The Parkinson*s Progression Markers Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON56457

Source
ToetsingOnline

Brief title
PPMI Clinical

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Michael J Fox Foundation
Source(s) of monetary or material Support: PPMI is sponsored by The Michael J. Fox Foundation (non-profit organisation) and funded by the Foundation in partnership with more

than 30 biotech and pharmaceutical;non-profit and private funders.

Intervention

Keyword: Biomarkers, Parkinson's Disease, Pathobiology, Progression

Outcome measures

Primary outcome

Key PPMI outcomes will be longitudinal change in clinical (motor and non-motor) scales (e.g., MDS-UPDRS, MoCA) and PROs and digital outcomes, quantitative imaging (DAT, SBR, and MRI midbrain melanin), and biologic measures of synuclein, lysosomal function, and analytes related to neurodegeneration (e.g., neurofilament light chain inflammation). Detailed demographic, clinical and biological data will be collected to test specific hypotheses in subsequent analyses and other associated protocols. In addition, data quality metrics including compliance with study procedures, quality metrics related to biosamples and completeness of data collection will be monitored on an ongoing basis.

Secondary outcome

Detailed demographic, clinical and biological data will be collected to test specific hypotheses in subsequent analyses and other associated protocols.

In addition, data quality metrics including compliance with study procedures, quality metrics related to biosamples and completeness of data collection will be monitored on an ongoing basis.

Study description

Background summary

Parkinson disease (PD) is characterized by an insidious onset and inexorable but heterogenous progression. Reliable and well-validated biomarkers to monitor progression would contribute to research into both PD etiology and therapeutics. Much progress has been made in identifying and assessing PD biomarkers, and yet no fully validated biomarker or set of biomarkers for PD are currently available.

During the past decade, the PPMI study has established a longitudinal clinical and biomarker data resource on approximately 1,500 participants including cohorts with idiopathic PD, PD with genetic mutations, prodromal participants and healthy controls (ClinicalTrials.gov NCT01141023). The PPMI Clinical study is an extension of this initial PPMI study.

Study objective

The main study objectives include to:

a. Use clinical and biological data to estimate the mean rates of change and the variability around the mean of clinical, digital, imaging, biological and genetic outcomes in study participants.

b. Confirm existing and identify novel clinical, digital, imaging, biologic and genetic PD progression markers

c. Evaluate the probability of phenoconversion to PD for individuals with prodromal PD.

For these objectives, the study will make use of specific subgroups, as defined within the PPMI Clinical cohort:

- participants with a PD diagnosis (including patients with a LRRK2, GBA, SNCA or rare genetic mutation (such as Parkin o Pink1);
- prodromal participants (including individuals with RBD, olfactory loss, a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/ or other risk factors for PD with and without DAT deficit); and
- healthy controls.

Study design

PPMI Clinical is a longitudinal, observational, multi-center natural history study to assess progression of clinical features, digital outcomes, and

imaging, biologic and genetic markers of PD progression in study participants with PD diagnosis (including patients with a LRRK2, GBA, SNCA or rare genetic variants and individuals with prodromal Parkinson disease (including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without DAT deficit and healthy controls.

The Radboudumc, as a participating center, will include participants diagnosed with PD, without a genetic variant and individuals with prodromal Parkinson's disease.

All participants will be comprehensively assessed for a minimum of 5 years. Participants will undergo clinical (motor, neuropsychiatric and cognitive) and imaging assessments, and will donate biosamples including blood, urine, and cerebral spinal fluid (CSF) and skin biopsy.

Study burden and risks

For the baseline visit, participants come to the study site at Radboudumc in Nijmegen, which will take approximately 8 hours. After baseline, participants will be evaluated in clinic every 6 months for the first two years. Annual visits are anticipated to take about 6-8 hours (could occur over more than one day), while the 6-month in clinic visits will take about 2-4 hours.

After two years, all participants will continue to be evaluated every 6 months remotely and annually in the clinic, for up to 5 years of longitudinal follow up visits. Options for Remote 6-month visits include virtual visits by video link or telemedicine, or phone/audio only. The remote 6-month visits will take about 1-2 hours.

All study assessments are routine exams done in standard clinical practice and are generally well tolerated.

Because data collection is not performed for immediate diagnostic or therapeutic purposes, there will be no direct benefits for the subjects enrolled in this study. Patients will indirectly benefit from the study, as their data contribute to gain novel etiological insights for improvement of existing treatments, including more personalized disease management, and the development of new therapeutic approaches.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients
- Male or female age 30 years or older at Screening Visit.
- A diagnosis of Parkinson disease for 2 years or less at Screening Visit.
- Not expected to require PD medication within at least 6 months from Baseline.
- 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.
- Hoehn and Yahr stage I or II at Baseline.
- Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half -lives before DaTscan imaging.
- Confirmation that participant is eligible based on Screening DaTscan imaging.
- Able to provide informed consent.
- Either is male, or is female and meets additional criteria below, as applicable:
- Female of childbearing potential who is not pregnant, lactating or planning

pregnancy during the study and has a negative pregnancy test on day of Screening DaTscan imaging test prior to injection of DaTscanTM.

Health controls for prodromal cohort
For Screening:
- Confirmation that participant is eligible based on centrally determined predictive criteria, i.e., meeting one of the following criteria:
- Generalized risk, i.e., first degree biologic relative (parents, siblings) with PD; or
- Known risk of PD including RBD; or
- Known genetic variants associated with PD risk, i.e., LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1).
In addition, the participant needs a positive indication of Olfactory loss with the University of Pennsylvania Smell Identification Test (UPSIT), performed during the Screening visit, prior to DaTscan.
- Male or female.
- Age 60 years or older (except age 30 years or older for SNCA, or rare genetic variants (such as Parkin or Pink1) participants).
- Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before DaTscan imaging.
- Able to provide informed consent.

For ST Direct participation (as recruitment strategy for the prodromal cohort):
- Male or female
- Age 60 years or older
- No diagnosis of Parkinson's disease
- Living in the Netherlands

Additional criteria, as applicable:
- Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening DaTscan imaging test prior to injection of DaTscanTM.

For continuation to Baseline visit and ongoing follow-up:
- Confirmation that participant is eligible based on *Screening DaTscan imaging.

Exclusion criteria

Patients:
-Currently taking levodopa, dopamine agonists, MAO-B inhibitors (e.g.,

selegiline, rasagiline), amantadine or another PD medication, except for low-dose treatment of restless leg syndrome.
-Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline visit, except for low-dose treatment of restless leg syndrome.
- Has taken levodopa or dopamine agonists prior to Baseline visit for more than a total of 90 days.
-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).
-A clinical diagnosis of dementia as determined by the investigator, at screening.
-Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
-Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
-Current treatment with anticoagulants (e.g., coumadin, heparin, oral thrombin inhibitors) 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.
-Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

Healthy controls for prodromal cohort:
- Clinical diagnosis of PD, other parkinsonism, or dementia.
- Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening Visit.
- 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.
- Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
- Implants (such as dentals) or metal splinters in upper body that are not allowed to undergo a MRI scan.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-12-2021
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	11-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-08-2023

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04477785
CCMO	NL77098.091.21