SPECT Imaging Procedure Manual

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Sponsor:	Michael J. Fox Foundation (MJFF)
Main Study	
Protocol Identifier	002
Protocol Version	Version 3.0; 23-Jul-2024
Protocol Description	The Parkinson's Progression Markers Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort
Companion Study	
Protocol Identifier	004
Protocol Version	Version 3.0; 12-Oct-2022
Protocol Description	Early Longitudinal Imaging in Parkinson's Progression Markers Initiative Using [18F] AV-133 and DaTscan™ (PPMI Early Imaging)

Sponsor Signature Page

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Imaging Core Signature Page

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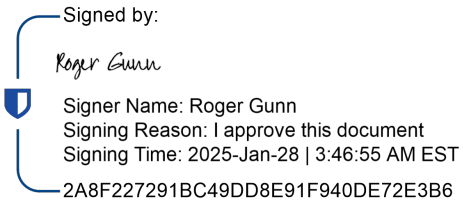

2025-Jan-28

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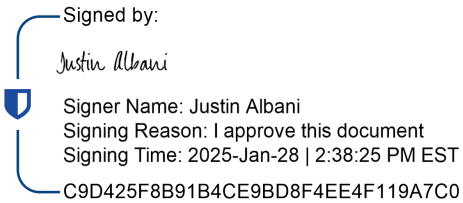

2025-Jan-28

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Table of Contents

1 Overview

The purpose of this manual is to offer comprehensive guidance and establish standardized procedures for imaging in this clinical trial. These standardized procedures are designed to ensure consistency, accuracy, and reliability of the acquired imaging, thereby supporting the trial's overall objectives and maintaining data integrity.

2 Parkinson's Progression Markers Initiative (PPMI) 002

The Parkinson Progression Marker Initiative (PPMI) is a longitudinal, observational, multicenter natural history study to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of Parkinson's disease (PD) progression in study participants with manifest PD, prodromal PD, and healthy controls. The overall goal of PPMI is to identify markers of disease progression for use in clinical trials of therapies to reduce progression of PD disability.

2.1 PPMI Sub-study 004

The PPMI protocol 004 sub-study aims to evaluate progression of DaTscan and [18F] AV133 imaging in PD and Prodromal participants over a period of up to 24 months. Approximately 50 early PD participants and 100 prodromal PD participants from the main study will be recruited for participation. The imaging will be used to assess the predictive value of early imaging.

3 PPMI Imaging Core

The PPMI Imaging Core serves as the central hub for ensuring the consistency, quality, and integrity of the SPECT imaging data collected during the trial. The Imaging Core's primary responsibilities include setup and approval of participating imaging centers, providing ongoing support, ensuring that all imaging data is collected and processed according to the trial guidelines, and performing a qualitative and quantitative assessment.

The Imaging Core monitors the quality of the imaging data submitted by each site. This includes performing quality control checks on the images received, providing feedback to sites, and requesting corrective actions if necessary. Together with the study sponsor, the Imaging Core will provide the necessary support to participating imaging centers to ensure optimal imaging results.

Imaging Core Lab responsibilities were transitioned from Invicro to XingImaging in November 2024. Imaging centers previously set up by Invicro must continue using the SPECT scanner and parameters approved for use by Invicro. Consistent use of the same imaging system and parameters is crucial to maintaining the longitudinal integrity of trial results.

3.1 Imaging Core Contact Information

For questions related to image data submissions to the Imaging Core, technical imaging questions or questions related to queries received, please contact:

corelab.support@xingimaging.com

For questions related to the PPMI clinical protocol, please contact your clinical site study coordinator or other applicable clinical team contact.

4 Study Documentation

A copy of this imaging manual and related documents will be available within the PPMI Electronic Trial Master File (eTMF), Florence, as well as the PPMI Site Management Core's (SMC) Learning Management System (LMS). Going forward, please consult both platforms to ensure you have the most current version of each manual and document.

Imaging Center Setup and Approval

5 Imaging Center Setup and Approval

5.1 Imaging Centers Previously Approved for PPMI Imaging by Invicro

All imaging centers that were previously setup and approved for imaging by the former imaging core, Invicro, are required to complete an abbreviated setup procedure. This process involves the following:

5.1.1 Imaging Center Personnel Training:

Training will be conducted through a web-based learning module. The training will focus on the image data transfer and query resolution procedures using XingImaging's image data management platform. Once the training is completed, imaging centers will be granted access to the platform and will be required to conduct a test transfer.

5.1.2 Test Image Transfer:

A test of the participant image transfer process using XingImaging's image data management platform is required for all sites. The test transfer should consist of DICOM image files, preferably from a recently acquired PPMI participant. If the data from a recently acquired PPMI participant is not available for transfer, a phantom may be submitted.

Imaging centers previously setup by Invicro must continue using the SPECT scanner and parameters approved for use by Invicro. Consistent use of the same imaging system and parameters is crucial to maintaining the longitudinal integrity of trial results.

Upon completion of the training and the successful receipt of the test transfer, the imaging core lab will notify imaging centers that they are approved to begin submitting PPMI participant imaging to the image data management platform.

5.2 Imaging Centers Not Previously Approved for PPMI Imaging

Imaging centers must undergo a qualification process before beginning to scan participants for the PPMI trial to ensure that they meet the trial's technical and operational standards. Centers who were not previously approved for PPMI imaging must complete the steps listed below.

5.2.1 Technical Questionnaire:

The first step in this process is the completion of a questionnaire which collects information on the site's imaging personnel, imaging equipment, including the make, model, and technical specifications of the SPECT camera, collimators, and processing software. This information is reviewed by the imaging core lab to assess the compatibility of the equipment with the trial's requirements.

5.2.2 Protocol Verification:

Following completion and review of the questionnaire, the imaging core lab will provide imaging centers with the acquisition parameters unique to their SPECT scanner make and model for the purposes of building a dedicated protocol in the system for use in this trial. Once the protocol has been established, the imaging center will be requested to provide screen captures of the relevant acquisition and reconstruction screens to the imaging core lab for review.

5.2.3 Phantom Acquisition:

Following review of the SPECT system protocol screen captures, the imaging center is required to perform a phantom scan using the approved scanner protocol that will be used for participant imaging. The phantom acquisition is designed to evaluate the scanner's performance in terms of

uniformity and sensitivity. The images from this acquisition will be submitted to the imaging core lab for analysis. The imaging core lab will assess the images for adherence to the trial's quality standards, including correct acquisition parameters and absence of artifacts.

5.2.4 Imaging Center Personnel Training:

Training will be conducted through a web-based learning module. The imaging core lab will provide user-specific accounts to the relevant clinical and imaging staff, granting them access to the training system. The training will cover the overall study objectives, the imaging schedule, the imaging procedure and guidelines to follow, as well as the procedures for image data submission to the application and query resolution.

At least one primary imaging staff member responsible for conducting study imaging must undergo training by the imaging core lab. The imaging center is responsible for ensuring that all additional personnel are trained by the primary staff member initially trained by the imaging core lab. All additional training activities must be documented, and a copy of this documentation should be sent to the referring clinical site(s). For any further assistance with training or questions, please contact the imaging core.

Imaging Schedule of Assessments
&
Participant Naming Convention

6 Imaging Schedule of Assessments

Table 1: Schedule of SPECT Assessments for Clinical (Main) Study (Protocol 002)

Scan [a]	Healthy Control	PD	Prodromal
Screening Scan [b,c,d,e]	X	X	X
Baseline Scan [k]	X	X	X
Visit 04 (12 months) [f]	-	X	X
Visit 06 (24 months) [f]	-	X	X
Visit 10 (48 months) [f]	-	X	X
Visit 12 (60 months) [f]	X [g]	-	-
Visit 13 (72 months) [f]	-	X [h]	X
Visit 15 (96 months) [f]	-	-	X
Visit 17 (120 months) [f]	-	-	X
Withdrawal Visit [i]	-	X	X
New Clinical Diagnosis Visit [j]	-	X	X

[a] To lessen participant burden, a participant's previously acquired SPECT imaging may be used in place of a newly acquired scan at any visit if the previous scan was acquired within 6 months of the study scheduled SPECT, it meets protocol acquisition standards, and passes QC requirements for the research study analysis. Participants may require a repeat dopamine active transporter (DaT) scan if the previously acquired DaT is older than 6 months from the date of the visit.

[b] Only participants who consented to the Screening visit under Clinical protocol amendment 3.2 (Version 3.2 dated January 30, 2023) will complete the Screening and Baseline visit per the amendment 3.2 schedule of assessments and the SPECT scans acquired will be used to evaluate eligibility.

[c] Newly enrolled participants in PPMI Clinical will start with the Screening Visit.

[d] Participants may not have the following drugs within 6 months of the Screening Visit: dopamine receptor blockers (neuroleptics), metoclopramide, and reserpine.

[e] Brain SPECT screening imaging appointments will occur within 60 days prior to baseline.

[f] Brain SPECT imaging will occur within ±45 days either side of the Target Visit Date.

[g] Optional based upon Investigator and participant discretion.

[h] If the participant is beyond Year 6, conduct this activity at the next annual visit.

[i] If a participant withdraws from the study and agrees to attend one more visit, follow the Clinical protocol Event Driven Modification of Scheduled Visits for withdrawal from study.

[j] Follow the Clinical protocol Event Driven Modification of Scheduled Visits to determine if imaging should be completed.

[k] **If a DaT SPECT scan was conducted during Screening and was completed within 6 months of Baseline, a DaT SPECT scan is not required at Baseline.**

Table 2: Schedule of SPECT Assessments for Sub-study (Protocol 004)

Scan	Early PD participants
Visit 02 (6 months)	X

7 Participant Naming Convention

Each participating site and study participant will receive a unique study-specific identification number. Both the site and participant numbers must be entered into XingImaging's image data management platform when transferring image files to the imaging core lab and must be used in all study documentation and communications with the imaging core lab.

- Site Numbers for this study consist of 3 digits.
- Participants moving from PPMI 001 to PPMI Clinical will retain their previously assigned 4 or 5-digit Subject ID.
- New participants enrolled in PPMI Clinical will be assigned a Subject ID up to 7-digits.

Sites should redact all protected health information (PHI) to protect the privacy of participants before submitting image data to the imaging core lab. This process involves redacting or removing any direct identifiers, such as names, addresses, contact details, or any other information that could be used to trace the identity of the participant. XingImaging's image data management platform performs a secondary de-identification upon submission to the imaging core lab.

Data Submission to the Imaging Core, Query Management & Data Archival

8 Data Submission To The Imaging Core Lab

Visit details and image files will be transferred to the imaging core lab through a web-based image management system. The DICOM image files will be uploaded directly into the application, while visit information will be entered directly into an electronic form within the system. The visit information and image series listed below are required to be available to complete the submission.

All acquired imaging must be transferred to the imaging core lab, preferably within 24 hours, but no later than 3 business days. All queries issued by the imaging core lab must be responded to within 5 business days.

The visit information and image series listed below are required to be available to complete the submission.

Instructions on use of the image management platform are provided in a separate manual which is available within the PPMI Electronic Trial Master File (eTMF), Florence, as well as the PPMI Site Management Core's Learning Management System (LMS).

8.1 Visit Information:

- Site and Subject ID
- Scan Date
- Visit Identifier
- Initial and Residual Dose Measurements and Times of Assay and Administration Time
- Scan Start Time, Equipment Used and Detector Radius Used
- Scan Comments: Please include information which may be helpful to the imaging core lab (e.g. participant positioning, parameter variations, etc.). Information provided may help avoid queries.
- Equipment Quality Assurance information

8.2 Image Files:

- Raw Projection SPECT Files in DICOM Format
- Reconstructed SPECT Files in DICOM Format

9 Query Management

The imaging core lab will perform a thorough quality control review of the received images, assessing them for adherence to the trial protocol and overall image quality. If any issues are identified, the imaging core lab will provide feedback to the imaging center through queries issued within XingImaging's image management platform and request corrective actions if necessary. This may include repeating the imaging procedure or implementing changes to the imaging process.

10 Data Archival

In accordance with Good Clinical Practice (GCP) guidelines (or regional regulations, whichever sets the higher standard), maintain an archive of all image data in a readable format, consistent with the format submitted to the imaging core.

Please contact the imaging core if your center has questions around meeting this data archival requirement.

Radiotracer Information and Procedures

11 Radiotracer Information and Procedures

Brain SPECT imaging is utilized in the PPMI study to assess participant eligibility and measure striatal dopamine transporter binding. The radiotracer used for brain SPECT imaging will be ^{123}I-DaTscan™. However, certain sites may be authorized to use ^{99m}Tc-TRODAT-1 if ^{123}I-DaTscan™ is unavailable. Radiotracer ordering and handling are detailed within this section.

11.1 Radiotracer Dose Ordering

11.1.1 ^{123}I-DaTscan™

The costs of the DaTscan™ doses used in this trial are covered by the trial sponsor. Study-specific, prefilled Dose Order forms are available for use and must be completed and submitted to GE Healthcare by email or fax using the contact information indicated on the form. GE Healthcare will send a confirmation email once the order is processed.

Copies of the DaTscan Dose Order form are available within the PPMI Electronic Trial Master File (eTMF), Florence.

11.1.2 ^{99m}Tc-TRODAT-1

Local procedures should be followed for ordering ^{99m}Tc-TRODAT-1.

11.2 Radiotracer Dose Administration

^{123}I-DaTscan™ and ^{99m}Tc-TRODAT-1 are radioactive substances and must be handled with proper safety precautions to minimize radiation exposure during administration. Radiotracers should only be received, used, and administered by authorized personnel in designated clinical settings, following strict local regulations.

The dose syringe must be measured for radioactivity using a calibrated dose calibrator before administration and again following administration to measure residual radioactivity in the syringe in order to calculate the net administered activity. The initial and residual radioactivity measurements are required to be entered into XingImaging's image data management platform when submitting the image files.

The clocks used to record the radioactivity measurement times and the time of administration must be synchronized with the clock used to record the start time of the SPECT scan.

11.2.1 ^{123}I-DaTscan™

The required DaTscan™ dose for this study protocol is 3-5 mCi (111-185 MBq).

- Required Dose Range: 3-5 mCi (111-185 MBq)
- Administration: Slow intravenous injection (over approximately 20 seconds)
- Method: Through an indwelling intravenous catheter
- Flush: Infusion line flush of 15-20 mL of normal saline
- Maximum Dose: Do not exceed 5 mCi (185 MBq)
- Minimum Activity: Do not administer if the activity falls below 3 mCi (111 MBq)

11.2.2 ^{99m}Tc-TRODAT-1

The required 99mTc-TRODAT-1 dose for this study protocol is 25 mCi (925 MBq)

- Target dose: 25 mCi (925 MBq)
- Administration: Slow intravenous injection (over approximately 20 seconds)
- Method: Through an indwelling intravenous catheter
- Flush: Infusion line flush of 15-20 mL of normal saline

SPECT Imaging Visit Procedures
&
Imaging Equipment Information

12 SPECT Imaging Visit Procedures

12.1 Participant Scheduling

The clinical site staff are responsible for scheduling the participant's imaging visit with the SPECT center. Typically, the clinical site study coordinators are responsible for the scheduling of study-related activities. Effective communication between the clinical site and the imaging center is essential to timely scheduling in accord with the study visit windows.

12.2 Participant Preparation

Adhere to the following guidelines for participant preparation in addition to following local procedures.

- The responsible physician or a designated staff member at the SPECT imaging center will confirm the participant's ability to complete the SPECT imaging study.
- A urine or blood pregnancy test must be performed within 24 hours before the SPECT scan for women of childbearing potential. A negative result is required before administering the radiotracer.
- The participant's weight must be measured on the day of each SPECT scan using a calibrated and medically approved device (not verbally relayed by the participant).
- Fasting is not required for SPECT scans in this study.
- Participants should be pretreated with a thyroid-blocking agent (e.g., saturated solution of potassium iodide [SSKI]) prior to receiving the radiotracer. For participants with iodine allergies or sensitivities, potassium perchlorate (400 mg) will be administered instead of potassium iodide.

12.3 SPECT Imaging Protocol

The SPECT imaging protocol is designed to ensure consistent and high-quality images across all clinical sites. Adherence to the protocol is essential for the accurate assessment of the imaging data and the overall success of the trial.

Imaging Core responsibilities were transitioned from Invicro to XingImaging in November 2024. Imaging centers previously set up by Invicro must continue using the SPECT scanner and parameters approved for use by Invicro. The instructions included within this manual remain constant with prior PPMI imaging guidelines for continuity of the image acquisition. Consistent use of the same imaging system and parameters is crucial to maintaining the longitudinal integrity of trial results.

The exact imaging parameters followed may differ slightly by site and will be decided as part of site set up by the Imaging Core.

12.3.1 Participant Positioning and Scanning Procedure

- Approximately 3.5 hours post injection, have the participant void, and position the participant in the scanner
- The participant should be positioned supine on the imaging table, with their head secured to minimize movement during the scan. A comfortable and stable positioning system should be used to ensure that the participant remains still throughout the imaging procedure. Motion artifacts can significantly degrade image quality and may require a repeat scan.

- The SPECT field of view (FOV) should encompass the entire head to include the brain from most superior cortical regions through the inferior portion of the cerebellum.
- Position the SPECT detector heads as close to the participant as possible, aiming for a target radius of 15 cm. Document the actual radius used during imaging.
- Begin ^{123}I-DaTscan™ SPECT scans 4 hours post injection (targeting ± 30 minutes)
- Begin ^{99m}Tc-TRODAT-1 scans 3.5 hours post injection (targeting ± 30 minutes)

12.3.2 SPECT Acquisition Parameters

General SPECT acquisition guidelines are listed below. These parameters are optimized for capturing the distribution of the radiotracer in the brain and should not be altered without prior approval from the imaging core lab. Ensure that the SPECT camera is properly calibrated and that all applicable settings are correctly applied before beginning the scan.

1. **Collimator:** Low-energy high-resolution (LEHR)
2. **^{123}I-DaTscan™ Energy Window:** 159 keV with a 20% window (±10 %)
3. **^{99m}Tc-TRODAT-1 Energy Window:** 140 keV with a 20% window (±10 %)
4. **Matrix:** 128x128
5. **Rotation:** 360° with a step-and-shoot acquisition
6. **Frame Time:** 30 seconds per projection, with a total of 120 projection (60 per detector)
7. **^{123}I-DaTscan™ SPECT Start Time:** 4 hours post injection (targeting ± 30 minutes)
8. **^{99m}Tc-TRODAT-1 SPECT Start Time:** 3.5 hours post injection (targeting ± 30 minutes)

12.3.3 Reconstruction Protocol

The imaging center will reconstruct the SPECT images following their standard protocol for clinical brain SPECT scan reconstruction.

12.3.4 SPECT Imaging Center Quality Control

Immediately following image acquisition, a quality control check should be performed by the technologist to assess the images for motion artifacts, correct positioning, and overall image quality. If any issues are identified, the scan may need to be repeated.

13 Imaging Equipment

13.1 Approved Equipment

The quality of the imaging data acquired in this clinical trial relies heavily on the use of high-performance, well-maintained imaging equipment. Only equipment that has been reviewed and approved by the imaging core lab may be used for participant imaging in the trial. The primary piece of equipment is the SPECT camera, which must be capable of producing high-resolution images with minimal artifacts. The camera must be equipped with a low-energy high-resolution (LEHR) collimator, which is essential for achieving the necessary image quality for SPECT brain studies.

In addition to the SPECT camera, other associated equipment such as the image processing workstation, radiopharmaceutical dose calibrator, and participant positioning devices must also

meet the trial's standards. The imaging center must ensure that all equipment is in good working order and is properly calibrated according to the manufacturer's specifications.

Any deviation from the approved equipment, such as the use of an alternative collimator or processing software, must be justified and pre-approved by the imaging core lab.

13.2 Equipment Changes

It is crucial that any changes to the imaging equipment used in the trial be reported to the imaging core lab immediately. Changes could include upgrades to the SPECT camera or software, replacement of key components, or the introduction of new ancillary equipment. Even minor changes can impact the consistency and quality of the imaging data, so they must be carefully evaluated by the imaging core lab.

If an imaging center plans to upgrade or replace its SPECT camera, it must notify the imaging core lab before making the change. The imaging core lab will assess whether the new equipment is compatible with the trial's protocols and whether requalification is necessary. The imaging center may be required to perform a new phantom scan and submit the images for review to ensure that the new equipment meets the trial's quality standards.

In cases where an imaging center needs to make an urgent equipment change due to unforeseen circumstances, such as equipment failure, the site must contact the imaging core lab as soon as possible.

13.3 Equipment Maintenance and Calibration

Proper maintenance and calibration of imaging equipment are essential to ensure consistent image quality throughout the trial. Imaging centers are responsible for implementing a regular maintenance schedule for their SPECT camera and associated equipment, following the manufacturer's recommendations and any additional guidelines provided by the imaging core lab.

Calibration of the SPECT camera should be performed regularly, with particular attention to the energy window settings, collimator integrity, and system sensitivity. Calibration should be documented in a logbook or electronic record, and these records must be made available to the imaging core lab upon request. Any discrepancies or issues identified during calibration must be addressed promptly, and corrective actions must be documented.

In addition to routine maintenance and calibration, the imaging center should perform regular quality control checks, such as daily flood field tests and weekly resolution tests. These checks help ensure that the equipment is functioning optimally and that any potential issues are identified and corrected early. The imaging core lab may request periodic submission of quality control data to verify that the site is maintaining the required standards.

14 History of Change

Version History		
Version Number	Version Date	Description of Change
1.0	2025-Jan-22	Original