



# SPECT Technical Operations Manual

<b>Document Version</b>	Final v4.0; 27-Jul-2021
<b>Sponsor for PPMI Main Study</b>	Michael J. Fox Foundation
<b>Main Study</b>	
Protocol Identifier	002
Protocol Version	Version 1.2; 01-Feb-2021
Protocol Description	The Parkinson's Progression Markers Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort
<b>Sponsor for Companion Study</b>	Michael J. Fox Foundation
<b>Companion Study</b>	
Protocol Identifier	004
Protocol Version	Version 2; 19-Jun-2020
Protocol Description	Early Longitudinal Imaging in Parkinson's Progression Markers Initiative Using [ <sup>18</sup> F] AV-133 and DaTscan™ (PPMI Early Imaging 2.0)

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**Document Title**            SPECT Technical Operations Manual

**Document Version**        Final v4.0; 27-Jul-2021

**Protocol Identifier**        002

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**Document Title**      SPECT Technical Operations Manual  
**Document Version**    Final v4.0; 27-Jul-2021  
**Protocol Identifier**    002

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## Table of Contents

<b>1</b>	<b>Overview</b>	<b>6</b>
1.1	Purpose of the Technical Operations Manual	6
1.2	Trial Design	6
1.3	General Requirements	7
1.3.1	Imaging Center Compliance	7
1.3.2	Schedule of Assessments	8
1.3.3	SPECT Image Data Submission Timelines	10
<b>2</b>	<b>Imaging Center Set-up</b>	<b>10</b>
2.1	Technical Assessment Questionnaire	11
2.2	Technical Site Training	12
2.2.1	Physical (On-site) Technical Site Set-up	12
2.2.2	Remote Technical Site Set-up	12
2.3	Approval to Scan	13
<b>3</b>	<b>Technical Binder</b>	<b>13</b>
<b>4</b>	<b>Scan Identification (Naming Convention)</b>	<b>13</b>
<b>5</b>	<b><sup>123</sup>I-DaTscan™ Radiotracer Information</b>	<b>14</b>
5.1	<sup>123</sup> I-DaTscan™ Dose Ordering	14
5.2	<sup>123</sup> I-DaTscan™ Dose Preparation	15
5.3	<sup>123</sup> I-DaTscan™ Dose Administration	15
<b>6</b>	<b>SPECT Imaging Overview &amp; Procedures</b>	<b>15</b>
6.1	<sup>123</sup> I- DaTscan™ Imaging Protocol	15
6.2	<sup>123</sup> I-DaTscan™ Reconstruction Protocol	16
<b>7</b>	<b>Participant Safety and Adverse Events</b>	<b>16</b>
<b>8</b>	<b>Image Data Archiving and Submission</b>	<b>17</b>
8.1	Data Submission Checklist	17
8.2	Previously-Acquired Scan Submission	17
8.3	Image Data Submission	18
8.4	iPACS Submission Form Comments Section	23
8.5	Scanner QC & Maintenance Documentation	23
8.6	QC and Query Resolution Process	23
8.7	Archiving Instructions	25
<b>9</b>	<b>QC &amp; Calibrations</b>	<b>26</b>
9.1	Scanner Quality Assurance	26
9.2	Dose Calibrator	26
9.3	Phantom Data	26

<b>10 SPECT Scanner Replacement or Upgrades .....</b>	<b>27</b>
<b>11 Supporting Information .....</b>	<b>28</b>
11.1 Invicro Contacts.....	28
11.2 TOM Amendment History.....	29
11.3 Abbreviations.....	30
<b>12 Appendices.....</b>	<b>31</b>
12.1 Appendix 1: Imaging Parameter Specifications .....	31
12.2 Appendix 2: PPMI Clinical Submission Form (Example) .....	32
12.3 Early Imaging 2.0 Submission Form (Example).....	34
Table 1: Schedule of SPECT Assessments for Main Study (Protocol 002).....	9
Table 2: Schedule of SPECT Assessments for Companion Study (Protocol 004) .....	10

## 1 Overview

The Imaging Core Lab is Invicro, a Konica Minolta Company (Invicro) based in New Haven, Connecticut, USA. In conjunction with the study sponsor, Invicro will provide the imaging center with any technical support necessary to ensure optimal imaging is achieved. Invicro will be responsible for imaging center evaluation, qualification, and training as well as, receipt, quality control (QC), query, and data management of single-photon emission computerized tomography (SPECT) imaging data.

Participating clinical site imaging centers will acquire images according to the trial-specific process standards detailed within this manual. Imaging centers will submit images and corresponding data (image data) to Invicro using iPACS, as the preferred method. iPACS enables the secure, controlled, and efficient submission of image data, in addition, to serving as the portal for query resolution. Before data from participants may be acquired, Invicro will train each imaging center on the image acquisition requirements, and the image data submission and query resolution processes.

### 1.1 Purpose of the Technical Operations Manual

Invicro has published this Technical Operations Manual (TOM) to instruct imaging centers in the following areas:

- Imaging center set-up procedures
- Image acquisition guidance (required image acquisition schedule, tracer, administration, and recommended techniques)
- Archiving of images and corresponding data
- Submission of image data to Invicro
- Query receipt and resolution process

**Note: For more information about the clinical trial, please request a copy of the current clinical trial protocol from your respective clinical trial site team.**

### 1.2 Trial Design

#### 1.2.1.1 Main Study

The main study (protocol 002) is a longitudinal, observational, multi-center study to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of Parkinson's Disease (PD) progression. The study population will include participants with manifest PD, prodromal PD, and healthy controls. The study is designed to identify markers of disease progression of PD for use in therapeutic development.

The PPMI Clinical study will include up to 4,500 participants at up to 50-55 international clinical sites. Participants will be in one of the following cohorts:

- Current PPMI 001 participants will be divided into the following cohorts:
  - Healthy Control
  - PD
  - Prodromal
- Newly enrolled PPMI Clinical participants will be divided into the following cohorts:
  - Healthy Control
  - PD
  - Prodromal

During the PPMI Clinical main study (002), participants will receive up to 6 single-photon emission tomography (SPECT) scans with DaTscan™, depending on the cohort designation. DaTscan SPECT scans will be used to evaluate eligibility for newly enrolled participants in the PPMI Clinical study and in the evaluation of imaging biomarkers for disease progression.

#### 1.2.1.2 Companion Study (004)

The companion study (protocol 004) is a longitudinal, multi-center study to assess progression of DaTscan and [<sup>18</sup>F] AV-133 imaging in PD participants for at least 18 months. Approximately 50 PD participants from the main study will be recruited from up to 5 clinical sites. All participants will be comprehensively assessed at baseline and every 6 months thereafter.

For the companion study (004), participants will have up to 3 DaTscan™ SPECT scans, depending on if the participant is transitioning from PPMI 001 to PPMI Clinical or newly enrolled in PPMI Clinical. DaTscan SPECT scans will be used to evaluate the predictive value of early imaging.

***Please Note: The algorithm used for eligibility determination is dependent on cohort designation, therefore it is imperative to correctly note a prospective participant's cohort when imaging is acquired, and imaging data are submitted.***

## 1.3 General Requirements

### 1.3.1 Imaging Center Compliance

- **Responsibilities:** Each imaging center is responsible for the following activities.
  - Always ensure consistent scan parameters and that the approved scanner is used for all participant assessments. Ideally, the same scanner is used for all assessments within and across all participants.
  - Acquire images according to the trial-specific process standards within and according to the protocol's Schedule of Assessments. Image acquisition and documentation should not deviate from the clinical trial protocol but may be different from your regular clinical 123-I Ioflupane SPECT imaging protocol. Please follow the procedures described in the TOM

exactly. **All SPECT scans must be submitted to Invicro within 24 hours.**

- Respond promptly to queries generated by Invicro within 24 hours for Screening scans, and 5 days for all other time points.
- Confirm that all technologists or other personnel who will be performing scans for this protocol are properly trained on the study-specific acquisition and reconstruction parameters, as well as, data submission and query handling procedures.
- **Regulatory compliance:** All site personnel must comply with the International Council for Harmonization E6(R2) guidelines on Good Clinical Practice (GCP) when documenting acquisition, archiving images, and submitting image data to Invicro.
- **Confidentiality:** Follow regional privacy practices to de-identify (ie, redact) all participant information (name, medical record number, etc) before submitting image data to Invicro. Image data submitted to Invicro via the iPACS system will automatically undergo de-identification.

### 1.3.2 Schedule of Assessments

Your imaging center may scan the first participant following completion of all training and approval requirements and confirmation of site activation from the Site Management Core. After the scans from the first participant are approved, scanning for the remainder of the participants may begin according to the protocol Schedule of Assessments as summarized in [Table 1](#) and [Table 2](#).

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

Scan	Healthy Control <sup>a,b</sup>	PD <sup>a,b</sup>	Prodromal <sup>a,b</sup>
Screening Scan <sup>c,d</sup>	X	X	X
Visit 04 (12 months) <sup>e</sup>	-	X	X
Visit 06 (24 months) <sup>e</sup>	-	X	X
Visit 10 (48 months) <sup>e</sup>	-	X	X
Premature Withdrawal (PW) <sup>f</sup>	-	X	X
Diagnostic Visit <sup>g</sup>	-	-	X

<sup>a</sup> Cohorts include participants newly enrolled in PPMI Clinical and participants transitioning from PPMI 001. Newly enrolled participants in PPMI Clinical will start with the Screening Visit. Participants transitioning from PPMI 001 to PPMI Clinical will not have a screening DaTscan, and these participants will start at the equivalent visit in PPMI Clinical from the PPMI 001 schedule.

<sup>b</sup> Participants may not have the following drugs within 6 months of the Screening visit: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine.

<sup>c</sup> A previously-acquired screening DaTscan™ image may be used if the scan was acquired within 6 months of the study scheduled DaTscan™ Screening visit, and meets criteria of the Imaging Core Lab to accept the scan for use.

<sup>d</sup> DaTscan™ screening imaging appointments will occur within 60 days prior to Day 1.

<sup>e</sup> DaTscan™ imaging will occur within ±45 days either side of the Target Visit Date.

<sup>f</sup> If a participant withdraws from the study and agrees to attend one more visit, the next scheduled annual visit should be completed. DaTscan™ imaging will be performed if not done in the previous 6 months.

<sup>g</sup> If the next planned visit is an annual study visit, this diagnostic visit will take the place of the next annual visit. The participant will undergo all assessments scheduled for that annual visit. If not already scheduled as part of that visit, or not completed in last 6 months, DaTscan imaging will be added. Annual visits are nested within the “Other SPECT Imaging Timepoint” selection option when submitting the data to Invicro in iPACS.

**Table 2: Schedule of SPECT Assessments for Companion Study (Protocol 004)**

Scan	Transitioning participants from Early Imaging 1.0 <sup>a</sup>	Newly enrolled participants for Early Imaging 2.0 <sup>a</sup>
Visit 02 (6 months)	X	X
Visit 04 (12 months)	X	-
Visit 05 (18 months)	X	X
Premature Withdrawal	X	X

<sup>a</sup> PD participants transitioning from Early Imaging 1.0 and newly enrolled in Early Imaging 2.0 will be recruited to the Early Imaging 2.0 protocol (004). Participants transitioning from PPMI 001 to PPMI Clinical will continue from the PPMI 001 study schedule into the next planned study visit under PPMI Clinical.

<sup>b</sup> If a participant withdraws from the study and agrees to attend one more visit, the next scheduled annual visit should be completed. DaTscan™ imaging will be performed if not done in the previous 3 months.

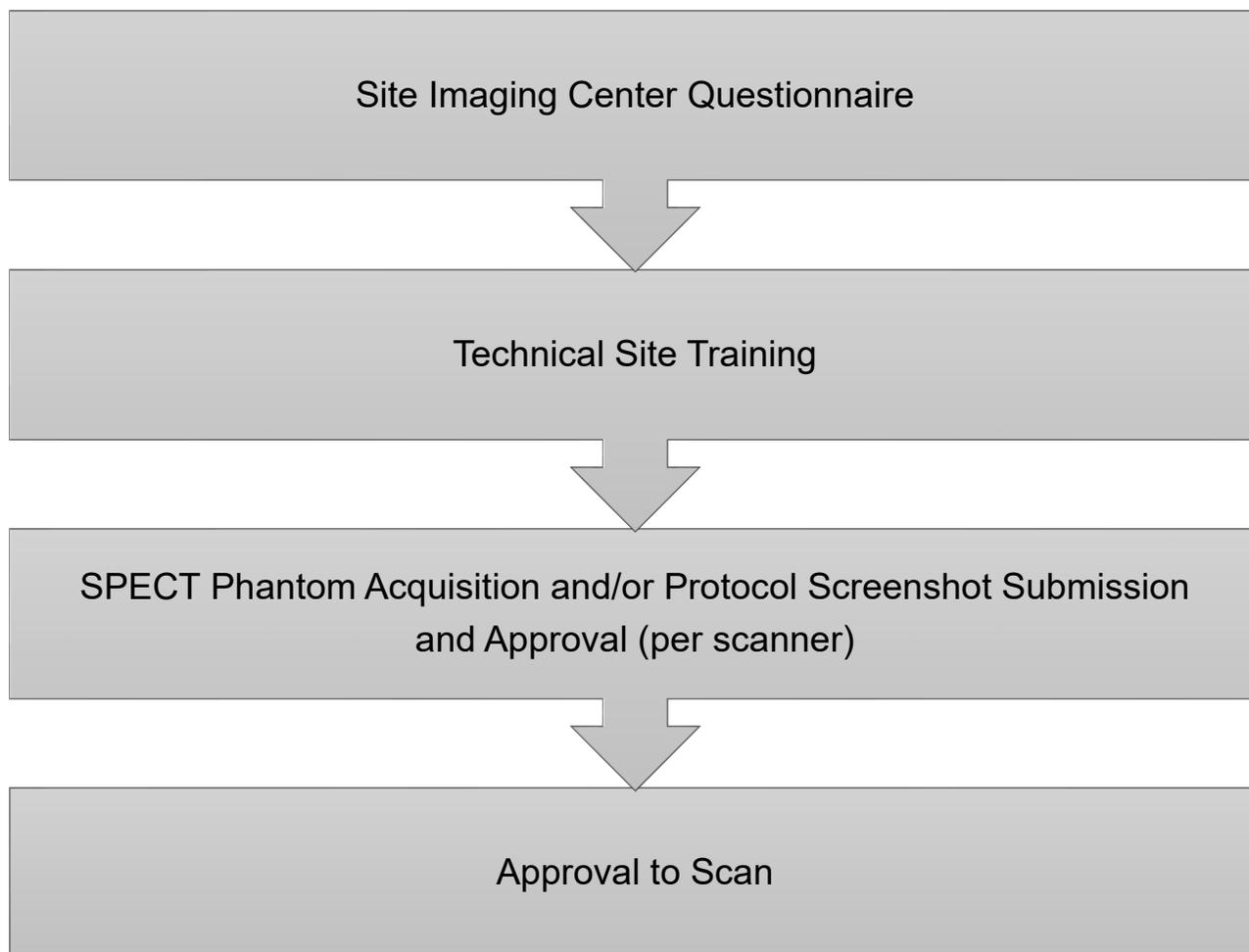
### 1.3.3 SPECT Image Data Submission Timelines

- The screening DaTscan™ SPECT scan report will be used by the clinical imaging center to assess new enrolled participant's eligibility for entry into the study. **It is therefore paramount that the <sup>123</sup>I- DaTscan™ SPECT data and corresponding imaging forms are transferred to Invicro within 24 hours of image acquisition.**
- Notification of applicable visual assessments and quantitative analyses data for eligibility will be provided to Blackfynn within 3-5 business days of receipt of the image data (with all queries addressed). Blackfynn will confirm whether a participant meets the SPECT eligibility (ie, eligible or not eligible) to the site.
- Subsequent <sup>123</sup>I-DaTscan™ SPECT scans and corresponding imaging documents must be submitted to Invicro within 24 hours of image acquisition.

## 2 Imaging Center Set-up

Participating imaging centers will be required to complete Invicro's set-up procedures prior to conducting study participant imaging. The purpose of these procedures is to ensure each imaging center participating in the study meets the high level of standard required by Invicro and the study sponsor, provide technologists and supporting staff with training on study imaging requirements, assess the performance of the imaging equipment to be used for the study, and ensure the protocols to be followed for participant imaging are properly established. These measures help assure the robustness and poolability of quantitative DAT imaging across imaging sites and cameras.

The following procedures are included as part of set-up:



## 2.1 Technical Assessment Questionnaire

The initial step in the set-up process is the center's completion of a technical assessment questionnaire. This form provides Invicro with contact information for key individuals, address information, specific scanner and computer system capabilities, and other specifications necessary for satisfactory completion of the study. Invicro will provide a brief overview of the set-up process to the site and imaging center at the time of sending the questionnaire.

The completed questionnaire is reviewed by Invicro for initial assessment of the imaging center's technical capabilities. If the center meets the technical standards required to perform as a participating center, Invicro 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.

In certain cases where Invicro has recently worked with or is currently working with an imaging center on another study and has already collected a questionnaire, the requirement for the center to complete a new questionnaire may be waived.

## 2.2 Technical Site Training

### 2.2.1 Physical (On-site) Technical Site Set-up

In instances where an imaging center has not worked with Invicro on a recent or concurrent trial, a physical (on-site) visit may be required. For such instances, a representative of Invicro will visit the SPECT imaging center to conduct the technical site training. This visit is typically performed in 2 sessions over one day.

The initial session entails a meeting among the imaging center staff, the clinical site personnel, and an Invicro set-up specialist. During this meeting the overall objectives and rationale for the imaging component of the clinical trial are reviewed. Individual responsibilities for obtaining the imaging measures and a walk-through of the communication flow, logistics, and potential problems (eg scanner availability, etc.) at the site are discussed and questions addressed.

The second part of the Physical Technical Site Set-Up Visit involves the Invicro set-up specialist and the nuclear medicine team or technologist. The session begins with a review of the normal clinical operations relating to scanner access, patient flow, and standard Quality Assurance (QA)/QC practices for the SPECT system. An acquisition protocol for use in the study is established on the SPECT scanner's acquisition computer, and an Invicro supplied phantom is acquired using the study-specific acquisition parameters.

### 2.2.2 Remote Technical Site Set-up

In instances where a SPECT imaging center has worked or is currently working with Invicro on a recent or concurrent trial, a physical set-up visit may not be necessary, and depending on study requirements, Invicro may conduct the imaging center qualification via a web-based portal training module in lieu of the physical visit.

Training for remote site setups will occur through a web-based learning module. Invicro will distribute user specific accounts to relevant clinical and imaging staff, providing access to the training portal. The web-based training portal provides users with study reference material, and a study-specific slide presentation covering overall study objectives, imaging timepoints and requirements, modality specific parameters, tips to avoid queries, and a walk-through of the electronic data transfer process.

In addition, imaging centers will be required to build the study-specific protocol in their SPECT scanner and submit screenshots of the relevant acquisition and reconstruction parameters to Invicro for review and approval.

***Please note, at least one primary staff member (technologist, physicist, or physician) responsible for the conduct of study imaging must be trained by Invicro. It is the responsibility of the imaging center to ensure all additional personnel are trained peer-to-peer by the primary staff member initially trained by Invicro and are supplied with a copy of this imaging manual, as well as all other study materials. All additional training activities must be documented, with***

*a copy of this training documentation provided to the referring clinical site(s). Please contact Invicro for assistance with additional training or questions.*

### 2.3 Approval to Scan

Following completion of the technical set-up procedures, an 'Approval to Scan' notification and a detailed technical site set-up report summarizing the dose, acquisition and reconstruction parameters, image archival, and the approved method of image transfer will be sent to the imaging center, with a copy to the clinical site and sponsor designees. The approval notification and technical report should be archived.

*Please Note: This 'Approval to Scan' notification indicates that the imaging center is now ready to scan their first study participant.*

## 3 Technical Binder

The imaging center will receive a link to an electronic technical binder containing all essential imaging study documents including, but not limited to, a copy of this TOM, the training presentation, radiopharmaceutical information, and key Invicro contact information. These documents are to be printed and made available to any staff which will need access to this information. Additionally, Invicro recommends each imaging center file all study documents that have been submitted, and all study related communications (eg, emails or faxes).

*Please Note: Study related documents may be updated throughout the trial and will be distributed to your imaging center.*

## 4 Scan Identification (Naming Convention)

It is very important that the imaging center uses a standard file naming convention so that all scans can be easily identified by Invicro. The participant naming convention will be provided by the clinical site personnel when scheduling the SPECT visit.

In this study, participants will be assigned a Site Number and a unique Subject ID number that must be included on the submission form. The Site Numbers in this study are comprised of 3 digits. Participants transitioning from PPMI 001 to PPMI Clinical will maintain the previously assigned 4 or 5-digit Subject ID. Participants newly enrolled in PPMI Clinical will be assigned a 6-digit Subject ID.

*Please note: the 4, 5 or 6-digit Subject ID number should be populated in both the Participant Name and ID fields with the Date of Birth populated with 01-Jan-1970 when setting up an acquisition on the scanner or during the de-identification of the scan file.*

## 5 <sup>123</sup>I-DaTscan™ Radiotracer Information

For this study, <sup>123</sup>I-DaTscan™ is used to determine participant eligibility and to provide assay of striatal dopamine transporter binding using SPECT brain imaging to assist in the evaluation of adult participants with suspected Parkinsonian syndromes (PS).

### **Important Reminders for all sites:**

- <sup>123</sup>I-DaTscan™, is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration. Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings, and handled with strict adherence to local regulations.
- The responsible physician or designee at the SPECT imaging center will confirm the participant's suitability for undergoing the SPECT imaging study.
- For women of childbearing potential (including those who have had a tubal ligation), a urine or blood pregnancy test will be conducted within 24 hours before the SPECT scan. The result must be negative for the participant to receive the DaTscan™ tracer.
- Obtain and record participant's weight at each visit.
- Fasting is not required for SPECT scans in this study.



**Follow your facility's standard processes for documentation of information regarding the participant and scan procedure. Information requested by Invicro during the submission process will include, but is not limited to, participant weight, dose activity assays, times of assays, date and time of injection and date and time of scan. An example of the electronic data submission form with requested information is provided in the appendices of this document.**

### 5.1 <sup>123</sup>I-DaTscan™ Dose Ordering

To order a DaTscan™ dose, the study-specific prefilled Dose Order form supplied by the Invicro Supply team via email must be completed and emailed or faxed to GE Healthcare via the email address or number indicated on the Dose Order form. A confirmation email will be sent from GE Healthcare once the dose order is processed.

Also noted on the Dose Order forms are the days of availability and lead times for dose orders and cancellations. The Imaging center staff should be aware of days of availability and approximate time of dose delivery to facilitate scheduling with the clinical staff.

The DaTscan™ vendor will be responsible for ensuring the imaging centers have their RAM license and/or other applicable licenses to allow the center to accept DaTscan™.

## 5.2 <sup>123</sup>I-DaTscan™ Dose Preparation

The <sup>123</sup>I- DaTscan™ dose may be provided to the imaging center in either a unit dose syringe or a single or multi-dose vial. It is the responsibility of the imaging center to ensure that they have the necessary equipment for radiopharmaceutical injection (including syringe shields and in some cases the equipment necessary to draw doses from vials).

## 5.3 <sup>123</sup>I-DaTscan™ Dose Administration

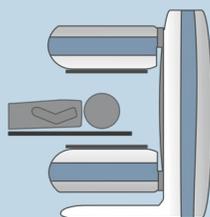
Participants should be pretreated with a thyroid blocking agent (eg, saturated solution of potassium iodide (SSKI)) prior to the administration of the radiotracer. Participants who are allergic or sensitive to iodine will be administered potassium perchlorate (400 mg) rather than the potassium iodide solution.

The required DaTscan™ dose for this study protocol is 3-5 mCi (111-185 MBq), administered as a slow intravenous injection (over approximately 20 seconds) through an indwelling catheter followed by an infusion line flush of 15-20 mL of normal saline. Do not exceed a dose of 5 mCi (185 MBq) and do not use when the activity is below 3 mCi (111 MBq).

For accurate determination of the amount of activity injected, the syringe is assayed prior to and immediately following injection with the assay amounts and times recorded in the appropriate fields when uploading through the web submission portal.

# 6 SPECT Imaging Overview & Procedures

## 6.1 <sup>123</sup>I- DaTscan™ Imaging Protocol



**Images will be acquired using a gamma camera that is capable of performing SPECT imaging. The required start time for imaging to commence is 4 hours (+/- 30 minutes) post DaTscan™ injection. Invicro will determine and approve the parameters to be used for this study as part of the set-up procedures prior to participant imaging.**

### *Participant positioning:*

- The participant should be informed about the total acquisition time and positioned for maximum comfort.
- The participant's head should be placed in the appropriate head holder and the 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. Since routine viewing software allows

correction of minor obliquities of head orientation, the participant's comfort (which reduces the probability of motion during acquisition) is more important than perfect alignment of the head.

- The participant should be told of the necessity to avoid (voluntary) movements of the head and asked for her/his active cooperation and be immobilized per standard procedures for brain imaging.
- In order to optimize image quality, detector heads should be as close as possible to the participant with a target radius of 15 cm. Record the actual radius utilized for imaging.

### **Acquisition protocol:**

As a general protocol, raw projection data, will be acquired into a 128x128 matrix with low-energy high resolution (LEHR) parallel hole collimators using a circular step and shoot mode with each step moving 3 degrees for a total of 60 projections per detector (180 degrees rotation per detector) for dual head systems, 30 seconds per projection, with a 20 % energy window centered on 159 keV (+/- 10 %), and an acquisition zoom of 1.23. Attenuation correction using low dose CT may be utilized when available and will be performed in accordance with local standard procedures.

### **Scanning procedure:**

- Approximately 3.5 hours post injection, have the participant void, and position the participant in the scanner
- Ensure the entire brain is within the FOV and that the participant is immobilized and comfortable
- If applicable, perform the CT for attenuation correction matching the SPECT coverage, before or after the emission acquisition, as per institutional guidelines
- Begin the SPECT scan 4 hours post injection (targeting  $\pm$  30 minute)
- Scan the participant using the acquisition protocol reviewed and approved by Invicro
- The following image data will be submitted to Invicro: SPECT projection, reconstructed and CT (if applicable) image data

## **6.2 <sup>123</sup>I-DaTscan™ Reconstruction Protocol**

The imaging center will reconstruct the SPECT images using their standard clinical DaTscan™ scan reconstruction. The Imaging Core Lab will also reconstruct the images using a standard iterative reconstruction algorithm and then correct them for attenuation.

## **7 Participant Safety and Adverse Events**

Each participant needs to be monitored for adverse events (AEs) while they are at the imaging center, as well as by phone 2 to 3 days following the scan. An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

The clinical site principal investigator (PI) is responsible for reporting AEs according to the AE reporting procedures described in the study protocol. Although not anticipated to happen frequently, AEs may occur during the participant's visit to the imaging center, and therefore, it is very important for the imaging centers to contact their respective clinical study site personnel immediately (ie, PI or study coordinator) if they become aware of any AEs during the imaging procedures. The clinical study coordinator should be contacted by phone and the time of that call documented along with specific information related to the adverse event.

***Please Remember: Archive the original document completed for the adverse event in the Technical Binder and send a copy to the clinical coordinator.***

## 8 Image Data Archiving and Submission

### 8.1 Data Submission Checklist

All imaging metadata and data files should be sent through iPACS. Modality specific electronic submission forms are required to be completed within iPACS for each data submission. Please reference Section 12.2 of this document, and the clinical protocol for details on the Schedule of Assessments.

Steps for image data submission:

- Uploaded Image Files (SPECT Projection, reconstructed and CT (if applicable) image data)
- Completed information contained in the iPACS submission form
- Prior to submission, scans should be assessed for completeness, artifact and/or participant motion and any relevant information documented accordingly in the iPACS submission form.

***Please Note: Correct reporting of the Subject ID and Cohort Designation in the submission form are critical for participant eligibility processing.***

### 8.2 Previously-Acquired Scan Submission

Previously-acquired DaTscan SPECT imaging for screening for Protocol 002 may be used if the scan was acquired within 6 months of the study scheduled DaTscan Screening visit and meets protocol acquisition standards.

A previously-acquired DaTscan SPECT scan that has already been submitted to Invicro for another study, that meets the requirements for inclusion, will not need to be re-submitted through the iPACS portal. However, sites will need to complete a *PPMI Request for Previously-Acquired DaTscan* form for the DaTscan imaging and provide it to the IND Site Management Core (SMC). This information will then be provided to Invicro.

A previously-acquired DaTscan SPECT scan that is not already in Invicro's database will need to be submitted through the iPACS portal and labeled as "Previously-Acquired / Screening" on the iPACS submission form.

A DaTscan SPECT scan that is acquired for two studies, and is not currently in the Invicro database, that meet the requirements for inclusion (including participant consent for both studies), will be submitted to the PPMI Clinical database through the iPACS portal and labeled as “Screening” on the iPACS submission form. Sites will also need to provide the other study’s Subject ID and site number. This information can be provided to Invicro Project Management through email.

### 8.3 Image Data Submission



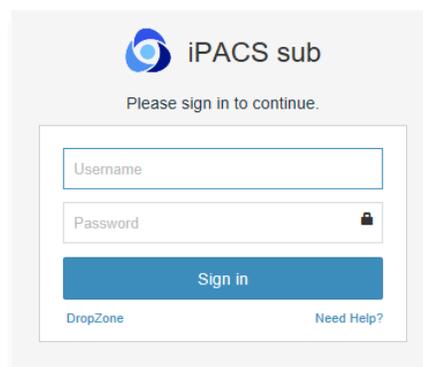
Imaging data will be transferred to Invicro using the iPACS web submission portal. Invicro's portal uses an electronic transmittal form to capture all relevant scan information, and programmatically de-identifies images in DICOM format during upload. Invicro will provide each user at the imaging site with a unique username and password to access Invicro’s iPACS web-based upload tool. In the event there are questions regarding the submission you may be contacted by a member of the Invicro team.

Follow the steps outlined below to perform an iPACS data submission:

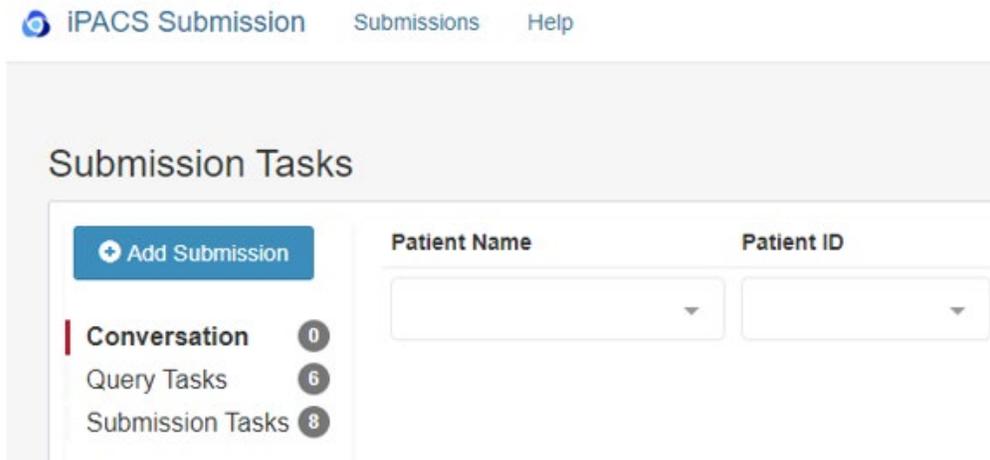
**1 Access** the submission portal using the web address provided below:

<https://corelab-submission.ipacs.invicro.com/>

**2 Log in:** a unique username and password is provided to personnel responsible for data submission.

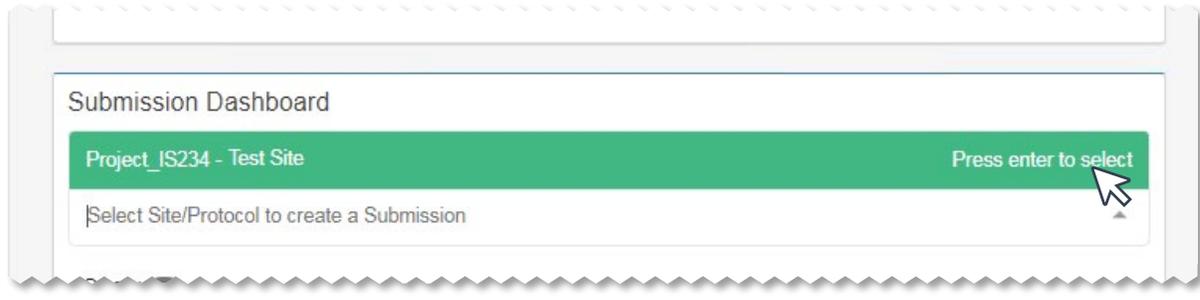


**3** Upon successful login, you will be directed to the Submission Dashboard. Click **Add Submission** to create a new submission.



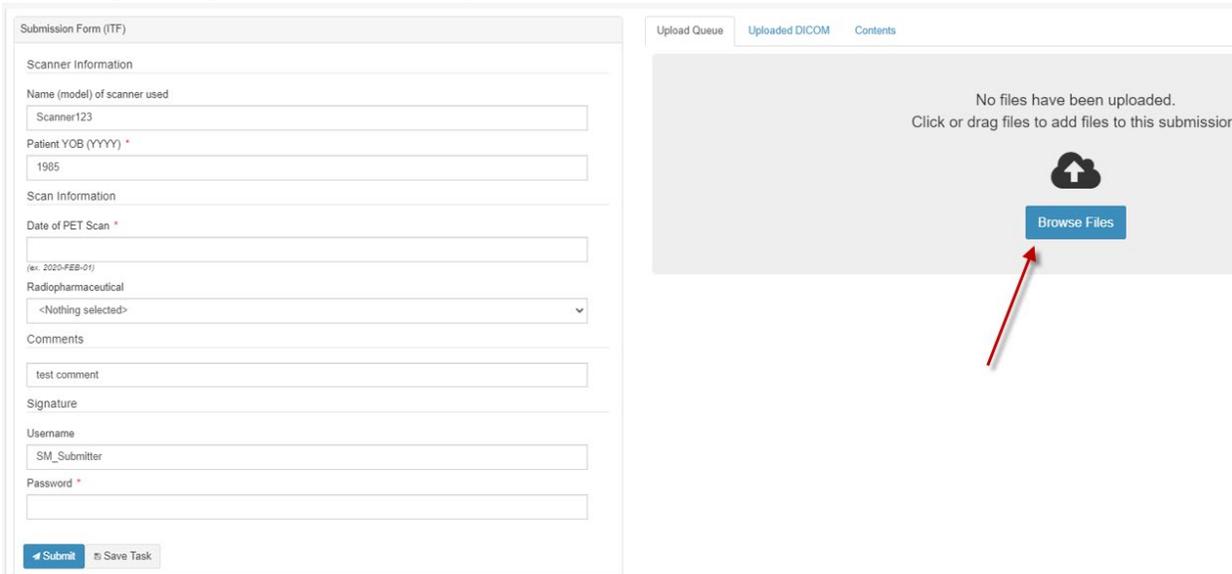
The screenshot shows the top navigation bar with 'iPACS Submission', 'Submissions', and 'Help'. Below is a 'Submission Tasks' section. On the left, there is a blue 'Add Submission' button. To its right are two dropdown menus labeled 'Patient Name' and 'Patient ID'. Below these are three task categories: 'Conversation' with a count of 0, 'Query Tasks' with a count of 6, and 'Submission Tasks' with a count of 8.

**4** Click on Site/Protocol to create a Submission dropdown listing and select the appropriate study/clinical site to submit under.



The screenshot shows a dropdown menu titled 'Submission Dashboard'. The selected item is 'Project\_IS234 - Test Site', which is highlighted in green. To the right of this item, the text 'Press enter to select' is visible with a mouse cursor pointing at it. Below the dropdown, there is a text input field with the placeholder text 'Select Site/Protocol to create a Submission'.

**5** The submission form will display a set of study and modality specific parameter fields to be completed. The file upload section is displayed on the right-hand side of the submission page for uploading of image data and other required documentation.



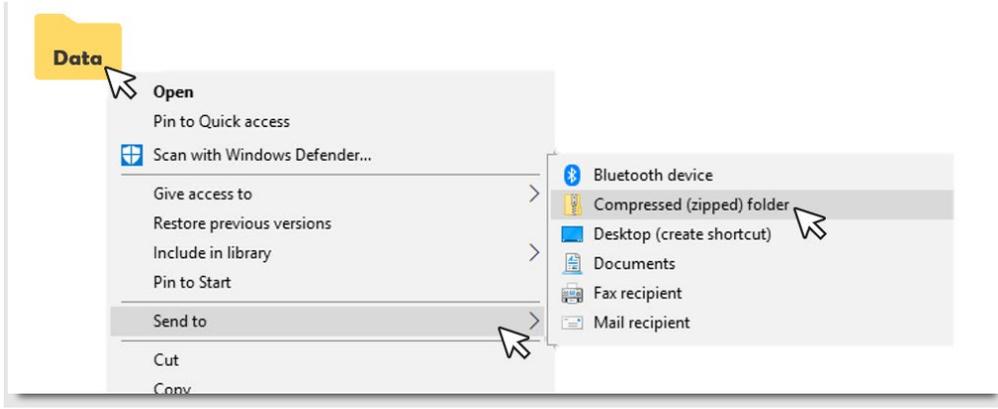
The screenshot shows two parts of the submission interface. On the left is the 'Submission Form (ITF)' with the following fields: 'Scanner Information' (Name (model) of scanner used: Scanner123, Patient YOB (YYYY) \*: 1985), 'Scan Information' (Date of PET Scan \*: empty, Radiopharmaceutical: <Nothing selected>), 'Comments' (test comment), 'Signature', 'Username' (SM\_Submitter), and 'Password \*'. At the bottom are 'Submit' and 'Save Task' buttons. On the right is the file upload section with tabs for 'Upload Queue', 'Uploaded DICOM', and 'Contents'. It displays the message 'No files have been uploaded. Click or drag files to add files to this submission.' and a 'Browse Files' button with an upload icon, which is highlighted by a red arrow.

**6** Fill in the submission form with the requested study-specific and modality information. Use the free text *Comments* field to provide any explanatory notes related to the data submission and acquisition procedures.

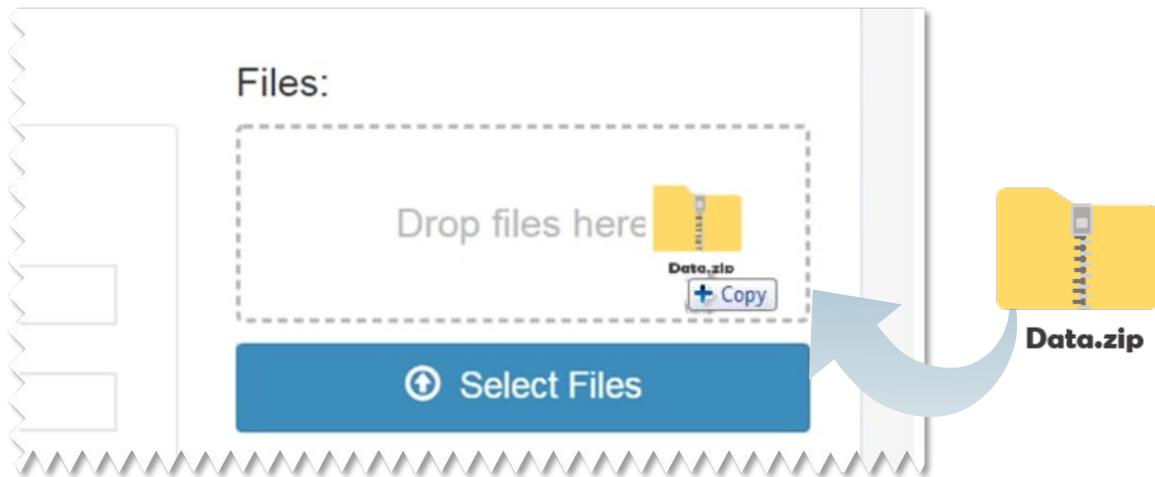
**Please Note:** It is very important that the correct cohort designation and visit number for each scan are entered in the submission form, as this determines the processing pipeline used for the scan. Participants enrolled in PPMI 001 will start at the equivalent visit in PPMI Clinical.

- **For the Main Study, current PPMI 001 participants will be divided into the following:**
  - **Healthy Control**
  - **PD**
  - **Prodromal**
- **For the Main Study, newly enrolled PPMI Clinical participants will be divided into the following:**
  - **Healthy Control**
  - **PD**
  - **Prodromal**
- **For the Companion Study (Protocol 004), there is only one cohort (PD)**

7 Prepare your image data folder for uploading into the submission form. Prior to uploading place your files in a compressed (zipped) folder.



8 Drag and drop the compressed zipped folder containing the files or click Select Files to search for and select the files for import.



9 To complete the submission, click on the **Submit** button. You will be prompted to enter your unique user password to complete the submission.

Signature \_\_\_\_\_

Username  
SM\_Submitter \_\_\_\_\_

Password \* \_\_\_\_\_

*In the event electronic submission is not available for the imaging center, physical shipment information will be provided on an as needed basis.*



**Upon completion of an iPACS submission, you will receive an auto-generated email notification from the corelab\_support inbox confirming successful transfer. The email will display a summary of the submission details. Please retain a copy of this email for your records and reference.**

**If you do not receive an email notification following submission, contact: [Corelab\\_Support@invicro.com](mailto:Corelab_Support@invicro.com)**

**For all other technical support related to iPACS and data submission, please, contact:**

**[Corelab\\_Support@Invicro.com](mailto:Corelab_Support@Invicro.com)**

#### 8.4 iPACS Submission Form Comments Section

A comments section is included in the iPACS submission form. This is a text-entry field where explanatory notes and useful information regarding the imaging procedure can be provided, for eg, justification for alternate imaging or parameter variations. Comments provided are reviewed during QC of the data and in some cases prevent the need for a query to be issued.

#### 8.5 Scanner QC & Maintenance Documentation

A scanner QC section is contained within the iPACS submission form. Utilize the provided fields to document recent routine preventative maintenance, software upgrades or repairs and QC checks performed.

Invicro should be notified in advance or immediately after any scanner events which may affect the performance of your SPECT scanner such as hardware/software upgrades, un-scheduled maintenance or repairs. In such circumstances, notify the Invicro study contacts provided in this TOM.

#### 8.6 QC and Query Resolution Process

Image data received at Invicro will undergo a rigorous quality inspection. QC checks will include the following, but not limited to:

- De-identification of all participants protected health information
- Accurate completion of the iPACS Submission form
- Completeness of image files
- Adherence to the imaging protocol and parameters approved by Invicro

Invicro will generate a query within iPACS should any question arise regarding the data submission.

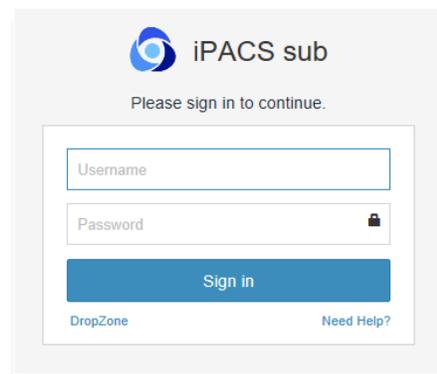
Respond to the queries promptly within 24 hours of receipt.

Depending upon the nature of the issue, the resolution of a query may involve simple provision of additional information, resending of one or more image data files, or other action to ensure the completeness of the image data files.

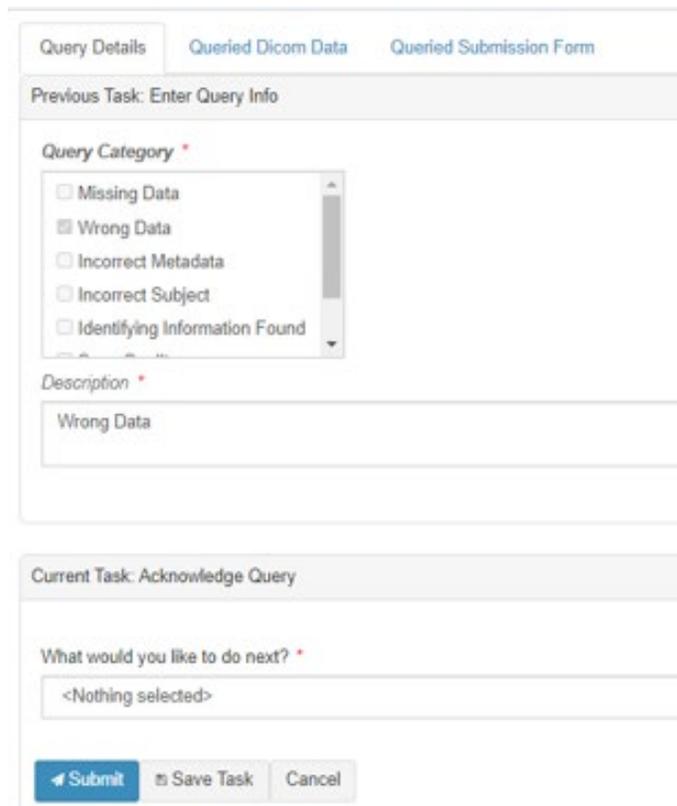
To resolve any issues that arise, Invicro will employ the query resolution process outlined below:

**1** You will receive an iPACS generated email notifying you a query has been issued on one of your data submissions. The email will include a link to the portal for resolution of the query.

**2** Log into the iPACS portal and navigate to the Submissions page. Queries will be listed in the Queries tab of the submission page.



**3** Select the query to be addressed and you will be brought to the **Respond to Query** page. The **Query Details** tab will show all queried categories and a description of the issue.



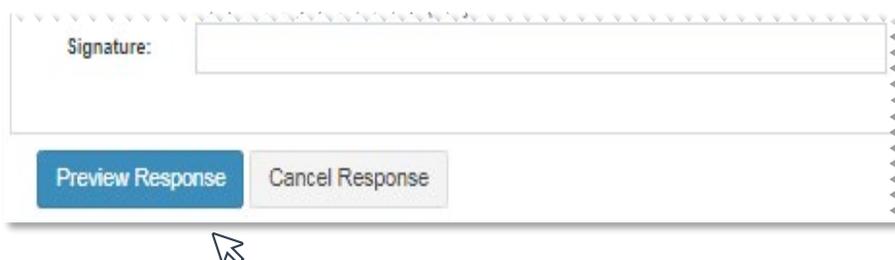
**4** Navigate to the bottom section with the heading, **Current Task: Acknowledge Query**. Under the **What would you like to do next?** section, choose **Edit Submission** to respond to the query from the drop-down list and then click **Submit**.

This action will bring you back to the **Submission Tasks** page. Click on **Submission Tasks**. Click on the queried submission and fill out the queried fields. You will once again be asked to authenticate the entry with your login password. Click on submit to re-submit the study to Invicro.

**5** Example of common query types and guidance to prevent/resolve queries:

Query type	Guidance to prevent/resolve queries
Time Point Verification	Ensure the correct visit is selected when submitting the data.
Incorrect Acquisition Protocol Followed	Take measures to minimize deviations to the approved imaging procedures and always utilize the acquisition protocol approved for use by Invicro. Provide explanatory comments within the Comments field.
Missing Series or Slices	Upload the missing data <i>within</i> the query form and provide a comment. Do not create a new submission.

**6** To complete the query, you will be requested to enter your iPACS password in the Signature field.



**7** Invicro will notify sites by email or phone if any outstanding queries are not resolved. Once Invicro has determined that the query has been sufficiently resolved, the query will be closed.

## 8.7 Archiving Instructions

In compliance with GCP guidelines (or regional requirements, whichever are a higher standard), maintain an archive of all image data in a readable format, using the same format that was submitted to Invicro.



**Retain the archived image data for 25 years after completion or discontinuation of the trial or per institutional guidelines, whichever is longer. Only after this period may documents be destroyed per local regulations. Please note, if the imaging center does not have the capability to archive the imaging data, Invicro requires that the data be saved for 30 days at minimum. Please contact Invicro if your center is unable to archive data for 30 days.**

## 9 QC & Calibrations

### 9.1 Scanner Quality Assurance

QC measures are to be performed according to the center and the camera manufacturer's standard procedures as implemented in the center's QC program for the SPECT camera and dose calibrator.

The SPECT camera should have and maintain up-to-date flood uniformity corrections (intrinsic and extrinsic) and center of rotation (COR) corrections. Invicro recommends that calibrations are to be completed on a schedule based on manufacturer recommendations and requirements. In addition, a daily  $^{57}\text{Co}$  flood scan should be done at the beginning of the day the scanning is to be completed. The  $^{57}\text{Co}$  flood scan should be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the quality of the SPECT scan the study participant's visit should be rescheduled. Verification that the daily QC scan has been performed should be documented on the iPACS submission form.

Software upgrades, changes in hardware and any other manipulations or changes to the imaging camera should be recorded on the iPACS submission form.

### 9.2 Dose Calibrator

QC of the dose calibrator should be performed throughout the course of the study. This typically will include daily constancy, quarterly linearity and annual accuracy tests.

### 9.3 Phantom Data

Invicro may request a phantom scan to be acquired on the SPECT scanner intended for use in the study as part of the initial set-up and qualification procedures or at any time throughout the course of a study. Phantoms may be requested if imaging centers are new to Invicro, an imaging center prefers to use a scanner which Invicro has not previously qualified, or the phantom data previously collected by Invicro does not meet the requirements of the study. Invicro may also request a phantom acquisition be performed should a qualified SPECT scanner undergo significant maintenance during the study, or if scanner performance issues are noticed during QC review of study participant data.

## 10 SPECT Scanner Replacement or Upgrades

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

## 11 Supporting Information

### 11.1 Invicro Contacts

**Note: When contacting Invicro please remember to indicate the following to ensure your inquiry can be addressed appropriately and expeditiously:**

- Protocol
- Site number
- Subject number (if applicable)

**For all questions related to iPACS image data transfer or technical account issues:**

[corelab\\_support@invicro.com](mailto:corelab_support@invicro.com)

**For all technical questions related to SPECT protocol set-up or image QC:**

**Andrea Perez**

Sr. Manager I, Imaging QC & Processing  
+1-203-401-4315 voice  
[aperez@invicro.com](mailto:aperez@invicro.com)

**For all other study related questions, including the request for credentials to upload images to iPACS or to check the status of an Independent review result:**

**Andrew Serrano**

Project Manager I  
+1-203-990-1638 voice  
+1-203-789-8037  
[aserrano@invicro.com](mailto:aserrano@invicro.com)

**Nichole Daegele**

Director, Project Management  
+1-203-401-4367 voice  
+1-203-789-8037 fax  
[ndaegele@invicro.com](mailto:ndaegele@invicro.com)

If shipping images on CD/DVD, you must use the **Invicro Fed Ex # 2295-4740-2** and **add the study Global ID # 006892 as the Reference** on the shipping bill.

## 11.2 TOM Amendment History

The table below is intended to summarize changes from the previous approved final TOM. Revisions or amendments to the protocol will not require an amendment to the TOM, unless substantive changes impact imaging methods.

Version	Version Date	Summary of Changes
Final v1.0	29-Apr-2020	Original
Final v2.0	28-Jul-2020	<ul style="list-style-type: none"> <li>Updated to add premature withdrawal visit Section 1.3.2 and Section 12 (Appendix 2)</li> <li>Updated to include Companion Study, Early Imaging 2.0 (Title Page, Section 1)</li> <li>Updated data submission process (Section 6)</li> <li>Editorial changes (global)</li> </ul>
Final v3.0	21-Oct-2020	<ul style="list-style-type: none"> <li>Updated to include previously-acquired DaTscan images (Protocol 002, Section 1.3.2)</li> <li>Added Previously-acquired Scan section (Section 8.2)</li> <li>Updated SPECT scan submission form (Protocol 002, Section 12.2)</li> <li>Editorial updates (global)</li> </ul>
Final v4.0	27-Jul-2021	<ul style="list-style-type: none"> <li>Updated Table 1 (Section 1.3.2)</li> <li>Updated Previously-Acquired scan details (Section 8.2)</li> <li>Updated SPECT submission form (Section 12.2)</li> <li>Updated based on Protocol 002 Version 1.2 (global)</li> <li>Editorial changes (global)</li> </ul>

### 11.3 Abbreviations

21CFR §11	US Code of Federal Regulations Title 21 Part 11
AE	Adverse event
CT	Computed tomography
COR	Center of rotation
DICOM	Digital Imaging and Communications in Medicine
FOV	Field of view
GCP	Good Clinical Practices
LEHR	Low-energy high resolution
MBq	MegaBecquerel
mCi	MilliCurie
mm	Millimeter
PD	Parkinson's Disease
PI	Principle Investigator
PS	Parkinson's Syndrome
QA	Quality assurance
QC	Quality control
SMC	Site Management Core
SPECT	Single-photon emission computerized tomography
SSKI	Saturated solution of potassium iodide
TOM	Technical Operations Manual

## 12 Appendices

### 12.1 Appendix 1: Imaging Parameter Specifications

Example of Typical SPECT Acquisition(s)	
<b>SPECT Imaging Mode:</b>	Step and Shoot
<b>Collimators:</b>	LEHR parallel hole collimators
<b>Energy Window:</b>	20 % energy window centered on 159 keV (+/- 10 %),
<b>Orbit:</b>	Circular
<b>Matrix</b>	128x128
<b>Acquisition Zoom:</b>	1.23
<b>Angular Range:</b>	3 degrees
<b>Seconds:</b>	30 seconds
<b>Number of Projections</b>	60 projections (180 degrees rotation per detector)
<b>Radius:</b>	15 cm

## 12.2 Appendix 2: PPMI Clinical Submission Form (Example)



### SPECT Submission Form

Clinical Site ID:

Subject Number (Participant ID):  (4-digit 1.0 transition subjects)  
 (5-digit 1.0 transition subjects)  
 (6-digit 2.0 new subjects)

Scan Acquisition Date (DD-MMM-YYYY):  -  -

Modality:  SPECT

*Note: If CT for Attenuation correction or anatomical location were acquired as part of the SPECT scan, please submit to Invicro with the SPECT data.*

Cohort:  Healthy  
 PD  
 Prodromal

Radiopharmaceutical:  <sup>123</sup>I-DaTscan

SPECT Imaging Timepoint:  Screening (6-digit 2.0 new subjects Only)  
 Previously Acquired / Screening (6-digit 2.0 new subjects Only)  
 Month 12/V04  
 Month 24/V08  
 Month 48/V10  
 Other SPECT Timepoint

(If other is selected) Other SPECT Imaging Timepoint:  Month 6/V02  
 Month 18/V05  
 Month 36/V08  
 Month 60/V12  
 Month 72/V13  
 Month 84/V14  
 Month 96/V15  
 Month 108/V16  
 Month 120/V17  
 Month 132/V18  
 Month 144/V19  
 Month 156/V20

For previously acquired scans only: Please enter UNK for any information that is unknown at the time this form is completed.

Weight:      lb  kg

Thyroid Blockade Method:

Thyroid Blockade Dose:

Thyroid Blockade Administered (HH:MM; 24hr):  :

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PPMI 2.0\_SPECT\_V11.0\_01APR2021

 **SPECT Submission Form**

Initial Activity in Syringe:  .   mCi  MBq

Initial Activity Time Measured (HH:MM; 24hr):  :

Date of Injection (DD-MMM-YYYY):  -  -

Time of Injection (HH:MM; 24hr):  :

Residual Activity Post Injection:  .   mCi  MBq

Residual Activity Time Measured (HH:MM; 24hr):  :

Scanner (Manufacturer and Model):

SPECT Scan Start Time (HH:MM; 24hr):  :

SPECT Scan Stop Time (HH:MM; 24hr):  :

Collimator:

Radius:

Comments:

Scanner Event Information:

Daily Quality Control (QC) performed  Yes  
and passed prior to scanning?  No, please explain:

Please list any new calibrations/maintenance performed  
to your scanner since the last subject data submission:

If you have not submitted any data to Invicro in the past  
three months, please list any new calibrations/  
maintenance performed in the last quarter:

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PPMI 2.0\_SPECT\_V11.0\_01APR2021

### 12.3 Early Imaging 2.0 Submission Form (Example)

PPMI 2.0 Protocol Number 004

 **Early Imaging SPECT Submission Form**

Clinical Site ID:

Subject Number (Participant ID):  (4-digit 1.0 transition subjects)  
 (5-digit 1.0 transition subjects)  
 (6-digit 2.0 new subjects)

Scan Acquisition Date (DD-MMM-YYYY):  -  -

Modality:  SPECT

Cohort:  PD

Radiopharmaceutical:  <sup>123</sup>I-DaTscan

SPECT Imaging Timepoint:  Month 6/V02  
 Month 12/V04 (Applicable to PPMI 1.0 transition subjects only)  
 Month 18/V05

Weight:        lb  kg

Thyroid Blockade Method:

Thyroid Blockade Dose:

Thyroid Blockade Administered (HH:MM; 24hr):  :

Initial Activity in Syringe:  .   mCi  MBq

Initial Activity Time Measured (HH:MM; 24hr):  :

Date of Injection (DD-MMM-YYYY):  -  -

Time of Injection (HH:MM; 24hr):  :

Residual Activity Post Injection:  .   mCi  MBq

Residual Activity Time Measured (HH:MM; 24hr):  :

Scanner (Manufacturer and Model):

SPECT Scan Start Time (HH:MM; 24hr):  :

SPECT Scan Stop Time (HH:MM; 24hr):  :

Was a CT for Attenuation correction or anatomical location acquired as part of the SPECT scan?  No  
 Yes, please submit to Invicro

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PPMI 2.0\_Early Imaging SPECT\_V1.0\_21JUL2020

PPMI 2.0 Protocol Number 004

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### Early Imaging SPECT Submission Form

Collimator:

Radius:

Comments:

**Scanner Event Information:**

Daily Quality Control (QC) performed  Yes  
and passed prior to scanning?  No, please explain:

Please list any new calibrations/maintenance performed  
to your scanner since the last subject data submission:

If you have not submitted any data to Invicro in the past  
three months, please list any new calibrations/  
maintenance performed in the last quarter:

EXAMPLE

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PPMI 2.0\_Early Imaging SPECT\_V1.0\_21JUL2020