

PROTOCOL

Title: PPMI Randomized Disclosure Assessment in the Parkinson's At-Risk Cohort: The RaDAR Study

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

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RaDAR PROTOCOL APPROVAL

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1. PURPOSE OF STUDY

This protocol is a web-based study conducted through the myPPMI platform (myppmi.org). It is for participants enrolled in an active Parkinson's Progression Markers Initiative (PPMI) protocol (002 Clinical study) and registered in the myPPMI platform. Individuals enrolled in the prodromal cohort of PPMI Clinical will be invited to participate. The aim is to evaluate differences in (i) study outcomes and (ii) behavioral and lifestyle changes in individuals who receive imaging, clinical, and biological personal research information versus those who have not yet received this information.

The Parkinson's Progression Markers Initiative (PPMI) Clinical is a longitudinal, observational, multi-center natural history study. It aims to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of Parkinson's disease (PD) progression. Study participants include people with manifest PD, prodromal PD, and healthy control volunteers.

1.1 Primary Objectives

The primary objective is to evaluate differences in exercise, diet, lifestyle changes, clinical trial enrollment, change in research and clinical diagnosis, retention in the delayed disclosure arm, and retention in PPMI Clinical study between individuals with prodromal PD symptoms who learn their research information at immediate (following consent) versus delayed (2 years following consent to RADAR study) timepoints.

1.2 Secondary Objectives

Secondary objectives include evaluation in differences in study outcomes (motor, neuropsychiatric, quality of life, and change in participant and Investigator global impression) between individuals with prodromal PD symptoms who learn their research information at immediate (following consent) versus delayed (2 years following consent to RADAR study) timepoints. The number of individuals in the delayed arm who choose to learn their research information early will be an additional study outcome.

2. STUDY OUTCOMES

The study outcomes will include change in investigator completed and participant completed assessments.

Participant-completed:

Primary outcomes:

- High Interest Questionnaire (developed for PPMI to capture increased risk for PD)
- Concerns for PD Scale (modified from studies in Alzheimer's Disease genetic disclosure to at-risk individuals to ascertain concern about PD)¹
- HELP Screener (screening tool to ascertain health-related behaviors)²
- Future Time Perspective questionnaire (validated survey to ascertain perspectives on the future)³

Secondary outcomes:

- MDS-UPDRS Part Ib and Part II
- Geriatric Depression Scale (GDS)
- State-Trait Anxiety Inventory (STAI)
- Quality of Life in Neurological Disorders (Neuro QoL)
- Changes in global impression outcomes

Investigator-completed:

Secondary outcomes:

- MDS-UPDRS Part III motor score
- Schwab and England ADL
- Changes in global impression outcomes

3. BACKGROUND AND RATIONALE

To date, most clinical research studies and clinical trials in neurodegenerative diseases do not share personal research information with participant stakeholders. When data is shared, it is often in the form of aggregate results that are not linked to the participant themselves. Yet PPMI participants have expressed interest in learning their research information. We have learned from studies like PPMI that participants with or at risk of PD are interested in learning their research information. Sharing research information with people that is concordant or confirmatory is unlikely to have a major impact, but these studies are underway in PPMI. However, individuals at risk of PD, who do not have a diagnosis, may be affected differently than people with PD or healthy participants in learning personal research information. Knowing one's research information may affect their responses on self-reported outcome measures. Physicians or study investigators may rate a participant's symptoms differently if they know a participant's study test result. For instance, someone with REM behavior disorder without a diagnosis of PD may be viewed differently if they have an abnormal DAT scan or an abnormal synuclein seed amplification assay result than someone with a normal result.

Studies on disclosure of *APOE* and amyloid PET imaging research data in family members of individuals with Alzheimer's disease reported transient changes in mood and physical activity, without evidence of long-term adverse impact.⁴⁻⁶ Such studies in prodromal PD have not been conducted to know the impact of learning biological, clinical, or molecular research information in these at-risk cohorts. Soon, therapeutic studies enrolling at-risk cohorts will use biomarker results as entry criteria. These studies will actively disclose (via the Return of Results initiative) or passively disclose (known based on study eligibility) results to people who are screening for these trials. To effectively inform the design of those trials, the selection of reliable and valid outcomes, and understand participant needs, there is a critical need to understand the impact of learning these results. This study will randomize participants enrolled in the prodromal PD cohort of PPMI into immediate versus delayed disclosure of their clinical, molecular, and imaging research information collected as part of the PPMI Clinical study.

4. STUDY DESIGN

This is a randomized study involving immediate or delayed disclosure of research information to individuals in the Parkinson's Progression Markers Initiative (PPMI) Clinical study prodromal cohort. This study will be presented to eligible participants through the myPPMI

portal, which is a program specific web-based portal for participants to learn about PPMI study related information and new research opportunities. Eligible participants will be presented with an opportunity tile (i.e., button), which will contain a link to learn more about returning research information, as well as this study. Participants will be required to consent prior to being randomized into the study. Following consent, participants will be randomized to have their available research information disclosed immediately or delayed disclosure 2 years after consent (i.e., enrollment into RaDAR). Participants will be randomized controlling for age of adult participants enrolled in the PPMI Clinical study (below 65 versus 65 and above) and sex (self-reported male versus female). After consent, participants will be assigned to one of the two groups and informed of this assignment in myPPMI. All randomized individuals will be given access to educational materials at the time of randomization and again at disclosure (for delayed group). Participants may also access these materials at any time, which provide information about research information disclosure, and each personal research information type, including but not limited to DaTscan imaging, MDS-UPDRS Part III, and aSyn SAA. Participants randomized to the immediate disclosure may choose to access their research information. They are not required to do so. Participants randomized to the delayed disclosure may choose to re-assign themselves to the immediate disclosure group to access their information without waiting; however, they will be asked to continue to complete the study surveys for the full 2 years. Participants may alternatively choose not to participate in this study, or choose to withdraw from randomization, and chose to view their personal research information under the standard process (i.e., immediate return of information upon consenting to general return of research information or choosing to view their information later).

5. STUDY POPULATION

This study will include people with prodromal symptoms of synucleinopathy (genetic risk variant carrier, REM sleep behavior disorder, and/or hyposmia) enrolled in the Parkinson's Progression Markers Initiative (PPMI) Clinical prodromal cohort.

6. RECRUITMENT METHODS

Participants actively enrolled in the PPMI Clinical prodromal cohort will be invited to join this study via email and the myPPMI opportunity tile. Site study staff may also discuss this study with eligible participants.

7. PARTICIPANT ELIGIBILITY

Participants must meet the following criteria to enroll:

- Actively enrolled in the PPMI 002 Clinical study prodromal cohort in the United States
- English speaking
- Registered user of myPPMI

8. OBTAINING INFORMED CONSENT

Individuals will be invited to participate in this study via an opportunity 'tile' surfaced on myPPMI. Participants must be registered within myPPMI to be presented with this study opportunity. Prior to viewing the informed consent, eligible individuals can learn more about return of research information, as well as this study. Individuals may choose not to participate and instead receive their research information immediately or later. If interested

and the individual agrees to participate, consent will be obtained electronically. Participants randomized to the delayed disclosure arm may choose at any time to end the delayed disclosure, or to withdraw from this study. The decision to withdraw will allow participants to access their research information without requiring additional consent. Participants will have the opportunity to save a digital copy of the signed informed consent documentation for their records.

9. STUDY PROCEDURES

All randomized participants would be given access to educational materials created specifically to provide information about research information disclosure, and each of the personal research information types, including but not limited to DaTscan imaging, MDS-UPDRS Part III, and aSyn SAA. Individuals randomized to immediate disclosure would then be given access to their available baseline and longitudinal research information. Individuals randomized to delayed disclosure would be given access to the education at any time; however, will need to wait to receive access to their personal research information for 2 years after enrollment in this study. All participants who are given access to view their research information and chose to receive their results will be asked to complete post disclosure surveys as part of the standard return of research information process.

Some research information is similar to, but should not replace, information from tests performed for medical care. Pre-consent language about the important difference between research information and medical testing is incorporated to mitigate such confusion.

Standard PPMI clinical outcomes will be collected from subsequent in person visits following consent. Four additional outcomes will be collected at Baseline (prior to randomization), 6 weeks, 1 year, and 2 years after enrollment, via surveys distributed through myPPMI. If a participant randomized to the delayed disclosure arm chooses to learn their research information early, they may choose to end the delayed disclosure and be allowed to access to their information early. Those participants will be asked to continue completion of the study surveys for the 2 year period.

10. RISKS TO PARTICIPANTS

Learning one's research information may cause psychological harm to the participant and/or family members. This is directly being studied in this trial and counseling is being offered for all participants through a centralized counseling service. This counseling service is available to all randomized participants regardless of their cohort. Learning research information may prompt participants to seek additional clinical consult outside the scope of this research, which may impact future care or access to insurance programs. There is a risk of disclosure of private information by participating in this study. However, safeguards are in place to reduce the risk of this happening as outlined in the PPMI Privacy Policy. Participants are provided with a link to the privacy policy which describes how their study information is kept private. In addition, data will be securely transferred between PPMI cores (designated study teams who collect, store, and handle study information) for the required workflows under the PPMI program. Any study data that is made available to researchers external to the PPMI study teams will be coded and will not

contain identifiers. While every effort will be made to maintain confidentiality, there is a small risk that information may be disclosed. There may be other privacy risks that the study team may not have foreseen.

11. POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct clinical benefits, although some participants may derive personal benefit to knowing their research information. We are collecting data on changes to lifestyle and behaviors as part of this study to better understand this.

12. COSTS FOR PARTICIPATION

There will be no cost to the study participant for participating in this study.

13. PARTICIPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or Sponsor's discretion at any time. Withdrawal from this study will not affect the study participant's continued participation in other PPMI protocols. Withdrawal from this randomized protocol will not prevent participants from being able to access their individual research information through previously established processes. Any information that has already been collected prior to the participant's withdrawal from this study will not be removed.

14. ADVERSE EVENTS

There will be no adverse event reporting as part of this observational randomized research disclosure study. All data collected as part of this study are for research purposes only and not for clinical care purposes. There will not be any routine clinical monitoring of the data collected nor any reports looking at trends and/or worsening of a participant's condition requiring medical intervention.

15. PRIVACY AND CONFIDENTIALITY OF DATA

The Institute of Neurodegenerative Disorders (IND) has built and maintains the myPPMI platform. IND is committed to safeguarding participants' privacy and personal data. The study team at IND processes participants' personal information as part of the PPMI study on behalf of The Michael J. Fox Foundation (MJFF). To protect participants' personal information, IND has put in place procedures to secure the information processed, such as restricting access to collaborators and vendors as applicable to job function, logging and monitoring network activity, multi-factor authentication, and pseudonymization.

16. DATA AND SAMPLE SHARING AND STORAGE FOR FUTURE USE

Data collected for this study will be maintained and stored indefinitely across PPMI Cores including the Indiana University PPMI Cores (Indianapolis, IN), the Site Management and Data and Technology Cores at the Institute for Neurodegenerative Disorders (New Haven, CT), and the Statistical Core at the University of Iowa (Iowa City, IA) for conducting analyses as pertains to the study as it pertains to the study including, but not limited to, enrollment and study outcomes. Data collected for this study will be incorporated into the PPMI database to create a fully harmonized PPMI database.

Study information will be accessed only by those who require access as pertains to the individual's role in the study. All organizations responsible for data storage, or other collaborators or vendors of the PPMI study who may review study information, will observe the highest precautions to ensure data integrity and security.

All data obtained during the conduct of this 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. Researchers will be required to comply with the PPMI data agreement to receive data. All personally identifiable information will be removed before it is shared outside the study.

17. ANALYSIS PLAN

Scores on investigator and participant completed primary outcomes will be compared between immediate versus delayed disclosure arms. Number of visits and procedures completed, retention in study, and retention in delayed disclosure arm will be reported. All participants randomized will be analyzed in their disclosure arm (intention to treat). Analyses will be conducted using either change from baseline to 2-years or 2-year specific values using linear or logistic regression, as appropriate, with adjustment for the two stratification variables, age and sex.

Two sensitivity analyses will also be conducted:

A per-protocol analysis will be conducted using only individuals who adhered to their assigned group. An as-treated analysis will be conducted including individuals into arms based on whether they accessed and observed their research information.

18. REFERENCES

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