. For example in studies of PD relatives tested for olfactory function and then undergoing dopamine transporter imaging, combining the loss of olfaction and dopamine transporter imaging density identifies a sub-group with increased risk of developing PD. (5) Imaging studies comparing dopaminergic ligands and metabolic tracers have provided complementary data enhancing the utility of both tracers.(6) The potential of combining in vivo radiotracer

imaging and/or nigral ultrasound with proteomic, metabolomic and transcriptomic analyses is currently under evaluation in several ongoing studies such as the PARS study and other risk marker assessment studies. (7) (8)

Biomarkers may be also used in clinical studies to better define or enhance the study cohort. While pre-defining the cohort may reduce generalizability of the study outcome, using biomarkers to define eligibility may ensure a more accurate diagnosis of the study subjects and therefore reduce variance in the outcome. In several studies of newly diagnosed PD in vivo dopaminergic imaging has identified about 10-15% with scans in the normal range termed scans without evidence of dopaminergic degeneration (SWEDD). (4, 9-10) Subsequent follow-up has indicated that those study participants with SWEDD are unlikely to have PD.(11) In the ELLDOPA study and REAL PET study data analysis using the imaging biomarker to define the study cohort changed the statistical significance of study outcomes. (9) (10) In other studies biomarkers are used as an a priori definition of the study cohort as in studies of subjects with a LRRK2 mutation. These studies utilize biomarkers to explore a specific etiology or sub-type of PD.

Perhaps the most important rationale for using biomarkers in clinical studies is the potential for longitudinal biomarker outcomes to provide critical data with a shorter duration of follow-up and a reduced sample size compared to that required of typical clinical outcomes. The sample size requirements for a progression study depend on the effect size and the variance of the outcome measure. For example, in vivo dopamine neuroimaging requires a similar sample size and observation interval to that of common clinical outcomes (change in UPDRS or need for dopaminergic therapy). (4) (12) Identifying biomarkers that could provide a more rapid assessment of drug effect would substantially accelerate development of putative disease modifying drugs.

<u>Progression Markers – Current Landscape</u>
Progression markers for PD are both a critical and as yet an unmet need. Validated biomarkers of disease progression are necessary to monitor the natural history of PD and to assess therapies that may modify disease progression.

Although no fully validated progression biomarker has been developed, several biomarkers have been tested in PD progression studies. In some studies biomarkers such as nigral ultrasound hyperechogenicity and microglial activation as a measure of neuroinflammation may be markers of disease risk, but do not appear to change with disease progression(13-14). (13) (14) However, other studies have identified biomarkers such as alpha-synuclein, elevated plasma urate and imaging measures such as DAT density that may predict or track disease. While there is little direct data that alpha-synuclein is a progression marker, the age related changes in alpha-synuclein and association with PD severity suggest that it may be possible to measure change as PD progresses. (15-16) Recent assessment of two large PD clinical trials has demonstrated that elevated urate may be associated with slowed disease progression, possibly predicting PD progression, but not tracking progression. (17)

Imaging tracers targeting presynaptic nigrostriatal function have been the most widely used biomarker to track PD progression. Most of these studies have used either F-Dopa and/or DAT tracers to monitor dopaminergic degeneration. (18) (19) (20-25) Dopamine ligands are useful to assess PD in so far as they reflect the ongoing dopaminergic degeneration in PD. In

the study most directly correlating changes in dopamine pathology and imaging outcomes there is good correlation between dopamine neuron loss and F-Dopa uptake, although conclusions are limited by a very small sample size of only five subjects. (26) Numerous other studies have shown that the dopamine transporter density is reduced in striatum in postmortem brain from PD patients. (27-29) In turn numerous clinical imaging studies have shown reductions in F-Dopa, VMAT2 and DAT ligands uptake in PD patients and aging healthy subjects consistent with the expected pathology of PD and of normal aging. Specifically these imaging studies demonstrate asymmetric, putamen>caudate loss of dopaminergic uptake and the imaging loss correlates with worsening clinical symptoms in cross-sectional evaluation. (22) (30-34) In addition, DAT ligands demonstrate reductions in activity with normal aging. (35-36) (37)

In longitudinal studies of PD progression, F-Dopa, VMAT2, DAT (ß-CIT and CFT), using both PET and SPECT have demonstrated an annualized striatal rate of reduction of about 4% to 13% in PD patients compared with 0% to 2.5% change in healthy controls. (6, 10, 12, 38-43) Evidence from studies of hemi-PD subjects provides further insight into the rate of progression of disease. In early hemi-PD there is a reduction in F-Dopa, VMAT2 and DAT of about 50% in the effected putamen and of 25-35% in the unaffected putamen. Since most patients will progress clinically from unilateral to bilateral in 3-6 years it is therefore likely that the loss of these in vivo imaging markers of dopaminergic degeneration in the previously unaffected putamen will progress at about 4-10% per annum. (23, 33, 44-45)

DAT and F-Dopa imaging have been used to assess the effects of possible disease modifying drugs in several clinical trials. However, several caveats limit the interpretation of these imaging data. (46) (47) There has been concern that the drug under testing or concomitant symptomatic medications might directly regulate the imaging outcome so that it would not be a true measure of disease progression. Given that recent studies demonstrate that the most common symptomatic medications (levodopa and dopamine agonists) do not have a short-term regulatory effect on DAT imaging, there is increased confidence in DAT imaging as a measure of progression. (48) Nonetheless, future imaging studies must include an assessment of the short-term effect of the test drug on the imaging outcome. A second caveat for imaging studies of disease progression has been the inconsistent correlation of changes in imaging outcomes and clinical outcomes in these clinical trials. The lack of clinical–imaging correlation may be explained since these outcomes reflect very different aspects of the disease (imaging – a physiological measure of dopamine presynaptic function, clinical – a functional measure of disability). Therefore imaging and clinical outcomes may best be considered complementary rather than correlative. Many clinical outcomes may be also confounded by symptomatic medications further complicating the correlation of clinical and imaging outcomes once symptomatic treatment has begun.

In summary, the studies of dopaminergic imaging as a tool for disease progression have both provided useful and important data but have also highlighted the difficulties in validating a progression marker and the as yet unmet need for additional tools to more fully and more rapidly assess disease progression.

1.2. Rationale for PPMI

Given the recent advances in molecular genetics, neurobiology, imaging technology and radiochemistry that have provided new tools that may be useful PD biomarkers and the recognition that the lack of PD progression biomarkers has created a roadblock for further studies of disease modifying therapies, there is increasing consensus that a major initiative to develop PD progression biomarkers is both necessary and feasible. The goal of this biomarker initiative is to create a consortium of academic centers, government agencies, PD foundations, and pharmaceutical and biotech companies to collectively design, fund, and implement a comprehensive program to establish markers of PD progression. This strategy has been successfully employed by a consortium of Alzheimer disease researchers to create the ADNI, a group that has now organized infrastructure and has developed a research cohort to examine progression biomarkers in AD.

In PPMI technologies including neuroimaging modalities, biochemical markers in the CSF and plasma, genetic markers and early clinical disease markers will be investigated. A major initial focus of this biomarker consortium will be to standardize biomarker acquisition and assessment and to establish well-defined quantitative biomarker outcomes that are consistent among many research sites and laboratories. Core laboratories for biomarker analysis will be used for uniformity of analyses and quality control.

Genetic approaches to understanding disease are complex and rapidly changing; however, we anticipate two approaches that may be applied to this study population. First, focused genotyping that aims to interrogate genetic variability that is implicated in the disease process, either by previous studies or as a plausible biological candidate. This would include, for example, the more common LRRK2 and GBA mutations, in addition to previously validated risk variants in SNCA and MAPT. Second, more broad application of genome wide analyses, both because such approaches may become a more cost effective alternative to focused genotyping and because at some point in the future these patient samples may be included in larger population based studies on the genetics of PD. Such methods would include genome wide association studies, whole exome sequencing and whole genome sequencing.

This approach to biomarker development is ambitious and requires cooperation among many in academics, industry, government, and the public sector. The lack of success of recent disease modifying therapeutic trials (4) coupled with the huge expense of these studies has highlighted the need for such an approach to identify and validate biomarkers of PD progression for future clinical studies of disease modifying drugs.

2. Study Objectives

2.1. Primary Objectives

The overall objective of this study is to identify clinical, imaging and biologic markers of PD progression for use in clinical trials of disease-modifying therapies.

Specific aims to accomplish this objective are:

a. Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biologic data that can be used by the PD research community.
b. Develop a comprehensive and uniformly acquired clinical and imaging dataset and biological samples that can be used to estimate the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients.
c. Investigate existing and identify novel clinical, imaging, and biomic Parkinson disease progression markers to identify quantitative individual measures or combination of measures that demonstrate optimum interval change in PD patients in comparison to healthy controls or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging, or biomic change.
d. Conduct preliminary verification studies on promising biological markers using stored collected samples.

3. Study Outcomes

3.1. Primary Outcomes

The mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients, and where appropriate the comparison of these rates between PD patient subsets and between PD and healthy subjects at study intervals from 3 months to 36 months. Specific examples of outcomes include MDS-UPDRS, DAT striatal uptake, and serum and CSF alpha-synuclein**.** PD patient subsets may be defined by baseline assessments, progression milestones and/or rate of clinical, imaging, or biomic change.

3.2. Secondary Outcomes

a) Correlations between the rates of change in the mean of clinical, imaging and biomic outcomes in early PD patient subsets and between PD and healthy subjects at study intervals from 3 months to 36 months.
b) Prevalence of measures of clinical, imaging and biomic outcomes in early PD patients and healthy subjects at study intervals from baseline to 36 months.
c) To establish the predictive value of early clinical non-motor features, baseline imaging and biomic outcomes for future course of disease.

4. Study Design and Populations

4.1. Overall Study Design

Observational, multi-center study to assess progression of clinical features, imaging and biologic biomarkers in Parkinson disease (PD) patients compared to healthy controls (HC) and in PD patient subtypes. PPMI will be a five-year natural history study (a minimum of 3-year involvement for each subject) of *de novo* idiopathic PD patients and healthy controls. Approximately 400 PD and 200 healthy controls will be recruited from about 20 clinical sites. All subjects will be comprehensively assessed at baseline and every three to six months thereafter. Subjects will undergo clinical (motor, neuropsychiatric and cognitive) and imaging assessments and will donate blood, urine, and cerebral spinal fluid (CSF). A blood sample for DNA will be collected. Data will be collected by each site under uniformly established protocols and data will be stored and analyzed at designated core facilities.

4.2. Selection of Study Population

4.2.1. Inclusion Criteria **(Parkinson Disease Subjects)**

4.2.1.1. Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.

4.2.1.2. A diagnosis of Parkinson disease for 2 years or less at Screening.

4.2.1.3. Hoehn and Yahr stage I or II.

4.2.1.4. Not expected to require PD medication with at least 6 months from Baseline.

4.2.1.5. Male or female age 30 years or older at time of PD diagnosis.

4.2.1.6. Confirmation from imaging core that screening DAT scan is consistent with dopamine transporter deficit.

4.2.1.7. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.

4.2.1.8. Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

4.2.1.9. Women may not be pregnant, lactating or planning pregnancy during the course of the study. Women of childbearing potential must have a negative urine pregnancy test at the Screening visit. Urine pregnancy screening is not required for women who are surgically sterile or post-menopausal (last menstruation $\geq$ 12 months prior to screening).

4.2.2. Exclusion Criteria **(Parkinson Disease Subjects)**

4.2.2.1. Atypical PD syndromes due to either drugs (e.g., metoclopramide, flunarizine, neuroleptics) or metabolic disorders (e.g., Wilson's disease), encephalitis, or degenerative diseases (e.g., progressive supranuclear palsy).

4.2.2.2. Currently taking levodopa, dopamine agonists, MAO-B inhibitors, amantadine or other PD medication.

4.2.2.3. Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline.

4.2.2.4. Has taken levodopa or dopamine agonists prior to Baseline for more than a total of 60 days.

4.2.2.5. A clinical diagnosis of dementia (49) as determined by the investigator (Appendix 1).

4.2.2.6. Received any of the following drugs that might interfere with DAT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening.

4.2.2.7. Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.

4.2.2.8. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.

4.2.2.9. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

4.2.2.10. Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
4.2.2.11. Previously obtained MRI scan with evidence of clinically significant neurological disorder.
4.2.2.12. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body or any other known contra-indication to MRI.

4.2.3. Inclusion Criteria **(Healthy Control Subjects)**
4.2.3.1. Male or female age 30 years or older at Screening.
4.2.3.2. Confirmation from imaging core that screening DAT scan is consistent with no dopamine transporter deficit.
4.2.3.3. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
4.2.3.4. Willing and able to comply with scheduled visits, required study procedures and laboratory tests.
4.2.3.5. Women may not be pregnant, lactating or planning pregnancy during the course of the study. Women of childbearing potential must have a negative urine pregnancy test at the Screening visit. Urine pregnancy screening is not required for women who are surgically sterile or post-menopausal (last menstruation $\geq$ 12 months prior to screening).

4.2.4. Exclusion Criteria **(Healthy Control Subjects)**
4.2.4.1. Current or active neurological disorder.
4.2.4.2. First degree relative with idiopathic PD (parent, sibling, child).
4.2.4.3. MoCA score $\leq$ 26.
4.2.4.4. Received any of the following drugs that might interfere with DAT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening.
4.2.4.5. Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
4.2.4.6. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
4.2.4.7. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
4.2.4.8. Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
4.2.4.9. Previously obtained MRI scan with evidence of clinically significant neurological disorder.
4.2.4.10. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body or any other known contra-indication to MRI.

4.3. Age and Gender Matching

Enrollments will be monitored centrally by the Steering Committee with the goal of achieving age and gender balance across the study overall. Individual sites should generally attempt to match healthy control subjects as closely as possible in age (target within 5 years) and gender to the PD subjects enrolled at the site. Sites will be instructed if recruitment restrictions need to be implemented as the study progresses in order to maintain a balanced population.

5. Investigational Plan

5.1. Subject Identification Numbers

5.1.1. Subject Identification (ID) Number

A Subject ID Number will be assigned in sequential order by the site from a list provided to the site by the CTCC. This 4-digit number will be used to identify the subject on all study forms and lab specimens.

5.1.2. CTCC Unique ID Number

Subjects will be instructed how to obtain a 9-digit Unique Identification Number at the Screening Visit. This ID system has the ability to track individual subjects across multiple CTCC studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC Unique ID Number that is associated with their electronic "fingerprint."

Once a subject signs the informed consent, the subject and the study coordinator or designated study staff will go to a secure website on a computer at the research clinic and enter the subject's nine data elements. The CTCC Unique ID Number will be printed and provided to the subject. The study coordinator will record this number on the CTCC Unique ID CRF.

If a subject has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, that number should be used for this study. The site can regenerate a subject's CTCC Unique ID Number by returning to the secure website, enter the <u>same</u> nine data elements in the exact same way they were entered the first time to receive the same CTCC Unique ID Number.

5.2. Schedule of Activities

Refer to the protocol synopsis Schedule of Activities that summarizes the assessments to be conducted at each visit.

5.3. Study Procedures at Each Visit

PD and Healthy Control subjects will undergo all procedures as outlined in the sections below for each cohort. Assessments that require completion by the site investigator (unless

otherwise approved and delegated) include: Neurological Exam, MDS-UPDRS Part Ia (coordinator may conduct if requested in advance, as long as the assessment is completed consistently for all subjects/all visits), Part III, Part IV, Hoehn & Yahr Stage, Modified Schwab & England ADL, and Primary Diagnosis.

Specific procedures for the clinical labs, biomic labs, imaging, neuropsychological testing and lumbar puncture are indicated in section 6 and corresponding operation manuals.

5.3.1. Screening Visit (within 30 days from Baseline): All subjects will undergo a screening evaluation within 30 days prior to enrollment. This evaluation will include the following activities and will take about 3 hours to complete:

- An explanation of the purpose, procedures, potential risks and benefits of this study and informed consent will be obtained
- Review of the subject's medical and family history
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature)
- General physical examination
- General neurological examination with review of primary diagnosis
- Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Parts I- III (PD subjects only)
- Hoehn and Yahr (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Montreal Cognitive Assessment (MoCA)
- Clinical laboratory assessments, including urine pregnancy test for women of childbearing potential
- Collect blood sample for DNA
- Dopamine transporter (DAT) imaging scan
- A review of the inclusion/exclusion criteria to confirm that the subject is eligible for participation in the study
- Review of adverse events in follow up to DAT imaging
- Review of adverse events by phone call 7$\pm$3 days following DAT imaging

5.3.2. Baseline Visit (Day 0): Eligible subjects will complete a baseline visit. The activities at the baseline visit will include the following activities and will take about 3-4 hours to complete:

- Repeat review of the inclusion/exclusion criteria
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Olfactory testing using the University of Pennsylvania Smell Identification Test (UPSIT)
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire (RBDSQ)
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- Scales for Outcomes in Parkinson's Disease (SCOPA-AUT)

- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Urine collection for research samples
- Brain magnetic resonance imaging (MRI), (MRI will include DTI sequences in selected sites only)
- Lumbar puncture for collection of cerebral spinal fluid (CSF)
- Review of concomitant medications
- Review of current medical conditions
- Review of adverse events at visit related to lumbar puncture
- Review of adverse events by phone call 7 ±3 days following lumbar puncture

5.3.3. Visit 01 (3 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- Review of concomitant medications

5.3.4. Visit 02 (6 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- Epworth Sleepiness Scale (PD subjects only)
- REM Sleep Behavior Disorder Questionnaire (PD subjects only)
- GDS-15 (PD subjects only)
- State-Trait Anxiety Inventory (PD subjects only)
- Questionnaire for Impulsive-Compulsive Disorders (PD subjects only)
- SCOPA-AUT (PD subjects only)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF (PD subjects only - not repeated if ST visit completed prior to V02)
- Review of current medical conditions
- Review of concomitant medications

- Review of adverse events at visit related to lumbar puncture
- Review of adverse events by phone call 7 ±3 days following lumbar puncture

5.3.5. Visit 03 (9 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- Review of concomitant medications

PD Subjects Starting PD Medication Before Month 12:
If the site becomes aware that a subject will begin PD medication before month 12 (before Visit 04), the site should determine if the subject is willing to return to the site to complete assessments before starting medications. If a subject is not willing to return prior to starting PD medication, conduct the next study visit per the regular visit schedule. If the subject agrees, the appropriate visit schedule below should be followed (see Section 5.3.18 for list of assessments):

- Before Visit 01: Complete ST visit assessments. Visit 01 will be missed and the subject will return to the regular visit schedule for Visit 02.

- At Visit 01 or prior to Visit 02: Complete ST visit assessments. Subject will return to the regular visit schedule for Visit 03.

- At Visit 02 or prior to Visit 03: Complete ST visit assessments. Subject will return to the regular visit schedule for Visit 04.

- At Visit 03: Complete Visit 04 assessments. The subject will return to the regular visit schedule for Visit 05.

- Prior to or at Visit 04: Complete Visit 04 assessments. The subject will return to the regular visit schedule for Visit 05 assessments.

The start of PD medication should be reported to the CTCC and documented on the appropriate source worksheet.

5.3.6. Visit 04 (12 months ±30 days)

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Clinical laboratory assessments, including urine pregnancy test for women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory

- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- DAT imaging
- MRI including DTI sequences (selected sites only)
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to DAT imaging and/or lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

PD Subjects Starting PD Medication After Month 12:
If the site becomes aware of a subject who will begin PD medication following completion of Visit 04, the site should determine if the subject is willing to return for an Unscheduled Visit prior to starting PD medication. If the subject is willing to return, conduct an Unscheduled Visit as described in Section 5.3.16, which should include the MDS-UPDRS and Hoehn and Yahr. The subject will then return to the regular visit schedule. If a subject is not willing to return prior to starting PD medication, conduct the next study visit per the regular visit schedule. The start of PD medication should be reported to the CTCC and documented on the appropriate source worksheet.

5.3.7. Visit 05 (18 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- Review of concomitant medications

5.3.8. Visit 06 (24 months ±30 days)

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Clinical laboratory assessments, including urine pregnancy test for PD subject women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- DAT imaging (PD subjects only)
- MRI DTI (PD subjects at selected sites only)
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to DAT imaging and/or lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

5.3.9. Visit 07 (30 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- A review of concomitant medications

5.3.10. Visit 08 (36 months ±30 days)

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Clinical laboratory assessments, including urine pregnancy test for PD subject women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

5.3.11. Visit 09 (42 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- Review of concomitant medications

5.3.12. Visit 10 (48 months ±30 days)

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Clinical laboratory assessments, including urine pregnancy test for PD subject women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- DAT imaging (PD subjects only)
- MRI DTI (PD subjects at selected sites only)
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to DAT imaging and/or lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

5.3.13. Visit 11 (54 months ±30 days)

- Vital signs (blood pressure, heart rate and temperature)
- MDS-UPDRS Parts I-III (PD subjects only) (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr scale (PD subjects only)
- Modified Schwab & England (PD subjects only)
- Blood draw for research samples
- Review of current medical conditions
- Review of concomitant medications

5.3.14. Visit 12 (60 months ±30 days)

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Clinical laboratory assessments, including urine pregnancy test for PD women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

5.3.15. Telephone Contacts

Telephone call visits will be conducted 7 ±3 days following a visit when lumbar puncture and/or DAT imaging has occurred to assess for adverse events. In addition, after Month 12, telephone call visits will take place 3 months following each in-person visit to discuss any questions, verify whether or not PD medications have been started and to confirm the date of the next scheduled visit.

5.3.16. Unscheduled Visits (Visit U01, U02, etc.), if required

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or to follow up on adverse events or as deemed necessary by the Site Investigator or Coordinator. The following activities will be completed at an Unscheduled Visit:

- Vital signs
- *General neurological examination
- *Collect blood for clinical laboratory assessments
- #MDS-UPDRS
- #Hoehn & Yahr
- #Modified Schwab & England (PD subjects only)
- Review of current medical conditions
- Review of concomitant medications

*Conducted only if clinically indicated
Completed for PD subjects being seen after month 12 for an unscheduled visit prior to starting PD medication, or as clinically indicated.

5.3.17. Premature Withdrawal of Participation
If the subject agrees, the following procedures should be performed when a subject withdraws early from the study:

- General neurological examination with review of primary diagnosis
- Height and weight
- Vital signs (blood pressure, heart rate and temperature)
- Review of subject's primary diagnosis
- Clinical laboratory assessments, including urine pregnancy test for PD women of childbearing potential
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- Montreal Cognitive Assessment (MoCA)
- Letter Number Sequencing
- Hopkins Verbal Learning Test – Revised
- Symbol Digit Modalities Test
- Benton Judgment of Line Orientation
- Animal Fluency
- MDS-UPDRS Parts I-III (Part IV will also be conducted for subjects who have started PD medication)
- Hoehn and Yahr
- Modified Schwab & England (PD subjects only)
- MDS-UPDRS Part III and Hoehn & Yahr will be conducted one hour following dosing in clinic for subjects who have started levodopa or dopamine agonist
- Blood draw for research samples – only if not done in the last 3 months
- Urine collection for research samples – only if not done in the last 3 months
- Lumbar puncture for collection of CSF – only if not done in the last 3 months
- DAT imaging – only if not done in the last 12 months (PD subjects only)

- MRI DTI (**PD** subjects at selected sites only) – only if not done in the last 12 months
- MRI DTI (**HC** subjects at selected sites only and PW visit conducted within first 12 months) – only if not done in the last 6 months
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events in follow up to DAT imaging and/or lumbar puncture
- Review of adverse events by phone call 7 ±3 days following visit

5.3.18. Symptomatic Therapy Visit (PD subjects only)

- Vital signs (blood pressure, heart rate and temperature)
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- GDS-15
- State-Trait Anxiety Inventory
- Questionnaire for Impulsive-Compulsive Disorders
- SCOPA-AUT
- MDS-UPDRS Parts I-III
- Hoehn and Yahr
- Modified Schwab and England
- Blood draw for research samples
- Urine collection for research samples
- Lumbar puncture for collection of CSF
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events at visit related to lumbar puncture
- Review of adverse events by phone call 7 ±3 days following lumbar puncture

6. Study Assessments

6.1. Clinical Assessments

6.1.1. MDS-UPDRS

The MDS-UPDRS is a multimodal scale assessing both impairment and disability and is separated into 4 subscales (Parts I-IV). The MDS-UPDRS includes components assessed by the study investigator as well as sections completed by the subject. Every effort should be made to have the same investigator perform the ratings for an individual subject throughout the course of the study.

- Part I: This assesses non-motor experiences of daily living and is comprised of two components:
  - ❖ Part IA contains 6 questions that are assessed by the Investigator and focuses on complex behaviors.
  - ❖ Part IB contains 7 questions that are part of the Patient Questionnaire completed by the subject.

- Part II: This assesses motor experiences of daily living. There are an additional 13 questions that are also part of the Patient Questionnaire completed by the subject.
- Part III: This assesses the motor signs of PD and is administered by the Investigator.
- Part IV: This assesses motor complications, dyskinesias and motor fluctuations using historical and objective information. The Investigator will complete this assessment once a PD subject has started PD medication.

Subjects who have started PD medication (levodopa or dopamine agonist) will have an annual assessment of the motor exam (Part III) and Hoehn and Yahr in a practically defined off state and then these assessments will be repeated one hour after receiving medication in clinic. These subjects will need to be reminded not to take PD medication on the day of each annual study visit. If possible, subjects on PD medication who withdraw prematurely from the study should also have the Part III assessment one hour after receiving medication during the Premature Withdrawal Visit.

6.1.2. **Hoehn and Yahr Stage**

The Hoehn and Yahr is a commonly used system for describing how the symptoms of Parkinson disease progress. The scale allocates stages from 0 to 5 to indicate the relative level of disability. This scale is included within the MDS-UPDRS and will be completed for all subjects.

- Stage zero: No symptoms.
- Stage one: Symptoms on one side of the body only.
- Stage two: Symptoms on both sides of the body. No impairment of balance.
- Stage three: Balance impairment. Mild to moderate disease. Physically independent.
- Stage four: Severe disability, but still able to walk or stand unassisted.
- Stage five: Wheelchair-bound or bedridden unless assisted.

6.1.3. **Modified Schwab & England Activities of Daily Living**

The Modified Schwab & England Activities of Daily Living (ADL) scale reflects the speed, ease, and independence with which an individual performs daily activities, or personal chores, such as eating, toileting, and dressing. This scale uses a rating scale from 0% to 100%, with 100% representing complete independence in performing daily activities and 0% representing a vegetative, bedridden state.

6.1.4. **The University of Pennsylvania Smell Test**

The University of Pennsylvania Smell Identification TEST (UPSIT) is a 40-item, multiple choice, scratch and sniff test used to evaluate odor identification. It is a forced-choice test in which subjects must identify an odor among four response alternatives. There are four booklets containing ten odorants each. The instructions will be explained to the subjects by the coordinator at the clinical site. Subjects may complete the UPSIT independently. It will be reviewed for completion prior to the end of the visit. The UPSIT will be scored by the coordinator reflecting the number of correct responses out of 40 items.

6.1.5. **Neuropsychological and Cognitive Assessments**

The **Montreal Cognitive Assessment (MoCA)**: In early Parkinson disease, when cognitive deficits occur, they are subtle and mild and the patients usually perform in the normal range on the widely used Mini Mental State Examination. The Montreal Cognitive Assessment (MoCA) is a rapid screening instrument like the MMSE but was developed to be more sensitive to patients presenting with mild cognitive complaints. It assesses short term and working memory, visuospatial abilities, executive function, attention, concentration, language and orientation. The total score ranges from 0 to 30.

The **Epworth Sleepiness Scale (ESS)**, (50) used extensively in PD related studies, is a self-administered questionnaire collecting information on the propensity to fall asleep in eight different situations encountered commonly in daily life. Each situation is rated from 0 (no chance of dozing) to 3 (high chance of dozing), and the total score ranges from 0 to 24. Total scores of zero to 10 are normal, scores from 10 to 12 are borderline, and scores from 12 to 24 are abnormal.

The **Geriatric Depression Scale (GDS-15)** is a self-report scale shown to be a useful measure of depressive symptoms in patients with Parkinson disease. (51) It is particularly easy for patients to use given its "yes/no" format. The GDS-15 is a validated shortened version of the original scale.

The WMS-III **Letter-Number Sequencing Test** (52) is a measure of verbal working memory. In this test, subjects are read a combination of random letters and numbers and are asked to repeat the string back to the experimenter organized so that numbers are first in ascending order and letters next in alphabetical order. The length of the string is increased at each trial. The total score is the number of trials correctly repeated.

The **Hopkins Verbal Learning Test-Revised (HVLT-R)** is a test of verbal, short-term memory/new learning requiring rapid encoding of information. (53) Subjects must learn a list of 12 words which are grouped into three semantically-related categories each consisting of four words (e.g., dwellings, precious gems, animals). Subjects are given three repeated learning trials followed by a 20-25 minute delayed recall and recognition phase.

The **Benton Judgment of Line Orientation Test** is a measure of spatial perception and orientation. It is recognized that disturbances of these functions result from brain disease. The booklet consists of 5 practice items in addition to the test stimuli, consisting of line segments appearing at various angled intervals in the top half of the booklet and multiple-choice response cards in the lower half. The test will be conducted such that 15 of the 30 items are completed at each administration.

The **Symbol Digit Modalities Test (SDMT)** screens cognitive impairment by using a simple substitution task that adults with normal functioning can easily perform. Using a reference key, the examinee has 90 seconds to match specific numbers with geometric figures. Responses may be oral or written, allowing the test to be used with a wide variety of people, including those with motor disabilities or speech disorders. The SDMT is

relatively culture free since it uses only geometric figures and numbers. Norms for adults are separated by age group and educational level.

The **State-Trait Anxiety Inventory (STAI-Y)** is a self rated assessment to measure emotional state anxiety in adults. (54) The 40-item state-trait anxiety questions will be administered. Responses resulting in a higher score indicate greater anxiety.

The **REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)** is a 10-item self rated questionnaire to assess sleep-wake disturbances. Patients with clinical characterizations of sleep behavior disorder may represent early manifestations of progressive neurodegenerative disorders, including Parkinson disease (55), thus making this an important tool for longitudinal prospective studies.

The abbreviated version of the **Questionnaire for Impulsive-Compulsive Disorders (QUIP-S)** is a 13-item self administered assessment. This questionnaire will measure impulse control disorders and other compulsive behaviors in subjects with Parkinson disease (56) as compared to a healthy control population.

The **Scales for Outcomes in Parkinson's Disease** assessment of autonomic dysfunction **(SCOPA-AUT)**] (57) is a 26-item self administered test developed to evaluate autonomic symptoms, such as gastrointestinal and urinary problems, in subjects with PD. The assessment will measure whether subject's experience an increase in autonomic dysfunction as the disease severity progresses.

6.2. Safety Assessments

6.2.1. Medical History and Physical/Neurological Examination

Medical and family history, as well as a complete physical and neurological exam will be captured on all subjects at Screening. A neurological exam will also be conducted annually and at the last completed visit. Healthy control subjects will have a complete neurological examination conducted at screening and every 12 months to ensure no changes have occurred since entry into the study.

6.2.2. Vital Signs/Weight/Height

Pulse rate (supine and standing), blood pressure (supine and standing), and oral temperature will be determined at every visit. The supine blood pressure and pulse rate will be determined after 1-3 minutes of quiet rest and the standing pressure and rate will be determined after 1-3 minutes in the standing position. Weight and height will be collected at the Baseline visit and annually.

6.2.3. Clinical Laboratory Tests

Routine clinical laboratory tests will be performed at screening and every 12 months as indicated in the table below. A central laboratory will be implemented in order to guarantee identical analysis methods, consistent normal ranges and thus common interpretation of laboratory changes. If not stated otherwise, venous whole blood will be collected in blood collection tubes (vacutainers). All samples for laboratory analysis must be collected, prepared, labelled, and shipped according to the laboratory's

requirement as detailed in the lab manual. The total amount of blood needed for the clinical lab tests will be no more than 10 ml.

METABOLIC PANEL	COMPLETE BLOOD COUNT
Sodium (Na) Potassium (K) Chloride (Cl) Carbon Dioxide (CO2) Blood Urea Nitrogen (BUN) Glucose Calcium (Ca) Creatinine (Crn) Bilirubin Total Albumin Total Protein Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase (ALKP) Uric Acid Prothrombin time (PT) – SC only Partial Thromboplastin Time (PTT) – SC only	White Blood Cell Count (WBC) Red Blood Cell Count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Platelet Count (PLT)

No more than 40 ml will be drawn at any visit, including both clinical and research blood samples.

6.3. Other Assessments

6.3.1. Dopamine Transporter Scan (DaTSCAN™) and SPECT Imaging

DaTSCAN™ is an investigational agent in the United States; however, it is approved for use in Europe. All subjects will undergo DaTSCAN™ at Screening. Parkinson subjects will also undergo follow up DAT scans as indicated in the visit schedule. The imaging procedures will be performed at the individual sites. At each imaging visit, subjects will be injected with up to 5 mCi of dopamine transporter. Within a 4 hour +/- 15 minute window following the injection, subjects will undergo SPECT imaging on the camera at the local site. The data and quality assurance procedures to be employed in this study are described in the operations manual.

Women of childbearing potential must have a urine pregnancy test on the same day a DAT scan is obtained. Results of the urine pregnancy test must be confirmed as negative prior to proceeding with the DAT scan. Subjects will be monitored by study personnel for adverse events on the day that DAT scan is obtained. Subjects will also be contacted by phone 7 $\pm$3 days following the injection/scan to assess adverse events. These events will be reported by the site investigator as required to the site's Institutional Review Boards and to his/her Radiation Safety Committee.

6.3.2. Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI)

All subjects will undergo a structural MRI brain scan at the Baseline visit. At selected sites with DTI 3T scanner capabilities, PD and healthy control subjects will undergo MRI (DTI) at Baseline and follow up vists as indicated in the visit schedule. MRI is being conducted to assess the structure of the brain. The diffusion tensor imaging will be

conducted to further assess the pathways that connect parts of the brain and the function of cells in those pathways.

6.3.3. **Biologic Sampling (Blood and Urine)**

Serum (about 10 ml) and plasma (about 10 ml) will be collected to conduct proteomic, metabolomic and other analyses. Blood will be obtained (about 8 ml) for the extraction of DNA to conduct sequencing and genomic analyses. Blood will also be obtained (about 5 ml) for the extraction of RNA to conduct biochemical analyses. Urine (about 10 ml) will be collected to conduct analyte analyses. All research samples will be sent to Coriell Medical Research Institute in Camden, New Jersey to be stored indefinitely for research purposes. Samples will be distributed to specialized research labs and will also be made available to researchers to conduct analyses related to PD and other disorders.

6.3.4. **Lumbar Puncture**

The lumbar puncture (LP) is performed by the site investigator or another qualified clinician appointed by the investigator. A lumbar puncture for the collection of 15-20 ml of CSF will be conducted for all subjects per the visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. The first 2 ml of CSF will be processed at the site's local lab facility to conduct standard analyses on cell count, protein and glucose levels. Subjects will be closely monitored during the procedure and following the procedure. Subjects will be contacted by phone 7 $\pm$3 days following an LP to assess for any adverse events. The CSF samples will be sent to Coriell Medical Research Institute in Camden, New Jersey to be stored indefinitely for research purposes. The CSF samples will be distributed to specialized research labs and will also be made available to researchers to conduct analyses related to PD and other disorders.

7. Concomitant Medications

7.1.1. Initiation of PD Medications

It is anticipated that the majority of PD subjects will be able to remain off PD medications for at least 6 months after Baseline. However, PD medications may be initiated at any time after enrollment at the discretion of the patient or treating physician. If PD medications are initiated before month 12, subjects will be asked to return for an ST visit or early Visit 04 (see Section 5.3.5). If PD medications are initiated following the Month 12 Visit, willing subjects will be seen at an unscheduled visit prior to initiating PD medications (see Section 5.3.6). The medication used is at the discretion of the treating physician. The investigator will document any new medications or changes in medication at each study visit on the Concomitant Medication Log.

7.1.2. Use of Concomitant Medications

All concomitant medications, including over-the-counter (OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted during the study period. All concomitant medications reported at the time of the screening visit and for the duration of the subject's participation should be recorded on the Concomitant Medication Log.

7.1.3. Participation in Clinical Trials

All PD and HC subjects may participate in clinical trials of experimental interventions after 12 months of participation in PPMI. The investigator will document the study drug dosage, if applicable, and, if unknown, will report on the identity of the study drug and dosage after it is unmasked.

8. Subject Withdrawals

Subjects will be advised in the written informed consent forms 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. A subject should be withdrawn from the study if the investigator considers it to be medically necessary, or if the subject withdraws consent. All reasons for subject withdrawals from the study will be recorded in the source documentation and appropriate eCRF.

9. Safety/Adverse Events

Site investigators and coordinators will be instructed to assess for adverse events at in-person study visits when an LP or DAT imaging activity is conducted, as well as by telephone approximately 7 days following such a visit.

9.1. Adverse Experience (AE) Definition

An adverse event is any untoward medical occurrence that is reported from the time of a DAT image/SPECT scan or lumbar puncture through the subsequent telephone visit (7 $\pm$3 days) following the procedure.

9.2. Serious Adverse Experience (SAE) Definition

A serious adverse experience is defined as any adverse experience that results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Hospitalization or prolongation of a hospitalization
- A persistent or significant disability/incapacity

A life-threatening adverse event is any adverse experience that places the subject at immediate risk of death from the event as it occurred.

Hospitalization is defined as any inpatient admission. For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit).

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event
- Social admission (e.g., subject has no place to sleep)
- Protocol-specific admission during a clinical study (e.g., for a procedure required by another study protocol)
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)

Inpatient admission does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits
- Outpatient/same-day/ambulatory procedures
- Observation/short-stay units
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Custodial care facilities
- Clinical research/Phase I units (another study protocol)

9.3. Recording of Adverse Experiences

All adverse experiences, whether observed by the investigator, elicited from or volunteered by the subject should be recorded on the Adverse Event Log eCRF. This will include a brief description of the experience, the date of onset, the date of resolution, the severity, and seriousness and whether the event was related to participation in the research study.

Some examples of adverse experiences are:

- Any reaction from the injection of imaging tracer or lumbar puncture.
- Injury or accidents during the 7-day period following imaging procedures or lumbar puncture.
- Abnormal lab results or changes from baseline which the Investigator considers clinically significant.
- Development of an intercurrent illness during the 7-day reporting period.
- Hospitalization for serious (non-elective) medical issues.

Any adverse event ongoing at the final 7 day reporting telephone visit should be followed until resolution or stabilization.

9.4. Intensity

The intensity (or severity) of each adverse experience should be assessed as follows:

- Mild – usually transient in nature and generally not interfering with normal activities
- Moderate – sufficiently discomforting to interfere with normal activities
- Severe – prevents normal activities.

9.5. Relationship

The assessment of the relationship of an adverse event to the subject's participation in this study is a decision based on all available information at the time the assessment is being made. Factors to be considered in assessing the relationship of the adverse event to participation in the research study include subject's medical history and concomitant medications.

9.6. Responsibilities for Reporting Serious Adverse Experiences

- The Investigator should notify the CTCC Project Manager (PM) by telephone within 24 hours of his/her becoming aware of the occurrence of a serious adverse experience. The PM will in turn notify the CTCC Clinical Monitor. The site Coordinator will fill out the MedWatch form provided by the CTCC, and email it to the CTCC Project Manager.

- Upon completion of the telephone report, the CTCC Project Manager will enter the appropriate subject information into the Incident Module.

- The following information should be supplied if available at the time of the telephone call: study number, site number, subject number, subject age and gender, date of onset of event, event description, whether event required treatment, death and autopsy report, an identification of which criteria for a serious experience have been met, the Investigator's current opinion of the relationship between the event and study participation.

- The Investigator will comply with his/her local Institutional Review Board (IRB) and Radiation Safety Committee regulations regarding the reporting of adverse experiences.

10. Reportable Events

The following incidents will be considered reportable events and will be reported to the CTCC within 24 hours of the event, or the Site Investigator's knowledge of the event.

- Initiation of any PD medication
- Change of diagnosis (PD and HC subjects)
- Participation in any other clinical trial or study
- Premature Withdrawal (e.g. withdrawal of consent)
- Serious Adverse Event
- Pregnancy
- Death

11. Referrals

If a clinical assessment, clinical lab or MRI result reveals a clinically significant abnormality (e.g., indication of suicidality, depression, or renal impairment on metabolic profile), the subject should be informed of this result and instructed to follow up with his or her primary care physician. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the Investigator should provide the subject with the appropriate referral as necessary.

12. Potential Risks

12.1. Blood Sampling

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn. Subjects will not receive results from any testing of their blood samples.

12.2. Lumbar Puncture

The most common risks of a lumbar puncture are pain at the site and a temporary headache usually due to a small amount of CSF leakage around the needle insertion site. Lying down for a few hours after the test can make a headache less likely to occur. There is a slight risk of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria. A temporary numbness to the legs or lower back pain may be experienced. There is a small risk of bleeding in the spinal canal. Subjects will have blood drawn at Screening to test for coagulopathies.

12.3. MRI / DTI

Subjects should notify the study doctor if they suffer from claustrophobia because they may become anxious while in the magnetic resonance scanner. There may be loud noises such as knocking or hammering that occur while the MRI is being conducted. Subjects should also inform the study doctor if they have a pacemaker or metal implants (screws, plates or clips) because this would preclude MR evaluation.

12.4. Imaging

Specific potential risks for DaTSCAN™ and SPECT imaging are as follows:

1) radiation exposure from DaTSCAN™, the 57Co transmission source, and from 99mTc containing markers,
2) potential pharmacological effects of DaTSCAN™,
3) having blood drawn and having an intravenous injection.

<u>Pharmacologic effects:</u> DaTSCAN™ is administered at radiotracer doses and is not expected to have any pharmacological or toxicological effects. DaTSCAN™ binds to the dopamine and serotonin transporter. At pharmacologic doses DaTSCAN™ might be expected to have stimulant-like effects and affect cardiovascular responses. However, in the proposed study the estimated mass dose of DaTSCAN™ is very low - <30/pmol kg. More than 180,000 doses of the drug have been administered to human subjects.

<u>Iodine:</u> Prior to each ^{123}I injection subjects will be pretreated with Lugol's solution, 10 drops of a saturated solution of potassium iodide) to reduce thyroid uptake of ^{123}I. Subjects may experience a metallic or bitter taste in their mouths from the iodine. Subjects with allergies to iodine might get itching, a rash, bloating, severe blood pressure changes (shock), and death if given iodine. Subjects who are allergic to iodine will be administered potassium perchlorate rather than Lugol's.

In addition to the known risks listed above, the imaging procedures in this study may cause unknown risks to the participant, or a developing embryo or fetus or possible risks to the future offspring of male participants.

13. Statistical Methods

13.1. Statistical Design

PPMI is an observational, multi-center study to assess progression of clinical features and imaging and biomic biomarkers in Parkinson disease patients and healthy controls. Subjects will be evaluated longitudinally for at least 36 months.

13.2. Primary Objective

To estimate the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients, and where appropriate to compare these rates between PD patients subsets and between PD and healthy subjects at study intervals from 3 months to 36 months.

13.3. Secondary Objectives

13.3.1. Correlations between the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients, and where appropriate to compare these rates between PD patients subsets and between PD and healthy subjects at study intervals from 3 months to 36 months..

13.3.2. To determine the prevalence of measures of clinical, imaging and biomic outcomes in early PD patients and healthy subjects at study intervals from baseline to 36 months

13.3.3. To establish the predictive value of baseline clinical imaging and biomic outcomes for the future course of disease.

13.4. Planned Analyses

Information summarizing planned analyses is described below. Further details regarding the analyses and plans for additional analyses will be contained in the PPMI Data Analysis Plan.

13.4.1. **Comparison of baseline characteristics among healthy subjects and PD subjects.** The first set of analyses will involve a comparison of baseline characteristics among all healthy subjects and PD subjects. Continuous variables will be examined using a t-test and dichotomous variables will be examined using a chi-square test. Appropriate assumptions will be assessed for each comparison and any necessary adjustments (i.e., transformations) will be made prior to analysis. All analyses will be conducted at the 0.05 level.

13.4.2. **Comparison of short-term change in progression endpoints.** The second set of analyses will examine the short-term change during the first six months for each progression endpoint. For continuous progression endpoints, the change over time will be modeled using a mixed model approach. For dichotomous progression endpoints, a logistic regression model will be fit. For each 'full' model of interest, an initial model will consist of all baseline characteristics, an indicator variable for whether the subject is a PD patient or healthy control, and all possible two-way interactions. We will utilize backwards selection to build a model for each progression endpoint.

13.4.3. **Examination of whether short-term change in progression endpoints is predictive of change in long-term endpoints.** The third set of analyses will examine whether short-term changes in the progression endpoints are predictive of changes in long-term endpoints in the MDS-UPDRS score. This analysis will examine a subset of the progression endpoints. Only progression endpoints that show differences between the healthy subjects and PD patients in analysis group 2 will be considered (since a marker that doesn't distinguish PD patients from healthy subjects would not be thought to be a biomarker for long-term outcome in PD patients). All progression endpoints that meet these criteria will be modeled in PD patients using a process similar to that described above. The primary focus will be on the long-term change in the UPDRS score. However, additional long-term endpoints may be considered as well. Because this modeling process involves longer term endpoints, which would be much harder to replicate, a ten-fold cross validation procedure will be used to test the predictive validity of each model. If successful, the final model will provide a subset of one or more short-term progression endpoints that are predictive of the change in one or more of the long-term endpoints. This would suggest that these short-term progression endpoints are valid biomarkers for future studies of interventions in PD patient populations.

13.4.4. **Examination of PD Subsets.** Each of the first three sets of analyses will be repeated comparing subsets of PD subjects, rather than PD subjects vs. healthy subjects. If successful, the final model from these subset comparisons will determine whether some of the short-term progression endpoints are more predictive of long-term change in the MDS-UPDRS score for some subsets of PD subjects and less predictive for other subsets of PD subjects.

13.5. Determination of Sample Size

As summarized above, much of the proposed analysis plan for the PPMI study is focused on a set of exploratory analyses with the goal of identifying short-term progression markers that can be used as biomarkers for future studies in PD patient population. Because of the exploratory nature of these analyses, it is very difficult to provide a formal sample size justification for the entire model building process. Furthermore, the PPMI study has a broad range of goals that reach beyond any single, pre-planned analysis. However, we can examine the ability of the proposed sample size to detect meaningful effects of interest for the preliminary comparisons of baseline characteristics and univariate assessments of progression markers across the groups of interest.

The table below provides generic information about the detectable effect sizes for three types of statistical analysis that may be performed on the PPMI data. For each analysis the two-sided alpha level is set to 0.05 and the beta level to 0.80. The first column gives the total sample size assumed to be available for the analysis, in the first two rows either 400 (total PD sample) or 300 (PD sample after allowance for 25% withdrawals). The third and fourth rows of the table correspond to the total sample size of 600 (400 PD, 200 HC) when, respectively 75% and 100% of the subjects are available for analysis. The second column gives the detectable correlation coefficient between two continuous measures (e.g., change in striatal

β-CIT uptake vs. change in total MDS-UPDRS). The third column gives the detectable difference in prevalence rates of some characteristic (e.g. presence of dopaminergic side effects) between two "halves" of the sample (e.g. the younger patients vs. the older patients, with age dichotomized at the median for the entire group). For the first two rows the third column gives the detectable "effect size", expressed as ratio of difference in means to standard deviation, for comparing two "halves" of the sample (e.g. younger vs. older patients as above) in relation to a continuous measure (e.g. change in total MDS-UPDRS). For the third and fourth row the comparisons are between PD patients and HC. The table suggests that the PPMI trial is adequately powered to detect effects that would generally be of clinical interest. While possible that smaller effects than those listed in the table might also be of clinical interest, it was determined that the added power for these comparisons did not offset any additional costs and logistical issues that would accompany a larger study in this population. Rather, the proposed study should prove to be effective for screening a large number of variables and identifying those that show the most promise for further exploration in follow-up studies.

Total sample size	Detectable Correlation	Detectable Difference in Prevalence	Detectable Difference in Means (Standardized)
300	**0.16**	**17%**	**0.33**
400	**0.14**	**14%**	**0.28**
450	**0.14**	**15%**	**0.28**
600	**0.11**	**13%**	**0.24**

14. Regulatory / Ethics

14.1. Compliance Statement

This study will be conducted in accordance with the Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines and any applicable national and local regulations.

All procedures not described in this protocol will be performed according to the study Operation Manuals unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the central laboratory manual unless otherwise stated.

14.2. Informed Consent

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read by and/or explained to each subject. Each subject will sign such an informed consent form. The subject must be assured of the freedom to withdraw from participation in the study at any time.

It is the Investigator's responsibility to make sure that the subject understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is

also the Investigator's responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form.

The CTCC must be given an opportunity to review the consent form prior to site IRB submission and before it is used in the study.

14.3. Institutional Review Board/Independent Ethics Committee
The CTCC will supply all necessary information to the Investigator for submission of the protocol and consent form to the IRB/IEC for review and approval. The Investigator agrees to provide the IRB/IEC all appropriate material. The trial study will not begin until the Investigator has obtained appropriate IRB/IEC approval. A copy of the approval letter and approved consent form must be submitted to the CTCC.

The Investigator will request from the IRB/IEC a composition of the IRB members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/IEC and the CTCC in accordance with institutional and government regulations. The CTCC will notify the site when the IRB/IEC may be notified of study completion. It is the Investigator's responsibility to notify the IRB when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site IRB/IEC's acknowledgement of study completion must be submitted to the CTCC.

14.4. Protocol Amendments
Changes to the protocol should only be made via an approved protocol amendment. Protocol amendments must be approved by the Sponsor, the study's Steering Committee and each respective site's IRB/IEC prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of subjects.

14.5. Subject Confidentiality
The site Investigator must assure that the confidentiality of subjects, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA). Subjects will be identified by code numbers on case report forms and other study materials submitted to the CTCC, the central laboratory, and Coriell.

After a subject signs an informed consent, it is required that the site Investigator permit the study monitor or regulatory agency personnel to review the signed informed consent(s) and that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (when available).

15. Documentation

15.1. Study File and Site Documents

The Investigator should have the following study documents accessible to the Monitor during the study.

- *Curriculum vitae* for investigator and coordinator
- The signed IRB/IEC form/letter stating IRB/IEC approval of protocol, consent forms, and advertisement notices, documentation of the IRB/IEC composition, and all IRB/IEC correspondence including notification/approval of protocol amendments, notification of serious adverse events to the IRB/IEC, and IRB/IEC notification of study termination
- IRB/IEC approved consent form (sample) and advertisements as applicable
- Signed protocol (and amendments, where applicable)
- Signed subject consent forms
- Copies of the completed CRF worksheets
- Authorization log (Log of Investigators, Study Staff and Staff Related Duties) with names, signatures, initials and functional role of all persons completing protocol assessments, providing back-up to the site Investigator and Coordinator, if applicable, as well as staff entering data to the eClinical system.
- Laboratory accreditation and relevant laboratory reference ranges
- Copies of laboratory reports/printouts
- Any source data/records not kept with the subject's hospital/medical records
- Signed and dated receipt of supplies
- Record of all monitoring visits
- Copies of correspondence to and from CTCC
- Investigator's Brochure (where applicable)
- Certificate for Human Subject Protection Program (HSPP) or equivalent program for each individual named on the Authorization log who has direct subject contact
- Copy of professional licensure/registration, as applicable, for each individual who has direct subject contact ensuring licensure is in the state/region in which the study will be conducted
- A Note to File indicating the assessments that will be considered source documents
- Any other documentation as required by the CTCC (e.g., Conflict-of-Interest/Financial Disclosure)

The Investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each subject. This documentation, together with the subject's hospital/medical records, is the subject's source information for the study.

15.2. Maintenance and Retention of Records

It is the responsibility of the Site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Site Investigators must retain all study records required by the CTCC and regulatory authorities in a secure and safe facility with limited access. The Site Investigator will be instructed to consult with the CTCC before disposal of any study records and to notify the CTCC of any change in the location, disposition, or custody of the study files.

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

15.3. Case Report Forms

Sites will enter subject information and data into the eCRF in the EDC application. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore the eCRFs must be completed according to the subject's source data on a per-visit basis for each subject screened or enrolled. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled at their site. Timely data entry is considered to be data entered into the EDC system within 2 business days of a subject's visit.

Sites will be supplied with a set of worksheets that correspond to the electronic case report form (eCRF). The worksheets will serve as source documents as described in the Operations Manual and are to be used to enter data into the eCRFs. Sites will enter all data into the subject's medical chart and/or onto source documentation worksheets prior to entering data into the eCRFs via computer stations connected remotely to the CTCC's central server through an Internet browser.

Electronic Signatures:
An electronic signature from the site Investigator is required on the following eCRFs:

- Signature Form
- Adverse Event Form

An electronic signature from the site Coordinator is required on the following eCRF:

- Signature Form

It is the site Investigator's responsibility to ensure that entries are proper and complete. During entry of data, error checks will be performed by the EDC system that will immediately flag problematic data (i.e., missing, out of range, inconsistent) allowing for sites to correct the data at that time. Error checks will be implemented in the EDC system based upon specifications defined in the data management plan.

15.4. Primary Source Documents

The Investigator must maintain primary source documents supporting data collected for each subject. This includes documentation of:

- General information supporting the subject's consent to participant in the study
- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events, and changes in medication usage including the date the medication commenced and completed

- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse experiences
- Original, signed informed consent forms for study participation

During monitoring visits the study monitor will need to validate data in the eCRFs against these source data.

16. Data Management

An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. This system is protected by 128-bit server certificates and utilizes authenticated, password-protected accounts for each site. The EDC system is designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study on an ongoing basis to the study principal investigators. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

Data review, coding and query processing will be done through interaction with the CTCC, site personnel and the Study Monitor. Queries will be generated in real-time as data are entered. Once the data are submitted to the EDC system, they are immediately stored in the central study database located at the CTCC and are accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail. As data recorded by sites in eCRFs are received, narrative text of adverse experiences and concomitant medications will be periodically coded using established coding mechanisms.

The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

Data will be securely transferred to the Statistics Core. Once the Statistics Core and the CTCC, in conjunction with the Sponsor and the principal investigator, agree that all queries have been adequately resolved and the database has been deemed "clean." The database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All data obtained during the conduct of the PPMI study, will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. Research data will be made available to researchers to conduct analyses related to PD and other disorders.

17. Study Monitoring

In accordance with ICH Guidelines for Good Clinical Practice 5.18 the study will be monitored to verify that:

(a) The rights and well being of human subjects are protected.
(b) The reported trial data are accurate, complete, and verifiable from source documents.
(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The study will be monitored by the Clinical Trials Coordination Center, who will provide study data to the Clinical Study Oversight Committee (CSOC). The CSOC will convene at least semi annually to review safety data.

The Steering Committee has the responsibility to monitor all procedures for safety and for GCP and regulatory compliance. The committee members have the expertise to monitor all aspects of this study.

The study will have ongoing monitoring to ensure that the trial is conducted properly. The monitoring activities will include:

- Verifying that the site investigators and coordinators have adequate qualifications, that resources remain adequate throughout the trial period, and that facilities, equipment, and staff are adequate to safely and properly conduct the trial.
- Verifying that the site investigators follow the approved protocol and all approved amendment(s), if any.
- Verifying that written consent was obtained for each subject participating in the trial.
- Verifying that the investigators are enrolling only eligible subjects.
- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- Monitoring adverse events, concomitant medications and intercurrent illnesses. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB, and other applicable regulatory requirement(s).
- Communicating deviations from the protocol, Standard Operating Procedures, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
- Federal regulations 21 CFR §56.109(f) and 45 CFR §46.109(e) state that an IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. Continuing review by the IRB routinely includes interim progress reports, as directed by the Board, review of proposed changes to research, adverse event reports, review of any protocol deviations, visits to the research site, and annual review of the research.

18. Study Governance

The PPMI Steering Committee (SC) will contain key members representing each area of study. A Scientific Advisory Board (SAB) will advise the SC on study design. PPMI oversight groups will establish criteria and consider applications for use of the biological samples and additional imaging study evaluations.

Appendix 1

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  - Acute confusion due to
    - a. Systemic diseases or abnormalities
    - b. Drug intoxication
  - Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

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