



PARKINSON'S
PROGRESSION
MARKERS
INITIATIVE

Play a Part in Parkinson's Research

PPMI

Imaging Technical Operations Manual

The PARKINSON PROGRESSION MARKER INITIATIVE

Version: 8.0
Date: 09 March 2017

Disclaimer: This document is a confidential communication of PPMI. The recipient agrees that no information contained herein will be published or disclosed without written approval. This document may be disclosed to appropriate institutional review boards, independent ethics committees, or duly authorized representatives of the US Food and Drug Administration, the Bureau of Pharmaceutical Assessment (Canada), or other regulatory authorities as appropriate, under the condition that confidentiality is requested.

Table of Contents

1.	Introduction.....	3
1.1	Background	3
1.2	Technical Features of PPMI.....	4
2.	Image Center Qualification Process.....	4
2.1	Completion of the SPECT Imaging Center Qualification Questionnaire:	4
2.2	Test Data Acquisition and Data Transfer:.....	4
2.3	Technical Set up Visit and Phantom Acquisition:	5
2.4	First Subject Acquisition:.....	5
3.	Technical SET UP Visits	5
3.1	Preparation for the set up visit.....	5
3.2	Technical Set Up Visit	5
3.2.1	Technical Set Up Agenda	6
4.	Nuclear Medicine Procedures	8
4.1	Quality Control and Scanner Calibration	8
4.2	Scanner Replacement or Upgrade	10
4.3	Image acquisition	10
4.4	Data Interpretation.....	12
5.	Image Reconstruction, Processing, Scan Identification and Archiving.....	12
5.1	Imaging Reconstruction and Processing	12
5.2	Scan Identification.....	12
5.3	Study Data Archiving.....	13
6.	Data Transfer	13
7.	Study Technical Documentation.....	15
8.	Communication with IND and trouble-shooting problems	15
	Figure 1 Anthropomorphic striatal phantom for initial center calibration during technical center visit.....	8
	Figure 2 Camera QA Event Log	9
	Figure 3 Scan information source document	11
	Figure 4 Imaging Data Transfer Source.....	14

1. INTRODUCTION

This manual describes technical features of dopamine transporter (DAT) single photon emission computed tomography (SPECT) for the study protocol entitled Parkinson Progression Marker Initiative (PPMI) and includes information about camera quality control and calibration, scan acquisition protocols, image processing and analysis and file transfer to the core imaging lab.

1.1 Background

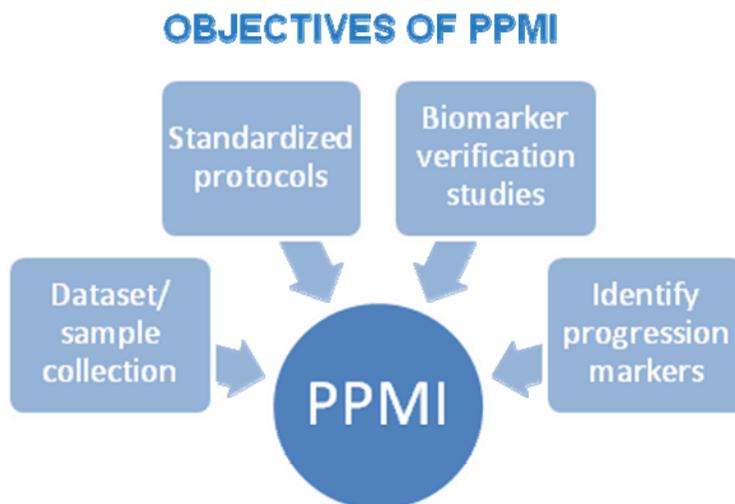
The primary objective of this study is to identify clinical, imaging and biologic markers of PD progression for use in clinical trials of disease-modifying therapies.

The specific aims to accomplish the primary objective are:

- a. Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biologic data that can be used by the PD research community.

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 biologic outcomes in early PD patients prodromal PD subjects, and PD subjects with a LRRK2, GBA or SNCA mutation.

Investigate existing and identify novel clinical, imaging, and biologic 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, SWEDD subjects, Prodromal subjects, PD subjects with a LRRK2, GBA or SNCA mutation, unaffected LRRK2, GBA or SNCA mutation carriers, or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging, genetic mutations, or biologic change.



1.2 Technical Features of PPMI

The development of multi-center quantitative measures, even in the context of a within subject design like PPMI, requires a more robust approach to camera calibration, image acquisition, and technical optimization than is necessary for qualitative diagnostic imaging. In this regard, the PPMI study incorporates several unique and investigational technical features to ensure the highest level of data which may be successfully pooled across the study centers and imaging centers. These technical features designed to accomplish this goal in PPMI include:

- 1) Individual technical center visits and image protocol set-up with optimization of camera protocols and standardization of center's processing methods.
- 2) Ongoing core imaging lab assessment of images as they are obtained via rapid quality control check of the imaging data submitted to the core lab and feedback to the imaging center.

2. IMAGE CENTER QUALIFICATION PROCESS

To ensure that an imaging center chosen as a participating imaging center meets the high level of standard required by the Imaging Core Lab (ICL), the Institute for Neurodegenerative Disorders (IND), the selected center will complete the following qualifying steps listed below:

2.1 Completion of the SPECT Imaging Center Qualification Questionnaire

This form (completed by the imaging center) provides IND with contact information for key individuals, specific camera and computer system capabilities, and other specifications necessary for satisfactory completion of the study.

The completed questionnaire is reviewed by IND for initial assessment of the center's technical capabilities. If the center meets the technical standards required to perform as a participating center, IND will contact the center informing them of the next steps necessary for completion of the qualification process for the study described in the following paragraphs.

2.2 Test Data Acquisition and Data Transfer

Imaging centers will be required to electronically transfer the test data (via DICOM push, sFTP, web upload, FTP or CD) to IND. This test data set can be a previously acquired de-identified (anonymized) subject data set or a point source. Centers will be provided with instructions on the transfer process. For the transfer, an IND staff member will be available to provide technical support to assist the center with the electronic transfer of the point source data. This serves as a test to discover any file transfer problems.

Once the test data set has passed quality control (QC), a member of IND's Core Lab team will contact the center to schedule the technical set up visit.

2.3 Technical Set up Visit and Phantom Acquisition

During the technical set up visit an ^{123}I anthropomorphic striatal phantom will be acquired. The phantom data will be transferred to IND for review and reconstruction. The center will receive a communication describing the activities that took place during the technical center visit. This communication will notify the center staff whether or not they are qualified to begin imaging subjects in the study.

2.4 First Subject Acquisition

After the first subject has been imaged, the center will be instructed to promptly transfer the data to IND for review. The center will be instructed NOT to enroll a second subject until IND has reviewed the first subject data and it has passed both the technical and scientific quality control procedures at the Core Lab.

Once the first subject data has passed both technical and scientific QC, the center will be sent a brief report indicating that they have been cleared to begin enrolling additional subjects.

The above steps are necessary to ensure that imaging centers follow protocol and source documentation guidelines, and image acquisition and data transfer procedures in order to produce data that is deemed acceptable by IND's quality assurance processes.

3. TECHNICAL SET UP VISITS

3.1 Preparation for the set up visit

Participating centers will be visited by a core lab representative prior to the initiation of subject enrollment for the purpose of familiarizing nuclear medicine technical staff with image acquisition, processing, data archiving, and data submission procedures.

Approximately one month prior to the anticipated enrollment of subjects into the study a technical set up visit will be scheduled. An agenda will be customized to the requirements of the center and clinical demands on the SPECT camera.

3.2 Technical Set Up Visit

During the visit, the set up specialist will review the center's SPECT instrumentation, collimators, and image processing software in order to develop an image and data processing plan for the center which supports pooling of quantitative DaTSCAN™ data with other imaging centers. In addition procedures for pharmaceutical dose assay, thyroid blockade and safety, image reconstruction and processing, file-naming, and data transfer procedures will be reviewed.

The technical visit is usually conducted in two sessions over one day. The center set up specialist understands that demands for camera time may influence the timing of the phantom acquisition

and every means will be taken to be flexible around the scheduling of the visit activities. A general agenda for a typical visit is described below:

3.2.1 Technical Set Up Agenda

Purpose

- Review subject flow and center study roles, responsibilities, and communication
- Review imaging procedures, rationale, and source documents
- Perform ^{123}I anthropomorphic striatal phantom acquisition
- Do test run of data send operation to core lab
- Go over quality assurance program and assessments to occur during the study
- Review mechanisms for feedback from core lab after each image sent
- Answer any questions, anticipate problems and solutions
- Confirm contact information
- Provide Center Study Binder containing;
 - Contact information
 - Technical Operations Manual
 - Camera QA Event Log forms (see Figure 2 for an example)
 - Instructions for completion of Camera QA Log
 - SPECT Scan Information Source Documents with instructions for completion (see Figure 5 for an example)
 - sFTP/FTP server, user, and password information or DICOM server information exchange
 - SPECT Imaging Data Transfer Information Source Documents (see Figure 3 for an example)
 - Center specific subject numbering protocol
 - Core Lab communications section for maintaining records of all communication with the Core Lab

Agenda

Session 1 (about 1 h)

Suggested participants: Neurology PI, Nuclear Medicine PI, study coordinator, nuclear medicine technologist and other key members of the neurology and nuclear medicine teams

- 1) Introductions and orientation
- 2) Outline of study technical imaging features
- 3) Review individual team member's responsibilities and communication from recruitment, to consenting and enrollment, to scan scheduling, image acquisition, etc.
- 3) Review core imaging lab technical documents and data submission procedures

- 4) Review imaging core lab quality control procedures

Session 2 (about 4 h)

Participants: Nuclear Medicine group

- 1) Briefly tour the imaging facilities and review study camera(s)/collimators and quality assurance procedures, document system software and version
- 2) Develop an acquisition protocol for specific SPECT tomograph to be used in the study
- 3) Test the acquisition protocol with an anthropomorphic ^{123}I phantom acquisition. The imaging core lab representative provides and prepares all the phantoms working with the center's technologist staff. The center must have 37-111 MBq (1.0-3.0 mCi) of liquid ^{123}I available for the phantom acquisition. Phantom acquisitions will be scheduled according to camera availability.
- 4) Review imaging data transfers procedures to the imaging core lab. Perform a dry run of acquired phantom data transfer, and troubleshoot problems, firewall issues, etc.
- 5) Provide information about ongoing follow-up and communication, final questions, and wrap-up.

Following the technical set up visit, a report summarizing the technical acquisition and reconstruction parameters, image analysis, and file transfer procedures will be sent to the center. This will also document the quality assurance program discussed for the camera. This technical report should be kept in the study binder and serve as a proscriptive technical summary for the center. Any modification or changes in image acquisition will be reflected in updates to the technical center visit report and may also be stored in the center study binder.

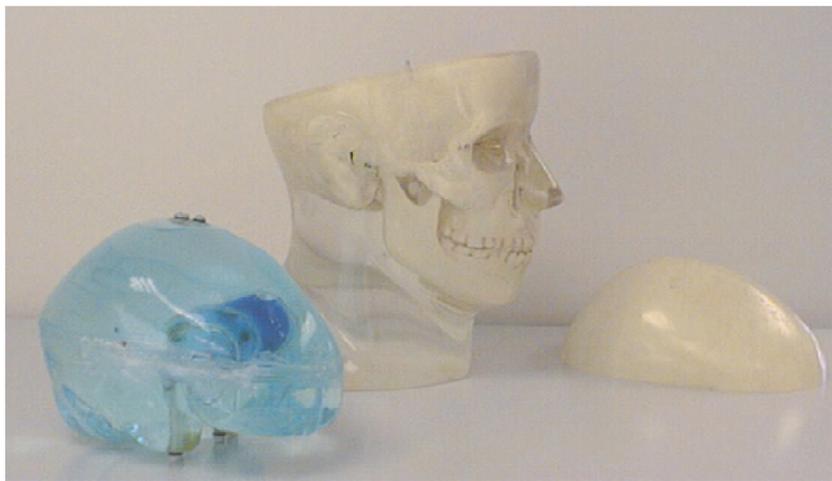


Figure 1 Anthropomorphic striatal phantom for initial center calibration during technical center visit.

This will be filled with ^{123}I to model striatal uptake of DaTSCAN™ and the data used to optimize and standardize the reconstruction and filtration of the SPECT image across the different imaging centers.

4. NUCLEAR MEDICINE PROCEDURES

4.1 Quality Control and Scanner Calibration

Instrument assessment and quality control measures are critical to the meaningful interpretation and pooling of quantitative SPECT data across study centers. These measures and calibrations may be considered to occur over two periods; 1) prior to subject enrollment and, 2) after the initiation of patient enrollment.

Within the month prior to the initiation, each center must have completed the following planar and SPECT Q/C data: $^{99\text{m}}\text{Tc}$ flood uniformity corrections with the clinical imaging collimators in place, COR correction, and energy correction according the manufacturer's specifications for the instrument. During the technical center visit the imaging core lab representative will verify the clinic's quality assurance procedures and a phantom will be obtained.

Quality control measures will be performed according to the clinic's and camera manufacturer's standard procedures as implemented in the center's quality control program for the SPECT camera and dose calibrator.

The minimal required calibration and quality control studies are summarized in Table 1 and need to be documented on the Camera QA log when performed:

Table 1

Frequency	Test	Rationale
<i>Performed prior to subject enrollment by IND team</i>	^{123}I Striatal phantom	Allows baseline measure for evaluation and comparability of recons, region sampling, etc
<i>Performed during study each day a protocol subject is scanned</i>	Routine SPECT and dose calibrator QC	Maintains integrity of scanner and dose calibrator

The Camera QA Event log will be completed on days when subject images are acquired. In addition, quality assurance data, software upgrades, changes in hardware and any other manipulations or changes to the imaging camera are to be recorded in a Camera QA Log source document which will be provided to the centers during the technical set up visit. See Figure 2 next page.

4.2 Scanner Replacement or Upgrade

It is important that subjects are imaged on the same scanner throughout their participation in the study.

If your center will be replacing or upgrading your scanner or acquisition software, it is critical that you inform IND *prior* to the replacement or upgrade occurring, so that IND can take the necessary steps to ensure the continuity of the imaging outcome measures in this longitudinal research study. IND may need to revisit the imaging center to acquire another phantom.

4.3 Image acquisition

The interval for DaTSCAN™ imaging visits for the PPMI study are based on a subject's cohort assignment (Parkinson's disease, prodromal, healthy control, SWEDD ((Subjects Without Evidence of Dopamine Deficit)), or genetic cohort). Refer to clinical protocol for current schedule of activities (SOA). The SOA for each cohort indicates visit/s where DaTSCAN™ imaging should be completed. Confirm with the clinical site coordinator the subject's visit at the time of imaging.

Prior to each injection (on the day of injection) all females of child bearing potential must have a negative urine pregnancy test in order to receive the DaTSCAN™ injection.

Radiopharmaceutical will be provided as a unit dose. Specific details of ordering the DaTSCAN™ dose will be discussed at the center visit. The dose should be assayed in a 10 ml syringe filled to a standard volume of 6 ml. In order to avoid geometry effects on determination of actual injected dose following injection of DaTSCAN™, the syringe should be filled to the initial volume and reassayed. These data should be recorded on the PPMI Scan Information Source Document (Fig 5). Subjects should be pretreated with saturated iodine solution (10 drops in water) or perchlorate (1000 mg,) prior to DaTSCAN™ injection. The target dose for subjects will be 185 MBq or 5.0 mCi of DaTSCAN™. The dose range for injection is 111 to 185 MBq or 3.0 to 5.0 mCi of DaTSCAN™. Do not exceed 185 MBq and do not use when the activity is below 110 MBq.

Subjects are to be imaged 4 ± 0.5 hours following the injection. Specifically-bound activity washes out from striatal binding centers slowly, but not negligibly, hence every effort should be made to maintain a consistent imaging time post injection of DaTSCAN™.



**PARKINSON'S
PROGRESSION
MARKERS
INITIATIVE**
FORM # PPMI 08/Dec/2016

SPECT Scan Information Source Document

PPMI

Site Number: Subject Number: **** If subject number is 4 digits, please enter "0" in the first box ****

Visit Number: Screening Month 12/V04 Month 24/V06 Month 48/V10 PW
 ST Unscheduled Month 36/V08 **Note: visit applies to Prodromal subjects only.**

Clinical Site Name: Imaging Center Name:

Scan Acquisition Date: / /

Age At Time Of Scan: (screening only) Gender: Male Female

Injection Information: Radiopharmaceutical:

Thyroid Blockade Method: Thyroid Blockade Dose: Time Blockade Administered: (24 hour clock) :

Date Injected: (dd/mm/yyyy) - - Injection Time: (24 hour clock) :

Initial Activity: . mCi MBq Time Measured: (24 hour clock) :

Residual Activity Post Injection: . mCi MBq Time Measured: (24 hour clock) :

Actual Dose: . mCi MBq

Subject Acquisition: Scan Identifier:

Scan Identifier should be named as follows in the patient name field in the header: 3 digit site number—4 or 5 digit subject number_ and the scan number (e.g. 123-1234_1) - Refer to Technical Operations Manual for more information.

Camera:

Acquisition Protocol Used: (use protocol created at set-up visit)

****NOTE: Device used to document "time injected" should correspond with device used to document scan start****

Start Time: (24 hour clock) : Stop Time: (24 hour clock) :

Collimator: Radius:

Technical Comments:



CONFIDENTIAL
The Institute for Neurodegenerative Disorders



A R N T T h 1 0 1 2 A

© Copyright 2016. All rights reserved.

MNIID1012
V10 PPMI 08/Dec/2016

Figure 3 Scan information source document

Scan information source documents the radiopharmaceutical dose, time imaging post-injection, the phantom and subject acquisition parameters. This form is completed for each subject and sent to core lab at the same time the images are transferred.

As a general protocol, raw projection data will be acquired into a 128 x 128 matrix stepping each 3 degrees for a total of 120 (or 4 degrees for a total of 90) projections in a window centered on 159 +/- 10% KeV with a total scan duration of approximately 30 – 45 minutes. Specific scan parameters including collimation and acquisition mode will be selected for each center on the basis of an assessment during the technical set up visit. Insofar as possible, it is recommended that acquisition be in step and shoot mode with each head rotating 360 degrees using a parallel hole collimator to permit the reconstruction of a viable image even if one head is faulty. The acquisition parameters for each study are recorded in the scan acquisition document at the time of the scan as indicated in Figure 3.

Please Note: For those imaging centers who completed their technical site visit prior to July 2013, please continue to image subjects according to the dual energy window acquisition protocol that was determined during this visit.

4.4 Data Interpretation

A visual interpretation for the screening DaTscan (PD Genetic Cohort subjects only) will be performed at the imaging core lab by well-experienced nuclear medicine experts. Clinical centers will receive a report indicating whether there is evidence of a dopamine deficit on the subject's scan for subjects where the DaTSCAN result is an eligibility criteria. The screening imaging interpretation will serve as final criteria for enrollment into the study.

5. IMAGE RECONSTRUCTION, PROCESSING, SCAN IDENTIFICATION AND ARCHIVING

5.1 Imaging Reconstruction and Processing

Both the imaging center and the core lab will reconstruct and attenuation correct the imaging data. Therefore it is imperative that the ICL receive both the reconstructed and the raw projection data. Imaging centers may implement either filtered back-projection or an iterative reconstruction algorithm using standardized approaches. Methods for homogeneous attenuation correction (Chang 0) and regional striatal analysis for extraction of count densities and determination of specific uptake ratios will be reviewed during the technical center visit.

5.2 Scan Identification

Each set of subject data transferred to the imaging core lab will be identified in the following manner:

-3 digit center code followed by 4 or 5 digit subject number followed by the scan visit number:

- Screening = 1
- Month 12/Visit 04 = 2
- Month 24/Visit 06 = 3
- Month 48/Visit 10 = 4
- Month 36/Visit 08 = V08 (for Prodromal only)

- Premature Withdrawal = PW
- Symptomatic Therapy = ST
- Unscheduled = U01, U02, etc.

Example for the Month 24/Visit 6 scan for subject number 1455 acquired from center 023 will be identified as “0231455_3”. If a subject skips a scan (i.e. does not have a scan performed at Month 12/Visit 4), label the scan according to the actual visit.

Please note: Please refer to the Schedule of Activities for an outline of the study visits.

5.3 Study Data Archiving

ALL SPECT raw and reconstructed study data should be archived prior to transfer to the Core Lab. These represent source data. The method of archiving should follow the center-specific Standard Operating Procedures (SOPs). Additionally, all study related source documentation should be maintained in the appropriate section of the Study Binder. All queries and/or correspondence will also need to be maintained and filed in the Technical Study Binder. All study documentation and SPECT data must be retained by the center in accordance with the protocol.

6. DATA TRANSFER

Individual center issues regarding transfer of image data will be addressed at the technical set up visit. Each center will be provided with transfer instructions. If necessary, the imaging core lab representative will assist the center in the implementation of transfer procedures. **It is recommended that image files be in DICOM3 format, although native scan format is also acceptable.** For each scan, and depending upon the camera manufacturer, the following files should be submitted to the core lab:

- 1) DaTSCAN subject: raw projection data
- 2) DaTSCAN subject: reconstructed image files

Using the procedures detailed in the previous section, the center should record the data to be sent on the scan acquisition document and data transfer documents (Figure 3 and 4). These documents should be sent to the imaging core lab. Receipt of the documents at the imaging core lab serves to notify the imaging core lab team that data have been electronically transferred. The imaging core lab will then review the imaging data against what was received to check for the presence of all expected data. All data will be interrogated for accuracy and completeness using a standard quality assurance procedure. If there is a problem with the data file sent, an imaging core lab representative will contact the center staff. Depending upon the nature of the problem, the resolution may involve simple provision of additional information, the resend of one or more image data files, or other action to ensure the completeness of the image data files.

7. STUDY TECHNICAL DOCUMENTATION

The key to technical documentation is the **technical binder**. It is recommended that the Nuclear Medicine group maintain the technical binder as a single source of information about the imaging aspects of the study, including recording when phantoms are acquired, QC changes, software upgrades, individual scan information sheets, etc. In addition, the technical binder serves as a reference document for the center summarizing all technical procedures for the study.

The technical binder contains the following:

- Contact information
- Technical Operations Manual
- Camera QA Event Log forms
- Instructions for completion of Camera QA Log
- SPECT Scan Acquisition Documents with instructions for completion
- sFTP server, user, and password information
- SPECT Imaging Data Transfer Information Documents
- Center specific subject numbering protocol
- Core Lab communications section for maintaining records of all communication with the Core Lab

The binder will be provided to each center at the technical center set-up visit along with instructions for maintenance of the technical source documents.

8. COMMUNICATION WITH IND AND TROUBLE-SHOOTING PROBLEMS

The description of the imaging data flow underscores the complexity of the trial and highlights the need for timely and efficient communication. All imaging data will be reviewed and the Data Receipt Form will be emailed back to centers. Any queries with the data will be directed to the Nuclear Medicine group at the center based on discussion during the technical center visit. *ANY* questions regarding the technical conduct of the trial, from issues around the receipt of radiopharmaceutical, to camera set-up, subject and phantom scan acquisition, image processing, file creation and transfer, etc are appropriate to direct to IND.

PPMI Imaging Core, Project Manager

Nichole Daegele

60 Temple Street, Suite 8B
New Haven, Connecticut 06510
USA

Telephone: +01 203 401 4367

Facsimile: +01 203 401 4304

Email: ndaegele@indd.org

Additional Personnel:

Principal Investigator (Neurology)

Kenneth Marek, MD

Tel: +01 203 401 4300

Fax: +01 203 401 4301

Email: kmarek@indd.org

Co -Principal Investigator (Nuclear Medicine)

John Seibyl, MD

Tel: +01 203 401 4300

Fax: +01 203 401 4301

Email: jseibyl@indd.org

For all technical questions, camera, image processing and file-naming contact:

Karen Johnson

Imaging Quality Control & Processing Specialist

Telephone: 203-508-1523

Fax : 203-401-4303

Email: kjohnson@indd.org

For file transfer questions, contact

Denise Jesko

Imaging Coordinator

Telephone: 203-401-4339

Fax: 203-401-4303

Email: djesko@indd.org

For questions concerning completion of the forms, or if you need more supplies, please contact:

Lindsay Hubbell

Data Coordinator

Telephone: 203-508-1542

Fax: 203-401-4303

E-mail: lhubbell@indd.org