



Parkinson's  
Progression  
Markers  
Initiative

# *PPMI*

## *Operations*

### *Manual*

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## 1.0 GENERAL INFORMATION

### Study Management Contacts

#### Institute for Neurodegenerative Disorders (IND) Site Management Core (SMC) Study Contacts

Whom to Connect with	Reason to Contact
<p><b>Vice President</b> <u>Bridget McMahon</u>            Phone: +1 443-695-5220            Email: <a href="mailto:bmcmahon@indd.org">bmcmahon@indd.org</a></p> <p><b>Senior Manager</b> <u>Jessica Dimos</u>            Phone: +1 203-645-9163            Email: <a href="mailto:jdimos@indd.org">jdimos@indd.org</a></p> <p><b>Manager</b> <u>Jillian Ricci</u>            Phone: +1 203-430-6160            Email: <a href="mailto:jricci@indd.org">jricci@indd.org</a></p> <p><b>Associate II</b>  <u>Erin Nichols</u>            Phone +1 765-586-5925            Email: <a href="mailto:enichols@indd.org">enichols@indd.org</a></p>	<p>Questions regarding protocol, day-to-day study operations, IRB/ethics submissions, training, electronic regulatory document management (Florence eBinder™) system, Greenphire participant payment questions, PPMI Clinical Progress Reports, participant site transfers, site visits; any study support.</p> <p><b>Note:</b> Contact SMC for any topics on the PPMI study, and they will triage to the related study core.</p>
<p><b>Associate II</b>  <u>Cari Rainville</u>            Phone: +1 203-215-9611            Email: <a href="mailto:crainville@indd.org">crainville@indd.org</a></p>	<p>Event coordination (conference calls, site visits), surveys, site personnel training and onboarding (Learning Management System, etc.), electronic regulatory document management (Florence eBinder™) system, general project support</p>

<b>Director, Medical Science Liaison</b> <u>Lynell Lemon</u> Phone: + 1 619-403-6774 Email: <a href="mailto:llemon@indd.org">llemon@indd.org</a>	SMC-managed PPMI Clinical referrals and ST Direct
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**Medical Monitor Contact**

Whom to Connect with	Reason to Contact
<b>PPMI Medical Monitor</b> <u>Andrew Siderowf</u> Phone: +1 215-280-2396 Email: <a href="mailto:Andrew.Siderowf@penmedicine.upenn.edu">Andrew.Siderowf@penmedicine.upenn.edu</a>	Urgent (e.g., after hours) questions about participant safety and enrollment (e.g., SAE reports, eligibility, protocol waivers); generally, communications around adverse event reporting and eligibility can be addressed to the SMC who will triage as needed to study leadership, including the medical monitor.

**Michael J Fox Foundation for Parkinson’s Research Study Personnel**

Michael J Fox Foundation for Parkinson’s	Study Responsibilities
<b>Director, Clinical Research</b> Tawny Willson	Manages Site Contracts and Study Budgets
<b>Officer, Research Operations</b> Gabrielle Tran	Manages/supports site payments, and Greenphire.

<b>Officer, Clinical Research</b> Maddie Kutler & Tara Pizzoferrato	Manages recruitment & retention materials (including translation)
<b>Site Managers, Clinical Research</b> Kayleigh Greenwood, Caitlin Kelliher, Maddie Kutler	Manages recruitment and retention efforts with assigned sites.

**PPMI Study Core Primary Personnel**

***PPMI IU Project Managers***

<i>Name</i>	<i>Role</i>	<i>Core</i>
Laura Heathers	Project Manager	Screening, Travel, Pathology, Digital
Gena Antonopoulos	Project Manager	Pathology, Digital
Michelle Totten	Project Manager	Screening
Jan Hamer	Project Manager	Biorepository
Audra Bright	Project Manager	Travel

<b>PPMI IU Cores &amp; Study Personnel</b>	<b>Study Responsibilities</b>
<b>Screening Core</b> Email: <a href="mailto:ppmi@iu.edu">ppmi@iu.edu</a> Phone: (888) -830-6299  <b>Laura Heathers and Michelle Totten, Project Managers</b>	Manages centralized screening for prodromal participants and referral to PPMI sites, confirms eligibility for genetic cohorts.

<p><b>Travel Core</b>  Email: <a href="mailto:ppmitravel@iu.edu">ppmitravel@iu.edu</a>  Phone: (317)-278-9440</p> <p><b>Laura Heathers and Audra Bright, Project Managers</b></p>	<p>Coordinates travel for centrally managed PPMI participants/candidates</p>
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PPMI IU Cores & Study Personnel	Study Responsibilities
<p><b>Biorepository</b>  Email: <a href="mailto:ppmibio@iu.edu">ppmibio@iu.edu</a>  Phone: 1-317-274-5744</p> <p><b>Jan Hamer, Project Manager</b></p>	<p>Supports Biorepository and specimen collection and management</p>

<p><b>Pathology Core</b>  Email: <a href="mailto:ppmipath@iu.edu">ppmipath@iu.edu</a>  Phone: (844)-280-0036</p> <p><b>Laura Heathers and Gena Antonopoulos, Project Managers</b></p>	<p>Coordinates brain tissue donations for PPMI participants</p>
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PPMI IU Cores & Study Personnel	Study Responsibilities
<p><b>Digital Core</b></p>	



<p>Email: <a href="mailto:ppmidigital@iu.edu">ppmidigital@iu.edu</a>  Phone: (317)-278-6508</p> <p><b>Laura Heathers and Gena Antonopoulos, Project Managers</b></p>	<p>Supports PPMI digital application(s) through adherence monitoring.</p>
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<b>PPMI Imaging Core &amp; Study Personnel</b>	<b>Study Responsibilities</b>
<p><b>Imaging Core</b></p> <p>Andrew Serrano, MBA  Project Manager II</p> <p>Alexis Clark  Senior Project Coordinator</p> <p><i><b>For all questions related to image data transfer or account credentials issues:</b></i>  <a href="mailto:corelab_support@invicro.com">corelab_support@invicro.com</a></p>	<p>Lead project manager for Imaging Core, manages external and internal communications, timelines, deliverables, site questions, site setup processes.</p> <p>Lead project coordinator for Imaging Core, supports site setup processes, site questions, dose onboarding items, timelines, internal and external communications, deliverables.</p> <p>Supports transfer of scans and corresponding data, account credentials.</p>

<p><b><i>For all technical questions related to scanner protocol setup or image quality control:</i></b></p> <p>Andrea Perez  Sr. Manager II, Imaging QC &amp; Processing  +1-203-401-4315 voice  <a href="mailto:aperez@invicro.com">aperez@invicro.com</a></p>	<p>Supports technical questions around scanner protocol setup, scanning procedures, or image quality control</p>
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<b>PPMI FOUND Study Personnel</b>	<b>Study Responsibilities</b>
<p><b>FOUND Study</b> (<a href="mailto:foundinppmi@ucsf.edu">foundinppmi@ucsf.edu</a>)  Cheryl Meng, Project Manager</p> <p>Kathleen Comyns, Project Manager</p>	<p>FOUND Study support/management</p>

<b>PPMI Data Management Core Study Personnel</b>	<b>Study Responsibilities</b>
<p><b>For all technical questions related to the Clinical EDC System:</b>  <a href="mailto:CTSDMC-PPMI@uiowa.edu">CTSDMC-PPMI@uiowa.edu</a></p>	<p><b>Supports Data Management including the EDC and Query System</b></p>
<p><b>Dixie Ecklund, Director of Operations</b>  <a href="mailto:dixie-ecklund@uiowa.edu">dixie-ecklund@uiowa.edu</a></p>	
<p><b>Trevis Huff, Lead Data Manager</b>  <a href="mailto:trevis-huff@uiowa.edu">trevis-huff@uiowa.edu</a></p>	
<p><b>Holly Ernst, Lead Project Manager</b>  <a href="mailto:holly-ernst@uiowa.edu">holly-ernst@uiowa.edu</a></p>	

<p><b>PPMI Statistics Core Study Personnel</b>  Christopher Coffey, PI Statistics Core  <a href="mailto:christopher-coffey@uiowa.edu">Email: christopher-coffey@uiowa.edu</a></p> <p>Dixie Ecklund, Director of Operations  <a href="mailto:dixie-ecklund@uiowa.edu">Email: dixie-ecklund@uiowa.edu</a></p> <p>Chelsea Caspell-Garcia, Lead Statistics Manager  <a href="mailto:chelsea-caspell@uiowa.edu">Email: chelsea-caspell@uiowa.edu</a></p>	<p><b>Study Responsibilities</b>  Supports statistical analyses that will be performed on the PPMI data and samples</p>
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## **Study Personnel**

Each site has identified one primary site Investigator and one primary coordinator on record; however, due to the number of participants and variety of activities involved as part of the PPMI Program, the site Investigator may appoint MDS-UPDRS credentialed sub-Investigators, as well as co-coordinators to the study team. Site Investigators may designate additional study personnel who will be conducting neurocognitive assessments, specimen blood draws and processing, skin biopsies, imaging, and CSF collection and processing, and regulatory management.

### **Please note the importance of consistency of study personnel.**

It is essential to maintain consistency in ratings as much as possible throughout the study by having the same site Investigator or sub-Investigator, coordinator/co-coordinator and other raters, as applicable, follow the same participant from screening through all subsequent follow-up visits. In instances where this is not possible, it will not be considered a protocol deviation, but close adherence is requested.

All key site personnel (e.g., site Investigator, sub-Investigator, coordinator, co-coordinator) involved in the conduct of the study, including those conducting assessments and/or entering data in EDC, will require a Clinical Trials Statistical and Data Management Center (CTSDMC) PPMI EDC login account and must have a completed Delegation of Responsibilities Form located in Florence, the electronic trial master file system (eTMF). Additional staff who are involved in the study (e.g., lead nuclear medicine PI, imaging manager, proceduralists, e.g., physician performing LP only, individual responsible for regulatory documents, etc.), but are not completing data entry do not require an EDC login account; however, they must have a Delegation of Responsibilities Form. The Delegation of Responsibilities Form must be updated whenever there is a change to the study team staff (including new additions, departures, and role changes). The Delegation of Responsibilities Form must be signed electronically by both the staff person and the site Investigator (or in the instance of departed staff, the site Investigator only).

### **Documentation of Site Personnel for PPMI**

PPMI will utilize a web platform called HubSpot as the contact resource management (CRM) system. Site personnel will provide their contact information on the HubSpot website via on-line forms, using either an initial contact form or a change form (for departures or changes to roles or responsibilities). Examples of these forms can be found in the Florence PPMI general folder. It may be helpful to review the form in advance of online completion. The form can be completed on behalf of other team members (e.g., a designated site staff member may complete it for other site staff).

Initial staff contact entry:

- The SMC will provide the site coordinator with a link to the HubSpot website to complete a contact form for each key personnel staff member (the coordinator can share the link with other staff members for their completion, if desired).
- The SMC will review and approve completed contact forms in HubSpot and notify the site if there are any queries.
- Once the form is reviewed as complete, the SMC will post a copy to Florence in the Investigator Site File under study contacts.

Staff changes (role or responsibility changes, staff departures):

- Site staff will notify the SMC of role or responsibility changes and departures.

Global site contact listing

- A global PPMI study contact list will be placed in the Florence PPMI 002 General Study File folder for reference and updated periodically.
- This listing is for PPMI purposes only and not for sharing outside PPMI.

Delegation of Responsibilities Form

- After initial site selection, all investigator changes must be first approved by the Steering Committee, or designee. Site will contact SMC who will liaise with leadership to facilitate the approval process.
- Changes in coordinator and any other site staff will be reviewed by the SMC to ensure appropriate training and applicable document collection is completed to facilitate the change.
- Complete the Delegation of Responsibilities form for new staff additions, or when there are changes to roles or delegated responsibilities.

### **IND SMC Office Closings**

In general, the IND SMC will be closed for the US holidays listed below. A date-specific schedule is posted in the Florence PPMI 002 General Study Binder. If you have an emergency on a day we are closed, please call the Medical Monitor at +1 215-280-2396.

**New Year's Day (January 1 and possible day before or after)**

**Martin Luther King Observance (3<sup>rd</sup> Monday in January)**

**President's Day (3<sup>rd</sup> Monday in February)**

**Spring Holiday (Friday before Easter)**

**Memorial Day (4<sup>th</sup> Monday in May)**

**Juneteenth (June 19, only when falls on a business day)**

**Independence Day (July 4 and possible day before or after)**

**Labor Day (1<sup>st</sup> Monday in September)**

**Columbus Day (2<sup>nd</sup> Monday in October)**

**Thanksgiving (4<sup>th</sup> Thursday and Friday in November)**

**Christmas (December 25 and possible day before or after)**

## **2.0 OBTAINING INFORMED CONSENT**

### **Prodromal Participants**

Sites will need to obtain consent from these individuals at two timepoints – first at the Screening Visit to determine eligibility to proceed to Baseline. Eligible participants who return to the site for Baseline activities will need to give informed consent for continued participation in the main PPMI Clinical protocol.

### **All Other Cohorts**

All newly screened PPMI participants will give informed consent using the main PPMI Clinical protocol consent.

### **Designation of Research Proxy**

Designation of a research proxy is voluntary; thus, identification of a substitute decision maker is not required to participate in PPMI. A research proxy (or Advanced Directive for Research Participation) may be identified or changed at any point during study participation; however, if a participant is no longer able to provide ongoing consent to participation and a research proxy has not yet been identified, the participant must be withdrawn from the study. It is understood that state and international laws, regulations, and institutional policy might vary on terminology and designation of a research proxy (e.g., Legally Authorized Representative is a commonly used term, which may be inclusive of a “research proxy”). As such, consent forms and signatures to document when a research proxy gives ongoing consent on behalf of the participant should be implemented as applicable.

### **GDPR Addendum**

General Data Protection Regulation, or GDPR, is an Addendum to the PPMI consent form. This addendum privacy statement is to inform participants about the European Union GDPR regulation, because information collected about participants in this study might be used by scientific researchers at for-profit companies, academic medical centers, or other non-profit organizations in the European Union (EU) or because the participant is an EU resident. The GDPR has some specific requirements about how the privacy of participant's personal data will be protected, used and shared during and after this study. The GDPR addendum should be signed by all participants regardless of local regulatory requirements due to the centralized data repository and data sharing.

### **3.0 ENROLLMENT**

#### **Participant Profile Information**

When a participant provides consent to participate, the following participant identifiers will be collected in the EDC system:

- First name
- Last name
- Email address
- Date of birth
- Sex at birth
- Confirmation of childbearing potential

In addition, the following (optional) identifiers will be collected:

- Middle name
- City/municipality of birth
- Country of birth
- Mailing address
- Phone number

#### **Participant ID Assignment**

A participant ID number will be assigned to all PPMI program participants. Active PPMI participants transitioning into the expanded PPMI Clinical Protocol will keep their previously assigned PPMI ID number. New participants will be automatically assigned a six-digit ID number as soon as a participant joins the PPMI Program. If a participant screen-fails or decides not to enroll in the study, their ID number will NOT be re-used. The PPMI participant ID number will be used to identify a participant on all study-related documents.

### **Activities Prior to Enrollment**

#### PD/PD with Genetic Variant/Healthy Controls (recruited locally at site):

Once a potential participant provides written informed consent and Screening activities are conducted, the following additional activities should be noted:

- A determination will be made based on the SPECT Imaging results whether the participant is eligible to proceed to the Baseline visit. The site must receive confirmation of eligibility before any Baseline activities may be started.
- Before a participant is considered enrolled into the study (i.e., an eligible participant who completes the Baseline visit and counts towards the total enrollment goal), the site Investigator (or sub-Investigator) and coordinator should review the Inclusion/Exclusion eCRF to assess that the participant meets all eligibility criteria and complete the Inclusion/Exclusion page in EDC. Any uncertainty regarding the participant's eligibility should be referred to the IND SMC Site Manager prior to completing the Baseline visit in the EDC.

#### Prodromal (recruited locally at site):

Once a potential participant provides written informed consent and Screening activities are conducted, the following additional activities should be noted:

- A determination will be made based on the UPSIT whether the participant is eligible to proceed to the SPECT scan visit. If not eligible, the participant will be screen failed.
- If UPSIT eligible, the participant may proceed to have a SPECT scan. A determination will be made based on the SPECT scan whether the participant is eligible to proceed to the Baseline visit. The site must receive confirmation of eligibility before any Baseline activities may be started. [Confirmation of eligibility based on SPECT imaging must be documented in the EDC system Screening visit before any Baseline visit activities may be completed.](#)



- The participant must provide informed consent to the PPMI Clinical protocol (via the “Main ICF”) prior to completing any Baseline visit activities.
- Before a participant is considered enrolled into the study, the site Investigator (or sub-Investigator) and coordinator should review the Inclusion/Exclusion eCRF to assess that the participant meets all eligibility criteria and complete the Inclusion/Exclusion page in EDC. Any uncertainty regarding the participant’s eligibility should be referred to the IND SMC Site Manager prior to completing the Baseline visit in the EDC.
- NOTE: Participants who are in the RBD subgroup and have a PSG+ result from a sleep study, can enroll regardless of UPSIT or SPECT results. Overrides are built into the EDC in the Prodromal History CRF.

Prodromal/PD with Genetic Variant (recruited by the IU Screening Core):

- Potential participants for the Prodromal cohort, as well as potential participants with a diagnosis of PD with a genetic variant, will be referred by the IU Screening Core to a remote referral site to begin the PPMI Clinical protocol activities and described below. The potential participant will first provide informed consent for the Screening visit and SPECT imaging.
- A determination will be made based on the SPECT scan whether the participant is eligible to proceed to the Baseline visit. The site must receive confirmation of eligibility before any Baseline activities may be started.
- If the participant is eligible to proceed to the Baseline visit, and the participant agrees to continue follow up in PPMI Clinical, the IU Screening Core will inform the participant of their eligibility and refer the participant to the clinical site. The clinical site may be the same as the imaging site, or it may be different from the imaging site, depending on geographic location. Confirmation of eligibility based on SPECT imaging must be documented in the EDC system before any Baseline visit activities may be completed.
- The participant must provide informed consent to the PPMI Clinical protocol prior to completing any Baseline visit activities.
- Before a participant is considered enrolled into the study, the site Investigator (or sub-Investigator) and coordinator should review the Inclusion/Exclusion eCRF to assess that the participant meets all eligibility criteria and complete the Inclusion/Exclusion page in EDC. Any uncertainty regarding the participant’s eligibility should be referred to the IND SMC Site Manager prior to completing the Baseline visit in the EDC.

Ineligible Participants/Screen Fails:

A participant will be considered enrolled into PPMI Clinical if the participant consents to participate, all eligibility criteria are met, and the Screening and Baseline visits are completed in the EDC system. If a participant does not complete enrollment, no other study activities should be completed, and the individual should be marked as a screen fail in one of the following two ways:

1. If a participant declines further participation in PPMI Clinical prior to completing a Baseline visit, the “Screen Fail” electronic case report form (eCRF)\* should be completed under the Event Driven tab in the EDC, and this should be documented in Question #1 on the eCRF.
2. If a potential participant does not meet all eligibility criteria, they will be considered a screen-fail and the “Screen Fail” eCRF\* should be completed under the Event Driven tab in the EDC system. The appropriate cohort *Inclusion/Exclusion Criteria* eCRF should additionally be completed in this case.

\*A “Demographics” eCRF must be completed for the participant prior to completing the “Screen Fail” eCRF. The “Socio-Economics” eCRF should additionally be completed if this information is available for the participant.

## Protocol Waivers

**Purpose:** A protocol waiver (eligibility exception or eligibility waiver) is a prospective decision to permit accrual of a participant who does not satisfy the approved inclusion/exclusion criteria for enrollment. Protocol waivers may be granted at the discretion of the PPMI Medical Monitor.

A protocol waiver will be documented via a Note to File (NTF). The NTF will be generated by the PPMI Site Management Core (SMC) and uploaded to the respective Investigator Site File in Florence.

**Procedures:** The site staff will contact SMC in advance of the participant’s enrollment. Information to be provided by the site includes participant ID, cohort, and eligibility criterion that is being requested. If requested in advance of participant ID assignment (i.e., creation of the participant’s profile in EDC), the site will follow up with SMC to finalize the NTF.

Once a request is made, the SMC will follow the steps below:

- Contact PPMI Medical Monitor to review and approve the request.
  - SMC to file the Medical Monitor’s correspondence internally.
- Notify the site of the approval, if granted; SMC to prepare documentation of the approval via a note to file (NTF), using the current NTF template (located in the respective study-specific Florence General folder)
- Once the participant ID is supplied, finalize the NTF. The NTF will detail the request and approval.
- The NTF file name convention will be PPMI 002 NTF Site ###\_PPT [insert Participant ID] DDMMYYYY.
- SMC to upload completed NTF to Florence site folder under *Other, Notes to File Misc*.
- Upon completion of upload, SMC to apply electronic signature to document in Florence.
- SMC to maintain log of NTFs issued with site #, participant ID, date issued, and reason for waiver.

## 4.0 IMAGING

***Refer to the SPECT Imaging Trial Operations Manual (TOM) for details regarding the DaTscan™ product (ordering, storage, administration and accountability).***

### **Ordering DaTscan™ (US Sites)**

The Imaging Core will supply the GE Healthcare (GEHC) Dose Order Form created for each PPMI site. Instructions provided by GEHC outline the ordering process and will be provided along with the order form. Each form includes the specific code for the PPMI study. The form will highlight to GEHC that the dose is to be supplied at no charge.

### **Placing a new DaTscan™ dose order (US Sites)**

- Currently DaTscan™ dose is produced on Monday, Tuesday, Wednesday, and Thursday for injection on the day following production (barring holidays and production site shutdowns). DaTscan™ is available for delivery and injection Tuesday – Friday.
- GEHC requires a lead time of three business days to place a DaTscan™ order. Orders should be placed by 11am EST three business days prior to injection.
- For each participant scheduled for imaging, 1 vial will need to be ordered.
- The participant cohort must be selected on the form.
- **Please review the form to confirm the accuracy of the order information.** Any inaccuracy may delay the receipt of the participant's eligibility.
- All sites must place dose orders with GEHC using the order form provided which will highlight that the vials are to be free of charge to the site for the PPMI study.
- Upon receipt of the order form, GEHC will provide an order confirmation via email or fax. If an acknowledgement is not received, please contact GEHC as instructed on the order form. Sites should file the order confirmation in the participant's study record.

### **Order Cancellation (US Sites)**

- GEHC requires a minimum of three working days to cancel a DaTscan™ dose order.
- Requests for cancellation should be made by 11am EST three business days prior to the date of the scheduled delivery by contacting GEHC at the number provided on the order form.
- GEHC should also be notified if the delivered dose was not used as planned or if a dose needs to be replaced.

### **Shipment to Sites (US Sites)**

For each shipment received, the DaTscan™ Acknowledgment of Receipt Form (see appendix) will need to be completed and the number of packages received (vials in this case) recorded. Please file this completed document with the site's source documents.

DaTscan™ will be delivered on the day of injection. DaTscan™ may be delivered to sites via FedEx or a local delivery service. If DaTscan™ is delivered to the site via FedEx, the shipment is expected to arrive in accordance with the times specified by the delivery service.

**NOTE:** Each DaTscan™ vial will contain 5 mCi at 12:00 pm Eastern Time the day of delivery. If a participant is scheduled for injection past 12:00 pm Eastern Time, additional vials may need to be ordered to ensure the appropriate amount of radioactivity is available at the time of the injection.

### **Ordering DaTscan™ (EU/Israel Sites)**

- There is an internal system in place to accommodate a differential coding between imaging centers normal 'paid-for' vials and PPMI orders.
- All sites must place dose orders with GEHC using the order form provided which will highlight that the vials are to be free of charge for the PPMI study.
- The participant cohort must be selected on the dose order form.
  - **Please review the form to confirm the accuracy of the order information.** Any inaccuracy may delay the receipt of the participant's eligibility.

- GEHC's Customer Service teams have been notified to expect and authorize free of charge vials to each of these centers.
- GE requires a lead time of three business days prior to injection to place a new DaTscan™ orders. Orders should be placed by 11am local time three business days prior to injection.
- Orders should be cancelled by 11am local time three business days prior to the requested delivery date (EU only).
- GEHC should also be notified if the delivered dose was not used as planned or if a dose needs to be replaced.

### **Storage of DaTscan™**

DaTscan™ should be stored at room temperature and is not to be frozen. Appropriate radiation precautions should be observed during the preparation and storage of the agent. Aseptic technique using sterile syringes and needles should be used.

### **Administration of DaTscan™**

DaTscan™ should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides within a designated clinical setting.

DaTscan™ is a 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. Clinical efficacy has been demonstrated across the range 3 to 5 mCi (111 to 185 MBq). Do not exceed 5 mCi (185 MBq), and do not use when the activity is below 3 mCi (110 MBq).

To minimize the potential for pain at the injection site during administration, a slow intravenous injection (about 15 to 20 seconds) via an arm vein is recommended.

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 re-assayed.

**Participants should be pretreated with saturated iodine solution (10 drops in water) or perchlorate (1000 mg,) prior to DaTscan™ injection.**

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

## Accountability of DaTscan™

After each injection day, complete the DaTscan™ Acknowledgement of Receipt Form and the Investigational Medicinal Product Accountability Log (see appendix) and file with the site's source documents.

**NOTE:** In the event there is a problem with the DaTscan™ during the study (e.g., issues with delivery or administration), the site should notify GEHC and the Imaging Core. Once the issue is resolved, the Imaging Core will convey information to the IND SMC as necessary.

## <sup>99m</sup>Tc-TRODAT-1 (Lagos only)

***Refer to the SPECT Imaging Trial Operations Manual (TOM) for details regarding the <sup>99m</sup>Tc-TRODAT-1 product (ordering, storage, administration and accountability).***

## SOURCE DOCUMENTATION

### Instructions for Source Documentation

PPMI will use a direct-data-entry, electronic data capture (EDC) system designed and managed by Clinical Trials Statistical and Data Management Center (CTSDMC). **It is expected that all study visit data will be entered during the study visit, except in the instance a paper source document is expected to be completed (e.g., certain assessments, as described below).** Tablet devices will be provided by the study for completion of data collection in the EDC system during study visits. Most study assessments allow for direct data entry into the EDC; therefore, the electronic case report form (eCRF) is the expected source for those assessments. An eCRF is an auditable electronic record designed to record data required by the clinical study protocol. eCRFs may have special display elements, electronic edit checks, and other properties or functions, and are used for both capture and display of the data. Given the nature of the assessment, some assessments will need to be completed on paper copy, and the data will then be promptly entered into the EDC system. For these assessments, the paper source CRF should be kept in the participant's study record.

Sites should always use the direct-data-entry EDC system unless the site encounters extenuating circumstances, such as internet interruption during the study visit. If needed, sites may use paper copy CRFs to record information collected during the study visit and then promptly input the data into the EDC system. A full set of current CRFs will be available to the PPMI General Study folder in Florence. If paper copy CRFs are completed

for a study visit, these CRFs should be kept as the source documents in the participant’s study record. When paper CRFs are used, data entry into EDC is expected to be completed within 72 hours of participant visit.

Detailed instructions for the EDC system can be found in the *Study Materials area* within the EDC system.

### **Assessments & Instructions for eCRF Completion**

***Refer to the PPMI Assessments and eCRF Completion Manual for detailed instructions regarding assessments with alternating versions, administration of study assessments, and completion of eCRFs.***

### **Types of Visits**

Several types of visits may be conducted in PPMI, and the type of each visit should be documented on the *Visit Status* eCRF at the end of every study visit. Detailed information about each visit type can be found in the “Study Visit Procedures” (Section 10) of the PPMI 002 Clinical Protocol. Please contact an IND SMC Site Manager if you need more guidance around which type of visit should be conducted and documented.

### **Assessment and Study Supply Ordering**

Refer to the *Assessments Manual\_Source Bundle* sub-folder under Protocol Guidance in the PPMI Document Guide in Florence.

- This folder contains the “PPMI Cognitive Assessment Instruction and Paper Source Bundle”, which will be printed by the site and contains the following assessments: Benton Judgment of Line Orientation (scoring sheet), Letter Number Sequencing, Lexical Fluency (F, A, S), Montreal Cognitive Assessment, Modified Semantic Fluency (Animals Only), and Symbol Digit Modalities Test.
- In addition, paper booklet source documents for the Modified Boston Naming Testing, Hopkins Verbal Learning Test-Revised, and Trail Making Test will be provided to sites by the IU Screening Core. The IU Screening Core will also provide the UPSIT kits. When a site is activated in PPMI, IU will send an initial bulk shipment of these assessment booklets and kits. Additional biospecimen kits and assessment supplies may be ordered using the online kit module at <https://kits.iu.edu/ppmi>.

## **5.0 SIGNIFICANT STUDY EVENTS**

There are important events that might occur during a participant's follow up in the study, such as initiation of PD medication, a new diagnosis made by the site Investigator, an SAE, pregnancy, or death. This information will be captured within the study database as described below and may result in additional follow-up with the site.

### **Initiation of PD Medication**

Please refer to the PPMI 002 Clinical Protocol section 11.2 for guidance on scheduling a "Need for PD Therapy" visit. Once a site has been notified that a participant has initiated the use of PD medication the applicable medication information should be recorded in the LEDD Medication Log.

### **Adverse Event Reporting**

Site staff should assess for adverse events according to the PPMI 002 Clinical protocol.

- On the day of the assessment, document the adverse event review on the *Adverse Event In-Clinic Assessment* eCRF in the EDC.
- Document the adverse event telephone follow-up on the *Adverse Event Telephone Assessment* eCRF in EDC.
- Document all adverse events occurring within the study procedure adverse event reporting period on the *Adverse Event Log* in EDC.
- If an adverse event might be associated with more than one study procedure, repeat the recording of the AE to indicate each relationship on a separate row.
- If there is any change in severity over the course of an ongoing adverse event, each change in severity is entered on a new row.

### **Serious Adverse Event Reporting-PPMI002 Clinical Protocol**

The site Investigator should assess whether an adverse event meets the criteria of "Serious Adverse Event" according to the PPMI Clinical protocol. Any event assessed as "serious" is documented on the *Adverse Event Log* in EDC. Such events will be 'flagged' in the EDC database and the SMC will be notified, which might result in additional follow up with the site regarding the event. Sites are responsible for reporting SAEs to their ethics board (per reporting requirements) and to GE Healthcare as instructed below.

➤ *Reporting Requirements to GE Healthcare following DaTscan™ injection*

The **PPMI GE Healthcare SAE Report Form** template is available in the Florence PPMI General Study File under Safety Reporting. Completed reports and related communications should be filed in your Florence Investigator Site File in the Safety Reports folder.

In the event of an adverse event following administration of the imaging agent ( $^{123}\text{I}$ -DaTscan™), the site will notify **BOTH** GE Healthcare and PPMI of the following:



- **Any SAE occurring within 24 to 48 hours following injection**, regardless of relatedness to DaTscan™, must be reported **immediately**, but no later than 24 hours of becoming aware of an event, using the PPMI GE Healthcare SAE Report Form.
- An SAE occurring **more than 24 hours following injection AND related** (“related” is defined as unlikely, possible, probable, or definite) to administration of DaTscan™, must be reported directly to GE using the PPMI GE Healthcare SAE Report Form.

Complete the **PPMI GE Healthcare SAE Report Form** and email the form to **BOTH** GE Healthcare Pharmacovigilance and PPMI Site Management Core. If email is not feasible, you may use the telephone number listed below.

<b>GE Healthcare Pharmacovigilance</b>	<b>PPMI Site Management Core</b>
<p><b>Email:</b> <a href="mailto:gpv.drugsafety@ge.com">gpv.drugsafety@ge.com</a></p> <p><b>Safety Telephone Numbers:</b></p> <ul style="list-style-type: none"> <li>• US and Canada: 800 654-0118, Option 2, then Option 1</li> <li>• Other countries: + XX [appropriate country code] 774-843-3800, Option 2, then Option 1</li> </ul>	<p><b>Email:</b> <a href="mailto:PPMI_SAE@indd.org">PPMI_SAE@indd.org</a></p>

### Serious Adverse Event Reporting- PPMI004 Early Imaging

The site Investigator should assess whether an adverse event meets the criteria of “Serious Adverse Event” according to the **PPMI Early Imaging (AV-133) protocol**. Any event assessed as “serious” is documented on the *Adverse Event Log* in EDC. Such events will be ‘flagged’ in the EDC database and the SMC will be notified, which may result in additional follow up with the site regarding the event. Sites are responsible for reporting SAEs to PPMI Site Management Core (SMC) and Invicro as instructed below.

➤ *Reporting Requirements following [<sup>18</sup>F] AV-133 injection*

The most current version of the **PPMI Early Imaging (AV-133)-004 SAE Report Form** template is available in the Florence PPMI 004 – Early Imaging General Study File under Safety Reporting. Completed reports and related communications should be filed in your Florence Investigator Site File in the Safety Reports folder.

In the event of an adverse event following administration of the imaging agent ( $[^{18}F]$  AV-133), the site will notify **BOTH** Invicro and SMC of the following:

- **Any SAE occurring within 24 to 48 hours following injection**, regardless of relatedness to  $[^{18}F]$  AV-133, must be reported **immediately**, but no later than 24 hours of becoming aware of an event, using the PPMI 2.0 Early Imaging (AV-133)-004 SAE Report Form.

Complete the **PPMI Early Imaging (AV-133)-004 SAE Report Form** and email the form to **BOTH** Invicro and SMC.

<b>Invicro</b>  Email: safetyreporting@invicro.com	<b>PPMI Site Management Core</b>  Email: PPMI_SAE@indd.org
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### Serious Adverse Event Reporting - PPMI 015 AV-133 Prodromal Imaging

The site Investigator should assess whether an adverse event meets the criteria of “Serious Adverse Event” according to the PPMI 015 AV-133 Prodromal Imaging protocol. Any event assessed as “serious” is documented on the *Adverse Event Log* in EDC. Such events will be ‘flagged’ in the EDC database and the SMC will be notified, which may result in additional follow up with the site regarding the event. Sites are responsible for reporting SAEs to PPMI Site Management Core (SMC) and Invicro as instructed below.

➤ *Reporting Requirements following  $[^{18}F]$  AV-133 injection*

The most current version of the **PPMI 015 AV-133 Prodromal Imaging SAE Report Form** template is available in the Florence PPMI 015 - sub study General Study File under Safety Reporting. Completed reports and related communications should be filed in your Florence Investigator Site File in the Safety Reports folder.

In the event of an adverse event following administration of the imaging agent ( $[^{18}F]$  AV-133), the site will notify **BOTH** Invicro and SMC of the following:

- **Any SAE occurring within 24 to 48 hours following injection**, regardless of relatedness to  $[^{18}F]$  AV-133, must be reported **immediately**, but no later than 24 hours of becoming aware of an event, using the PPMI 015 AV-133 Prodromal Imaging SAE Report Form.

Complete the **PPMI 015 AV-133 Prodromal Imaging SAE Report Form** and email the form to **BOTH** Invicro and SMC.

<b>Invicro</b>  Email: <a href="mailto:safetyreporting@invicro.com">safetyreporting@invicro.com</a>	<b>PPMI Site Management Core</b>  Email: <a href="mailto:PPMI_SAE@indd.org">PPMI_SAE@indd.org</a>
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### Conclusion from Study Participation

If a participant concludes study participation following *completion* of the Baseline visit, refer to the protocol “Withdrawal from the Study” section for information about what study activities might be needed. Document the information and reason for withdrawal from the study on the *Conclusion of Participation* eCRF in EDC. The SMC may follow up with the site to obtain additional information as necessary.

### Report of Pregnancy

If a participant is confirmed as pregnant, document this on the *Report of Pregnancy* eCRF in EDC. If this pregnancy occurred within 30 days following administration of DaTscan™, the information must be reported immediately, but no later than 24 hours of becoming aware of the event. The SMC may follow up with the site to obtain additional information as necessary.

### Participant Death

If a participant death occurs, document this on the *Conclusion of Participation* eCRF in EDC. The SMC may follow up with the site to obtain additional information as necessary.

## 6.0 LABORATORY SPECIMEN MANAGEMENT

*Refer to the LabCorp (formerly Covance) Lab Manual for instructions and details regarding processing and shipping PPMI 002 Clinical labs.*

*Refer to the PPMI Biologics Manual for instructions and details regarding collection of the PPMI 002 research samples.*

A copy of both manuals will be filed for your reference in the Florence eBinder PPMI general folder.

### **Pregnancy Test Kits**

Per the protocol, women of childbearing potential must have a urine (or serum if required by the site) pregnancy test prior to injection of DaTscan™ or PI-2620 (Tau). The result must be confirmed as negative prior to proceeding with the injection. **Sites should use their local lab for testing and supplies as these are not supplied or processed through LabCorp (Covance).**

## 7.0 SITE MANAGEMENT

### **Site Management Plan**

Site management of PPMI sites will be conducted on behalf of the PPMI Leadership by the Site Management Core (SMC) at the Institute for Neurodegenerative Disorders (IND), in coordination with other PPMI study cores (e.g., Indiana University Screening Core, Biorepository, Travel and Pathology Cores, Imaging, CTSDMC, and Analytics Core, and Statistical Core) and service providers (e.g., LabCorp), via ongoing support, review and oversight of site engagement, performance and data quality from site initiation through study conclusion to ensure:

1. The rights and well-being of human participants are protected.
2. The reported study data are attributable, legible, contemporaneous, original, accurate and complete.
3. The conduct of the study follows the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

These activities will be conducted via ongoing site engagement, on-site visits and remote interactions as described below. Site visits will occur when appropriate at a mutually agreeable time and for the purpose of face-to-face engagement and review of study activity, followed by a summary of discussions and any action items.

1. Site Visits
  - a. Pre-Study Visit (on-site or remote) to review site interest, capabilities and resources
  - b. Site Initiation Remote Visit (pre-study activation call)
  - c. Interim Site Visits
  - d. Closeout Visit
2. Remote Activities
  - a. SMC/site interaction (e.g., routine or ad hoc calls, communications, web-based meetings, newsletters)
  - b. SMC/IU Screening/Travel, Biorepository and Pathology Core calls
  - c. Training (protocol, procedures, systems as required)
  - d. Centralized regulatory document management and monitoring, via Florence eBinders™ system (Informed Consent review, etc.)
  - e. Centralized data monitoring
    - i. Compliance review in coordination with Indiana University Biorepository Core
    - ii. PPMI EDC ongoing review and report generation
    - iii. Remote review of data metrics
  - f. Safety Management
    - i. Safety assessments
    - ii. Adverse and serious adverse event reporting
3. Other activities
  - a. PPMI Annual Meetings
  - b. Special events

### **Site Activation Process**

1. Requirements for Site Activation
  - a. Administrative/Regulatory (e.g., IRB/Ethics approval, site contracts)
    - i. SMC will work with sites throughout the IRB/Ethics submission process.
    - ii. SMC will review the site's draft consent(s) for acceptability prior to IRB/Ethics submission.
    - iii. The SMC will request the date of IRB/Ethics review to track progress towards approval, if site is not able to use the central IRB.

- iv. MJFF will issue contract documentation to the site and notify SMC when contracts are both released and executed to help monitor progress.
    - b. Site Qualification and Role-Based Training  
Role-specific training and, as applicable, certification will be required prior to activation based off of the study personnel's Delegation of Responsibilities Log completed upon onboarding. Training will be provided in various formats, whether live, web-based or self-paced learning options, or if obtained outside of PPMI (e.g., MDS-UPDRS and Human Participants Research training), certification will be uploaded by the site to Florence.
    - c. Regulatory documents received and approved  
Documents will be supplied to the PPMI SMC via upload or email into the electronic site investigator file in the Florence eBinders™ system, the regulatory document management system. SMC will review and, if applicable, query the documents, and approve.
    - d. Study supplies (e.g., lab kits, paper assessments, tablets)
      - i. Paper source documents for purchased or licensed assessments that cannot be made available electronically due to copyright considerations will be supplied to the site by the IU Biorepository Core.
      - ii. In addition, the site will download from the Florence eBinders™ system the source documents requiring completion on paper (e.g., participant completed worksheets) before transcribing participant data into the EDC. The remainder of study assessments are directly entered in the PPMI electronic data capture system during the participant study visit.
- 2. Site Initiation Visit (Pre-activation call with SMC) and follow up. This call will be a check-in to ensure everything is in good order for the site to begin seeing participants in PPMI, as well as an opportunity to ask questions and exchange information. Follow up communications to include:
  - a. Site activation approval letter. A formal communication of approval will be issued to the site. Upon receipt, this document should be filed in the Florence investigator site folder under SMC correspondence. The SMC will also make the applicable cores aware of the site's activation.
  - b. SMC to be made aware of first scheduled participant visit, to ensure availability for questions or issues during the visit. Site-specific feedback from these visits will be solicited and helpful in supporting other sites as they begin protocol activities.

## **8.0 ESSENTIAL DOCUMENTS & ELECTRONIC TRIAL MASTER FILE (eTMF) SYSTEM**

### **Essential Documents**

PPMI is utilizing Florence eBinders™ for regulatory purposes. Florence eBinders™ is an essential regulatory compliant, web-based document management system for the filing of essential study documents. For purposes of the PPMI Clinical protocol (PPMI 002), essential study documents will be housed in the PPMI 002 Clinical binder in Florence. Other sub-studies under the PPMI program will have their own binders with sub-study specific documents.

The **PPMI 002 Study File** contains site specific Investigator Files (described below).

The general study folder is a study portal for general study documents, is accessible to all fully trained users who are granted access by the SMC and will contain study documents and templates for reference and downloading or duplicating, as needed. Contents of the folders are described in the table below and may be updated to meet future study needs.

Folder Title	General Description of Documents/Contents
<b>Assessments Bundle and eCRF Completion Manual</b>	This section contains worksheets for select patient-reported assessments –to be printed (these are complemented by purchased booklets and forms supplied to sites by the IU Biorepository Core), and current and previous versions of the Assessments and eCRF Completion Manual.
<b>Biologics and LabCorp Manuals and Documents</b>	This section contains current and prior versions of guidance documents, manuals, and certifications for LabCorp central laboratory and PPMI Biorepository.
<b>Global Communications</b>	This section contains general global communications such as past communications from PPMI leadership and Site Management Core regarding the latest study updates and findings, site and participant newsletters, email blasts, and reminders).
<b>Imaging Manuals and Documents</b>	This section contains current and prior versions for Imaging Manuals and documents.

Folder Title	General Description of Documents/Contents
<b>Informed Consent and Documents, Centrally Approved</b>	This section contains current and prior versions of centrally approved informed consents.
<b>Participant Education and Procedure Aftercare Materials, Centrally Approved</b>	This section contains specific participant-facing FAQs and study handouts (Skin Biopsy Wound care guide, etc.)-- all of which are centrally approved.
<b>PPMI System Platform User Guides</b>	This section contains current and prior versions of guidance documents from Florence eTMF, Greenphire, Clinical Trials Statistical and Data Management Center (CTSDMC), iPACs, PPMI EDC, myPPMI, REDCap, and WCG (formerly MyConnexus).
<b>Presentation and Training Materials</b>	<p><b>Presentation Materials Sub-Folder:</b> This section contains miscellaneous presentation materials from Annual Investigator meetings and Coordinator Calls.</p> <p><b>Training Materials Sub-Folder:</b> This section contains references to training slides.</p>
<b>Protocol, Operations Manual and Procedure Guidance</b>	<p><b>Protocol, Centrally Approved Sub-Folder:</b> This section contains current and prior versions of the centrally approved protocol.</p> <p><b>Operations Manual and Procedure Guidance Sub-Folder:</b> This section contains current and prior versions of the operations manual and protocol procedures guidance.</p>
<b>Recruitment and Retention, Centrally Approved</b>	This section contains current and prior versions of recruitment and retention materials, regularly shared scientific updates, and newsletters to continue engaging potential and current volunteers.
<b>Safety Reporting</b>	This section contains safety reporting instructions SAE template form, and reportable event guidance for unsuccessful CSF collection for PPMI Clinical.



Folder Title	General Description of Documents/Contents
<b>Study Contacts</b>	This section contains current and previous versions of the global contact list.
<b>Study Document Templates</b>	This section contains delegation of responsibilities forms, training logs, note to file templates the PPMI established logo, and various other templates and fillable forms.
<b>Study-Level Note To Files</b>	This section contains any study-level note to files.

**PPMI Investigator Site File:** Each PPMI site will have a site-specific electronic folder in Florence for the PPMI 002 Clinical protocol (***named PPMI 002 - Site XXX Site Name – Investigator Site File***) for the purpose of regulatory document management. Documents required for PPMI will be uploaded into this system. This folder and its subfolders are accessible to trained members of the site only, along with the SMC who will have monitoring oversight of and provide support for its use, as well as approval of documents submitted for inclusion. This electronic binder replaces the need for a paper regulatory binder. Contents are described but are not limited to those described in the table below and may be updated to meet future study needs.

Sub-Folder	General Description of Contents
01. SITE CONTACT INFORMATION	Personnel-Specific form samples (this data will be entered directly into the PPMI contacts resource management system, HubSpot); SMC uploads contact form for reference.
02. AGREEMENTS	<i>Placeholder*</i> for Note to file denoting institutional location of site contract (template provided in General Study File)
03. PROTOCOL	Current and Prior Approved Versions
04. INFORMED CONSENT	Current and Prior Approved Versions
05. PARTICIPANT-FACING ASSESSMENTS	Current and Prior Approved Versions (e.g., copies of paper-sourced participant worksheets)

Sub-Folder	General Description of Contents
06. RECRUITMENT_RETENTION RESOURCES	Current and Prior Approved Versions
07. CASE REPORT FORM (CRF)	Current and Prior Approved Versions (blank set of unique forms)
08. INSTITUTIONAL REVIEW BOARD (IRB)_INDEPENDENT ETHICS COMMITTEE (EC)	<ul style="list-style-type: none"> <li>• PPMI 1.0 Continuing Review and Study Closure Acknowledgment (for 1.0 sites)</li> <li>• IRB_EC Approval Letters; Correspondence; Progress Reports; Correspondence (to/from), Safety Reports</li> <li>• IRB_EC Roster (if not using WIRB as IRB)</li> </ul>
09. STUDY PERSONNEL	<ul style="list-style-type: none"> <li>• Curriculum Vitae</li> <li>• Delegation of Responsibilities Forms</li> <li>• Licenses</li> </ul>
10. IMAGING	<ul style="list-style-type: none"> <li>• Imaging Approvals to scan (MRI and SPECT)</li> <li>• Technical Site Setup Report</li> </ul>
11. TRAINING	Documentation of training (Protocol, Assessments, Biorepository, Clinical Trials Statistical and Data Management Center (CTSDMC) EDC, Certifications (e.g., MDS-UPDRS), Clinical and Biorepository Lab Training, Florence Binders, Human Research Education)
12. SITE VISITS	<ul style="list-style-type: none"> <li>• Correspondence</li> <li>• Site Visit and Action Items Logs</li> </ul>
13. CLINICAL LABORATORY	<ul style="list-style-type: none"> <li>• Lab Credentials (e.g., CLIA, CAP)</li> <li>• CV lab director</li> <li>• Local lab normal references (e.g., if local lab is utilized, e.g., for PT/PTT at other than Screening visit)</li> </ul>
14. BIOLOGICAL RESEARCH SAMPLES	<ul style="list-style-type: none"> <li>• Biological Sample Handling</li> <li>• Shipping Records</li> <li>• Manual</li> </ul>
15. SAFETY REPORTS	SAE reports
16. CORRESPONDENCE	Essential Correspondence with IU, MJFF, SMC, Other

Sub-Folder	General Description of Contents
17. TABLET	<ul style="list-style-type: none"> <li>• PPMI 2.0 Site Tablet Receipt and Acceptance Form (or note to file if site is using own device)</li> </ul>
18. OTHER	<ul style="list-style-type: none"> <li>• Consents for Monitoring</li> <li>• Miscellaneous</li> <li>• Nonconformance Reports related to missing lumbar punctures</li> <li>• Any site related Note to File documents</li> <li>• Any protocol deviation reports</li> <li>• Protocol deviation log for site</li> </ul>
19. COMMUNICATIONS	This folder is set up as a place to send emails with important documents directly into the tool using a contact created in the user's email address book. From there, communications can be moved to their intended location within the site's folder (see PPMI Florence User Guide Quick Tip).
20. FOR FILING	This is a folder set up as a workspace, where multiple documents can be imported at the same time via email or uploaded for later filing (i.e., moving to the appropriate folder (see PPMI Florence User Guide Quick Tip).

*\*Placeholders are digital “sticky notes” that hold a place for an expected Document. Users use these to indicate that they will need to fill Folders with specific key Documents, such as CVs, training, ICFs, approvals, etc.*

**Refer to Florence User Guide and Quick Start Guide in the PPMI 002 General Study File > FLORENCE folder.**

**Guidance Regarding PPMI Regulatory Document Completion**

The following section summarizes document requirements. **Please utilize file naming recommendations, as requested.**

**Delegation of Responsibility Form (files to be named DR\_Last Name\_First Initial)**

A Delegation of Responsibility Form (DR form) must be completed for each research staff member upon assignment of any PPMI project activities. Specifically, a DR form must be completed for any of the following staff members:

- The Site Investigator (SI)
- Any Sub-Investigators (Sub-Is)
- Study Coordinators (SCs, primary and co-coordinator(s))
- Rater(s) (clinician or nurse)
- Proceduralists (for lumbar punctures or skin biopsies)
- Regulatory Managers/Staff
- Data Entry
- CRC/CTU Supervisor or Manager
- Imaging Lead
- Lab Managers (for specialized research specimen processing)

For assessments or procedures managed by personnel outside the immediate research team (the SI, Sub-Is, SCs), a DR form can be completed for the Supervisor or Manager and is not required for everyone involved with the assessment/procedure. For example, the Supervisor or Manager of Lab collections, processing and/or shipping biospecimens would complete a DR form and not all lab personnel. This guidance applies to:

- Imaging Department (MRI/SPECT)
- Lab Department

The DR form should be filled out and saved as a draft with the start date blank and pending e-signatures to assist the Site Management Core (SMC) with determining the applicable training and regulatory documents required. Notify the SMC once each DR form is drafted for review.

The start date is the date that the staff member completes the applicable training. For example, the start date used on the DR form for the SI, Sub-Is, and SCs is the date protocol training is completed by that staff member. Applicable training for a staff member may consist of training in any of the following:

- Protocol
- Neuropsychiatric/cognitive
- MDS-UPDRS
- Florence (electronic Trial Master file)

- Clinical Trials Statistical and Data Management Center (CTSDMC)(PPMI EDC)
- Biospecimen collection, processing and shipment
- Imaging

To complete the DR form, enter the start date (based on the date training is completed) and then have the form e-signed in Florence (via addendum) by both the staff member and the site Investigator.

The DR form is to be updated when:

- A research staff member departs from the program
- If the role or responsibilities of a research staff member changes

**Curriculum Vitae (files to be named *CV\_Last Name\_First Initial*)**

- A ‘stamped’ electronic signature is to be applied to the document from within the Florence system after uploading to the Florence **Binders > PPMI 002 – PPMI 002 Site xxx Site Name – Investigator Site File > 09 STUDY PERSONNEL > Curriculum Vitae** folder.
- Refer to Florence eTMF Electronic Workflows and eSignature Guidance for instructions on applying eSignatures
- Each site file has a number of pre-placed placeholders; additional requested CVs can be added to the folder without needing a placeholder.
- Curriculum vitae (CV) must be on file for the following staff members:
  - The Site Investigator (SI),
  - Any Sub-Investigators (Sub-Is),
  - Study Coordinators (SCs, primary and co-coordinator(s)),
  - Cognitive Rater(s), not including any of the above, Proceduralists (for lumbar punctures or skin biopsies)
  - Imaging Lead (Director or Manager of the local imaging center(s) that will be involved in PPMI)

**NOTE:** Please ensure before submitting that the CV has the business (not home) address as well as the current professional title and institutional affiliation where the PPMI study is taking place.

**Licenses (File to be named *License\_Last Name\_First Initial*)**

**IT IS IMPORTANT TO MARK THE EXPIRATION DATE WITHIN THE FILE OF FLORENCE; the SMC tracks expiration dates via generated reports from Florence.**

A license must be on file for the following staff members:

- The Site Investigator (SI),
- Any Sub-Investigators (Sub-Is),

If the following staff members have a license, the license must be on file:

- Study Coordinators (SCs, primary and co-coordinator(s)) (i.e., RN, NP, PA),
- Cognitive Rater(s), not including any of the above, as applicable (i.e., psychology)
- Proceduralists (i.e. RN, NP, PA, MD, DO)

## **Training**

The following training activities will be provided and managed by the SMC via the Talent Learning Management System beginning in September 2023 and the applicable core(s):

- **Florence eBinders™**- Training for Florence will be conducted via review of a recorded video. Training must be on file for each staff member requiring a Delegation of Responsibility Form. The minimum training required is the Find and Sign training to permit viewing of documents and ability to apply electronic signatures (typically, Site Investigators will opt for this training). Following completion of Florence training, the staff member must sign an attestation form, by eSignature or otherwise, and ensure it is on file.
- **Clinical Trials Statistical and Data Management Center (CTSDMC) EDC** - Training for CTSDMC EDC will be conducted via web-conference or recorded video. A user agreement must be signed and sent to the CTSDMC in order to receive a user account with login and password. Training videos and a site training log may be found in the *Study Materials* section of the EDC. Once the training log is emailed to the CTSDMC, a training certificate will be emailed to both the user and the SMC. The SMC will file it in Florence accordingly. A user agreement and training certificate must be on file for each staff member requiring access to the EDC for data entry, query resolution or eCRF signing, specifically:
  - the Site Investigator (SI),
  - any Sub-Investigators (Sub-Is),
  - Study Coordinators (SCs, primary and co-coordinator(s)),
  - Cognitive Rater(s), if applicable

- **Biorepository** - Training for the Biorepository will be administered by the PPMI Biorepository Core (BRC) at Indiana University (IU), via web-conference, or mainly self-paced review of a recorded training session. The SMC will be responsible for providing the current recorded training to each staff member (coordinator or lab manager) handling the biorepository collection, processing and/or shipment..
- **Clinical lab (LabCorp)** - Training for the central clinical lab will be administered by LabCorp and a recording will be made available for sites. In addition, there will be training modules associated with use of the LabCorp eSite. This training specifically applies to any coordinator or lab manager handling the ordering of kits and shipping materials, sample collection, processing and/or shipment.
- **Assessments** - Assessment training will be conducted via web-conference, recorded video or one-on-one training. Refresher training may be required. Training on assessment procedures will be conducted as needed. Attestation of training will be completed and uploaded for each 'trainee' to **PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 11. TRAINING**.  
Training on the assessments is required for:
  - Cognitive Rater(s)
- **Protocol** - Protocol training will be conducted via web-conference, recorded video or one-on-one training. Refresher training may be required. Training on any amendment to the protocol will be conducted as needed. Attestation of training will be completed and uploaded for each 'trainee' to **PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 11. TRAINING**

Training on the protocol and amendment(s) is required for:

- the Site Investigator (SI),
- any Sub-Investigators (Sub-Is),
- Study Coordinators (SCs, primary and co-coordinator(s))

**Documentation of the following training, though training is not provided by PPMI, is required and will be the site responsibility:**

- **MDS-UPDRS** - Training will need to be on file for any designated staff member administering the MDS-UPDRS. This may apply to:
  - the site Investigator (SI),
  - any sub-Investigators (Sub-Is)
  - site coordinator (upon special permission and/or acknowledgement by SMC only)

Training can be completed at <https://mds.movementdisorders.org/updrs/> and the certificate uploaded into Florence.

File to be named **MDS-UPDRS\_Last Name\_First Initial** and uploaded into the following folder: **Binders PPMI 002 > PPMI 002 - Site xxx Site Name - Investigator Site File > 11. TRAINING > Certifications (MDS-UPDRS)**

- **IATA** - This training specifically applies to any coordinator or lab manager shipping the biorepository, pathology and/or central lab samples and will need to be on file for the applicable staff members.

Certificate to be uploaded into Florence.

File to be named ***IATA\_Last Name\_First Initial*** and uploaded into the following folder: ***Binders PPMI 002 > PPMI 002 - Site xxx Site Name - Investigator Site File > 11. TRAINING > IATA***

- **Human Subjects Research (HSR) Training** – Training will need to be on file for:
  - the Site Investigator (SI),
  - any Sub-Investigators (Sub-Is),
  - Study Coordinators (SCs, primary and co-coordinator(s))

Certificate to be uploaded into Florence.

File to be named ***HSR\_Last Name\_First Initial*** and uploaded to the following folder: ***Binders PPMI 002 > PPMI 002 - Site xxx Site Name - Investigator Site File > 11. TRAINING > Human Participants Education***

SMC and site staff can manage document due dates and expiration dates within Florence. It is recommended that this tool be used as a reminder for when updated documents need to be placed in Florence.

## **eTMF System**

As noted above, the Florence eBinders™ system, an electronic trial master file platform, is the regulatory document management system that will be utilized for PPMI protocols. This system eliminates the need for paper documents and instead utilizes binders with built in mechanisms for Part-11 compliant eSignatures to be applied, where required. Only authorized users with secure permission-based access control at the IND Project Management Core, Site Management Core, and the site will have access to the site-specific folder in Florence. The system allows the study team and site team to maintain an automated audit trail with document version control. The SMC team will access, review and approve documents remotely for monitoring purposes. The SMC Team may assign tasks to specific staff to help manage requests (e.g., due dates, expirations).

There will be two site user roles: 1) Site Staff and 2) Site Staff\_Signing Authority. The Site Staff\_Signing Authority role has more limited access (permits view of all documents and the ability to provide electronic signatures). Following completion of applicable Florence training, the study



team will authorize and assign access based on the site user’s role. Certifications of training will be filed in **Binders PPMI 002 > PPMI 002 Site xxx Site Name - Investigator Site File > 11. TRAINING > Florence.**

## Participant Transfer Process

When a PPMI participant wishes to continue participation at a different site, whether out of need or interest, the following processes will occur. *The new site must have IRB/Ethics approval of the same or greater protocol version (i.e. transferring from protocol version 1.0 at originating site to 2.0 at new site) as the transferring site for the transfer to take place.*

Transferring Site Activities	
<b>1</b>	<p>Contact SMC if a participant transfer is being discussed.</p> <ul style="list-style-type: none"> <li>SMC to provide transferring site with potential site nearest the participant’s desired location.</li> </ul>
<b>2</b>	<p>Confirm participant wishes to transfer to site provided; notify SMC.</p> <ul style="list-style-type: none"> <li>SMC to contact new site coordinator to confirm site can accept the transfer; if so, SMC to provide transferring site contact information to new site coordinator.</li> <li>Obtain written permission from participant to share name and contact information with new site coordinator before providing to new site coordinator.</li> <li>In notification to SMC, include participant’s Greenphire reimbursement details: direct deposit or ClinCard user (include last 4 digits of ClinCard, if applicable).</li> <li><b>Confirm all participant information in EDC is complete.</b></li> </ul>
<b>3</b>	<p>Contact new site coordinator to provide participant’s contact information, study visit schedule, and any other pertinent information (e.g., legally authorized representative).</p>
<b>4</b>	<p>Contact participant to confirm transfer. Provide new site coordinator contact information to participant should they have questions or concerns.</p> <ul style="list-style-type: none"> <li>If applicable, discuss the importance of establishing a clinical care provider (e.g., if relocating).</li> <li>Follow up with new site to ensure participant has been successfully contacted by new site and that the transfer will proceed; confirm with SMC.</li> </ul>

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SMC to ensure transferring site has submitted ALL completed CRFs and satisfied all queries before participant is consented at the new site.

- Submission of all completed eCRFs in EDC will ensure transferring site receives payment for completed assessments.
- Prior to SMC completing the transfer workflow, the originating site will be provided a .pdf export of any completed visit CRFs. The export will only include PPMI ID. This will allow the transferring site to maintain a copy of completed visit records since they will no longer have access to the participant data in the EDC once the transfer is complete. SMC will be included on all site correspondence for reference.
- \*SMC to confirm above activities completed, SMC to email new site (cc transferring site) to give approval to proceed with consent of participant, below.

(New site activities continued below)

## New Site Activities

1	<p>Following SMC approval to proceed, contact participant to introduce yourself and discuss next steps, including re-consent to new site-specific current consent form(s); electronic consent via DocuSign is preferred.</p> <ul style="list-style-type: none"><li>• <b>Once consent obtained, new site assumes responsibility for the participant and the originating site is relinquished of these responsibilities.</b></li><li>• CTSDMC to transfer participant to new site in EDC.</li><li>• SMC to notify new site, transferring site, and the following teams: Imaging Core, Biorepository Core, IU Travel Core (if applicable), Pathology Core (if applicable), FOUND (if applicable), LONI, Greenphire, and Data Management via email.</li></ul>
2	<p>Enter re-consent data in EDC (into next planned study visit)..</p>
3	<p>Schedule participant's next visit if not conducted at the time re-consent obtained.</p>

## Instances Where Transfer is not Complete

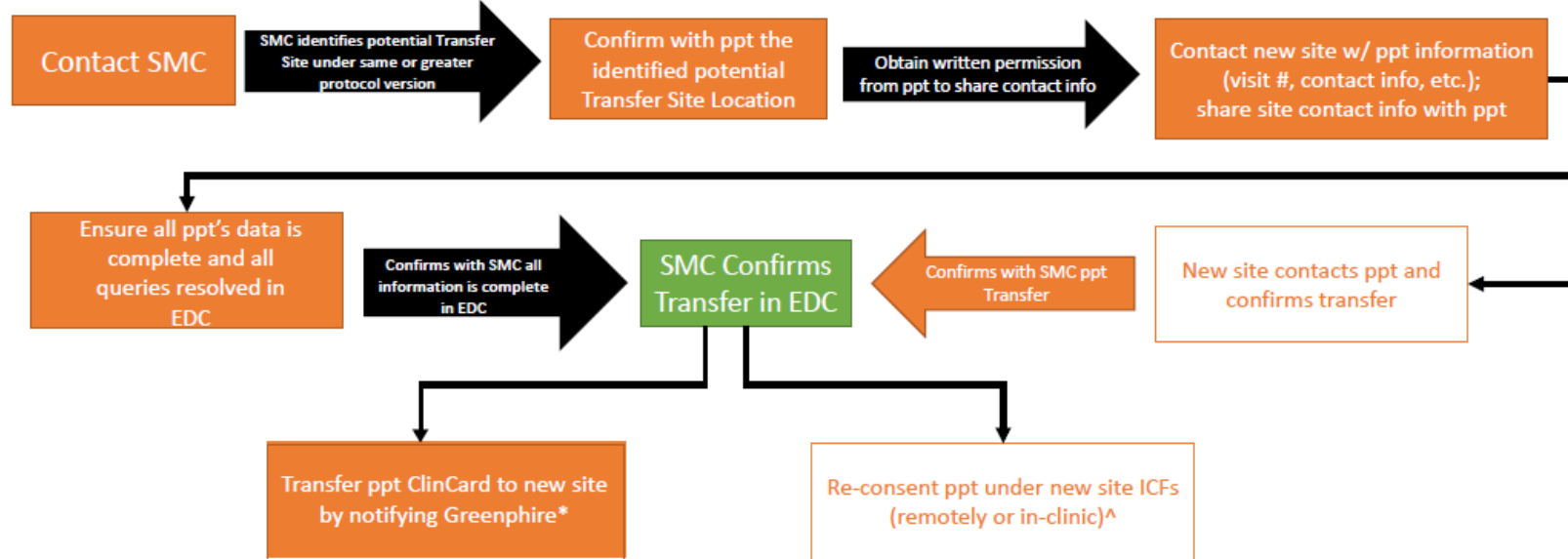
1	<p>Participant unable to be reached by new site.</p> <ul style="list-style-type: none"><li>• Transferring site to follow up with participant to determine continued interest in transferring.</li></ul>
2	<p>Participant changes mind about transfer.</p> <ul style="list-style-type: none"><li>• If participant relays this decision to new site, notify SMC and originating site.</li><li>• Originating site to follow up with participant to confirm participant's decision to remain at the current site.</li></ul>
3	<p>Participant decides to withdraw from PPMI altogether.</p> <ul style="list-style-type: none"><li>• If this decision is relayed by the participant to the new site, the new site must convey that back to the originating site.</li><li>• Originating site to discuss decision with participant and determine if participant is willing to have a final visit before concluding participation in EDC.</li></ul>

**Other**

1	<p>Transfer of Participant Greenphire Account</p> <ul style="list-style-type: none"><li>• To transfer a participant's Greenphire /ClinCard account to a new site, SMC will notify Greenphire Support to request transfer. In notification to Greenphire, SMC will include original site/new site and whether participant has direct deposit setup or ClinCard (including last 4 digits of ClinCard).</li></ul>
2	<p>As always, if any questions, do not hesitate to reach out to your SMC representative.</p>

# PPMI Participant Site Transfers

When a participant (ppt) wishes to transfer to a different site **AFTER** completion of PPMI visit at **CURRENT** site:



\*To transfer a participant's ClinCard to new site, SMC will notify ClinCard Support to request transfer.

*^Once ppt is re-consented under the new site's ICFs, new site assumes responsibility for the participant (ongoing AE's, etc.) and transferring site is relinquished of these responsibilities.*

## Table of Documents

The following table lists the documents by site and by personnel role that will be filed in Florence. Detailed instructions for Florence, including instructions for providing electronic signatures for certain documents can be found in the User Guide and Quick Start Guides in **PPMI 002 General Study File** in Florence.

### Site-Specific Documents

Document	Comment
Note to file denoting institutional location of site contract	<ul style="list-style-type: none"> <li>• DUPLICATE Template located in Florence <b>General study file</b></li> <li>• <i>File to be named: PPMI 2.0 Site XXX Contract Location DDMMYYYY Note to file</i></li> <li>• Fill placeholder and apply Investigator eSignature to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 02 AGREEMENTS &gt; PPMI 2.0 Site XXX Contract Location DDMMYYYY Note to file</b></li> </ul>
Protocol, IRB/Ethics approved	<ul style="list-style-type: none"> <li>• If possible, please rename file to: <b>PPMI 002 Site XXX IRB_EC Approval DDMMYYYY</b> (with date representing date of approval)</li> <li>• Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 03 PROTOCOL &gt; Current Approved Protocol</b></li> </ul>
Informed consent(s), IRB/Ethics approved	<ul style="list-style-type: none"> <li>• If possible, please rename file to: <b>PPMI 002 Site XXX Main/Prodromal ICF_DDMMYYYY (insert version date) Approval DDMMYYYY</b> (with date representing date of approval)</li> <li>• Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 04 INFORMED CONSENT &gt; Current Approved Informed Consents</b></li> <li>• Advanced directive, HIPAA (if separate) and any other applicable consent documents may be filed here (and named similarly).</li> </ul>
Participant-Facing Assessments, IRB/Ethics approved	Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 05 PARTICIPANT-FACING ASSESSMENTS &gt; Current Approved Version(s)</b>
Recruitment Retention Resources, IRB/Ethics approved	Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002- Site XXX Site Name - Investigator Site File &gt; 06 RECRUITMENT_ RETENTION RESOURCES/Current Approved Version(s)</b>

Document	Comment
Case Report Form (CRF), blank unique set download from General Study File	DUPLICATE from Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 General Study File/ CASE REPORT FORM/Current Version to PPMI 002 - Site xxx Site Name Investigator Site File 07 CASE REPORT FORM (CRF)</b>
IRB/Ethics Committee (EC) Approval Letter)	Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 08 INSTITUTIONAL REVIEW BOARD (IRB)_INDEPENDENT ETHICS COMMITTEE (EC) &gt; Current Approved Protocol/Approval Letters</b>
Imaging approval to scan	Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 10 IMAGING &gt; IMAGING APPROVALS</b>
Local lab (if using) CLIA, CAP, CV Medical Director, references normal ranges	<ul style="list-style-type: none"> <li>For sites using local labs for Screening. Note <b>all sites</b> will use central lab (LabCorp)</li> <li>Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 13. CLINICAL LABORATORY &gt; Lab_Miscellaneous</b></li> </ul>
Site Tablet Receipt and Acceptance Form (iPad)	Fill placeholder and apply eSignature to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 17 TABLET &gt; PPMI 2.0 Site Tablet Receipt and Acceptance Form</b> (also acceptable to upload signed and scanned version)

### Personnel-Specific Documents

Document	Inv/ Sub-I	Coord/ Co-Coord	Cognitive Rater	Imaging	Proceduralist	Regulatory Manager	Other	Comment
Staff Contact Form (completed in HubSpot, the PPMI Contact Resources Management System)	X	X	X	X	X	X	X	<ul style="list-style-type: none"> <li>Sample Located in Florence <b>General study file</b></li> <li>Site to complete contact forms in HubSpot for each team member</li> <li>SMC to place printout of approved contact in this folder for future reference</li> </ul>

Document	Inv/ Sub- I	Coord/ Co- Coord	Cognitive Rater	Imaging	Procedur- alist	Regulatory Manager	Other	Comment
Delegation of Responsibilities form	X	X	X	X	X	X	X	<ul style="list-style-type: none"> <li>• DUPLICATE Template located in Florence <b>General study file</b></li> <li>• Files to be named <b>PPMI 002 Site XXX DR – Last Name_First Initial</b></li> <li>• Upload and apply eSignatures of staff personnel and PI to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name &gt; 09 STUDY PERSONNEL &gt; Delegation of Responsibilities Forms</b> (may fill placeholders if provided; otherwise, upload into folder)</li> </ul>
Curriculum Vitae (includes current role, institution/address)	X	X	X	X	X			<ul style="list-style-type: none"> <li>• File to be named <b>PPMI 002 Site XXX CV_Last Name_First Initial</b></li> <li>• Upload and apply eSignature to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name &gt; Investigator Site File &gt; 09 STUDY PERSONNEL &gt; Curriculum Vitae</b></li> <li>• Fill placeholders if applicable; otherwise, upload into folder</li> </ul>
Professional License/Renewals (as applicable)	X	X	X	X*	X			<ul style="list-style-type: none"> <li>• Upload to Florence <b>Binders &gt; PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 09 STUDY PERSONNEL/ Licenses_Renewals</b></li> <li>• Fill placeholders if applicable; otherwise upload into folder</li> </ul>
Florence (full or Find & Sign, as applicable)	X	X	X	X	X	X	X	Upload training certification to appropriate folder in Florence, under <b>PPMI 002 &gt; PPMI 002 - Site XXX Site Name - Investigator Site File &gt; 11. TRAINING</b>
Clinical Trials Statistical and Data Management Center (CTSDMC) EDC training	X	X	X				X	
Certification (MDS-UPDRS) – designated rater(s)	X	(X)					(X)	
Biorepository training (Coord, Lab Manager if applicable)		X					X <sup>1</sup>	



Document	Inv/ Sub- I	Coord/ Co- Coord	Cognitive Rater	Imaging	Procedur- alist	Regulatory Manager	Other	Comment
Central clinical lab (LabCorp) training		X					X <sup>1</sup>	
IATA training (for persons shipping any biosamples)		X					X <sup>1</sup>	
Human Subjects Research Training (e.g., CITI, GCP)	X	X						
Protocol, Assessments	X	X	X					
Other	as required							

<sup>1</sup> If labs collected/processed/shipped from site's lab, lab manager requires training

## 9.0 APPENDICES

### Appendix A: List of Exclusionary Medications (Generic Name/Brand Names) for PPMI

(Version 2.3\_11SEP2023)

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents -> Exclusionary Meds\_Conditions

**Note:** This list includes **all exclusionary medications**, containing those listed by name in the protocol and names of medications referred to by medication classification/category in the protocol. Regarding anticoagulants\*, the medications listed here are exclusionary, and Site Investigators should use their discretion to make eligibility decisions about participants taking other anticoagulants. Please refer to the protocol for cohort-specific medication exclusions as well as the guidance document *List of Medications to Hold Prior to DaT Scan* for more information (Appendix C).

#### Exclusionary Drugs:

##### Levodopa Preparations (e.g. carbidopa/levodopa, levodopa/benserazide and others)

##### Dopamine Agonists:

- Apomorphine (KYNMOBI, APOKYN, APO-GO PEN BROMOCRIPTINE)
- Cabergoline (CABASER, DOSTINEX)
- Pergolide (PERMAX)
- Piribedil (PRONORAN, TRIVASTAL RETARD, TRASTAL, TRIVASTAN, CLARIUM)
- Pramipexole (MIRAPEX, MIRAPEX ER) (**Exception: low dose for RSL treatment-contact SMC for medical monitor approval**)
- Ropinirole (REQUIP, REQUIP XL) (**Exception: low dose for RSL treatment-contact SMC for medical monitor approval**)
- Rotigotine (NEUPRO)

##### MAO-B Inhibitors:

- Isocarboxazid (MARPLAN)

- Phenzamine (NARDIL)
- Rasagiline (AZILECT)
- Safinimide (XADAGO)
- Selegiline (ELDEPRYL, ZELAPAR)
- Tranylcypromine (PARNATE)

#### **Miscellaneous treatments for PD**

- Amantadine (GOCOVRI, SYMMETREL, OSMOLEX ER)
- Anti-Cholinergics (including but not limited to):
  - Trihexyphenidyl (ARTANE)
  - Benztropine Mesylate (COGENTIN)

#### **Neuroleptics/Anti-Psychotics:**

- Acetophenazine (TINDAL)
- Aripiprazole (ABILIFY, ABILIFY MAINTENA, ARISTADA)
- Brexpiprazole (REXULTI)
- Butaperazine (REPOISE, TYRYLEN)
- Cariprazine >3 mg (VRAYLAR)
- Chlorpromazine (THORAZINE, LARGACTIL)
- Chlorprothixene (TRUXAL)
- Clozapine (CLOZARIL, FAZACLO ODT, VERSACLOZ)
- Fluphenazine (MODECATE, MODECATE CONCENTRATE, MODITEN, PROLIXIN (*discontinued brand*), RHOFLUPHENAZINE)
- Haloperidol (HALDOL, HALDOL DECANOATE, HALOPERIDOL LA, PERIDOL)
- Loxapine (ADASUVE)
- Lursidone (LUTUDA)

- Mesoridazine (SERENTIL)
- Molindone (MOBAN)
- Olanzapine (ZYPREXA, ZYPREXA RELPREVV, ZYPREXA ZYDIS)
- Perphenazine (TRILAFON (*single drug*), ETRAFON, TRIAVIL, TRIPTAFEN)
- Pimozide (ORAP)
- Piperacetazine (QUIDE)
- Prochlorperazine (STEMETIL, BUCCASTEM)
- Promazine (PHENERGAN, PHENADOZ)
- Quetiapine (SEROQUEL, SEROQUEL XR)
- Risperidone (RISPERDAL, RISPERDAL CONSTA, RISPERADAL M-TAB)
- Thioridazine (MELLARIL, MELLARIAL-S)
- Thiothixene (NAVANE)
- Trifluoperazine (STELAZINE)
- Triflupromazine (STELAZINE)
- Ziprasidone (GEODON)

**Anticoagulants\*:**

- Dabigatran (PRADAXA, PRADAX, PRAZAXA)
- HEPARIN
- Warfarin (COUMADIN, JANTOVEN)
- Lepirudan (REFLUDAN)
- Bivalirudin (ANGIOMAX)
- Desirudin (LPRIVASK)

**Other Exclusionary Drugs/Supplements to consider:**

- Mucuna Pruriens (*herbal supplement*)

## **Appendix B: List of PPMI Exclusionary Conditions**

*(Version 2.0\_07Dec2021)*

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents -> Exclusionary Meds\_Conditions

### **Exclusionary Conditions:**

- Bone Marrow Transplant
- Chronic anemia requiring transfusion
- Chronic meningitis
- Hepatis B
- Hepatis C
- HIV
- History of organ transplantation
- End stage renal disease on dialysis
- Devices/Implants that interfere with the conduction of study procedures (contact SMC for conditions that limit MRI completion)

## Appendix C: PPMI List of Medications to Hold for DaTscan

(Version 2.0\_02Feb2022)

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents -> Exclusionary Meds\_Conditions

### List of Medications to Hold Prior to DaTscan

Drug Class	Hold Time
<b>Methylphenidates</b>	
Methylphenidate (CONCERTA) ( <i>long acting/ slow release</i> )	18 hrs
Methylphenidate (DAYTRANA) ( <i>transdermal patch</i> )	20 hrs
Methylphenidate (METHYLIN)	14 hrs
Methylphenidate hydrochloride (RITALIN)	48 hrs
<b>Amphetamine Derivatives</b>	
Amphetamine-dextroamphetamine (ADDERALL)	48 hrs
Lisdexamfetamine (VYVANSE)	48 hrs
Pseudoephedrine (SUDAFED)	24 hrs
Armodafinil (NUVIGIL)	72 hrs
Modafinil (PROVIGIL)	72 hrs
Phentermine (LOMAIRA, ADIPEX-P)	5 Days
<b>Bupropion</b>	
Bupropion (WELLBUTRIN)	24 hrs

For more information: *European Journal of Medical Molecular Imaging* (2020) 47:1885-1912

## Appendix D: PPMI Previously Acquired DaTscan Request Form

(Version 3.0\_19Mar2021)

Florence Location: PPMI General Study Folder -> Study Document Templates\_Forms



Parkinson's  
Progression  
Markers  
Initiative

### Request for Previously Acquired DaTscan

The following potential PPMI participant was previously in another study and would like to use a previously acquired DaTscan. In order for PPMI to obtain access to this scan for the PPMI Clinical study (PPMI 002), please see the following details below:

PPMI 002 Participant ID Number:

PPMI 002 Participant Cohort:

Check if participant is also screening for Early Imaging Protocol 004 substudy

PPMI 002 Site Number:

Participant PPMI Screening Visit Date (DD-MON-YYY):

PPMI 002 Study Visit Timepoint:

Study providing DaTscan imaging (full protocol name; please do not use an acronym):

Study Subject ID Number:

Study Site Number:

Previous Scan Date (should be within 6 months of Screening Visit) (DD-MON-YYY):

Study Visit Timepoint:

Submitted by (Name):

Date of Request (DD-MON-YYY):

**Instructions:** Submit to SMC Representative by email. SMC representative to review and coordinate with PPMI Imaging Core.

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### For SMC Completion:

Date Submitted to Imaging Core (DD-MON-YYY):

Submitted by (Name):

Request for Previously Acquired DaTscan  
V3.0 19Mar2021

## **Appendix E: PPMI Participant Lost to Follow Up Guidance**

*(Version 1.2\_12Jan2023)*

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents -> Lost to follow-up Guidance

### **PPMI Participant Lost to Follow-Up Guidance**

#### **Guidance:**

When an enrolled PPMI Clinical participant cannot be reached by the site, site personnel will either follow their internal Standard Operating Procedures (SOPs) or may take the following steps:

1. Site personnel attempts to contact participant through all available contact information (phone, email, emergency contact) and documents the attempt within the participant's study records (PPMI Study Participant Contact Log template below).
2. Approximately two weeks after the initial attempt, if no response is received from the participant, site personnel will contact the participant again through all available contact information. This follow-up attempt is documented within the participant's study records.
3. Approximately two weeks after the second attempt, if no response is received from the participant, site personnel may contact FOUND (415-571-4035 or at [FOUNDinPPMI@ucsf.edu](mailto:FOUNDinPPMI@ucsf.edu)) to confirm the participant's contact information and when the last contact with FOUND occurred (applicable for sites and participants who are a part of FOUND).
  - a. If FOUND does not have any updated information, or there is no response from the participant in two more weeks, the site personnel will send a certified letter (template below) to the participant's last known address requesting the participant to contact the site as soon as possible. This will be documented within the participant's study records.
  - b. If FOUND has additional or updated contact information for the participant, site personnel will perform two attempts, separated by two weeks, to contact the participant at the information provided by FOUND, before proceeding to send a certified letter (template below) to the participant's last known address requesting the participant to contact the site as soon as possible. These additional attempts will be documented within the participant's study records.



4. Approximately three weeks after a certified letter is sent, if no response is received from the participant, the participant will be considered lost to follow up and should be withdrawn from PPMI Clinical.
5. The site personnel will update the status of the participant within the Clinical Trials Statistical and Data Management Center (CTSDMC)EDC and document the date of and reason for withdrawal within the participant's study records. The site personnel will notify the FOUND team and Pathology Core, if applicable, of the participant's withdrawal from PPMI Clinical.

## Appendix F: PPMI Out of Clinic Visit Guidance

( v1.0\_11Jan2021)

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents -> Out of Clinic Guidances\_Shared Resources

### PPMI Out of Clinic (OOC) Visits – Planning and Setup Tips for PPMI Sites

When planning to conduct **all or part of** a study visit out of clinic, consider the following tips when planning and conducting the visit to help familiarize and prepare site staff and the participant for a successful study visit experience.

While a telemedicine/video conference is preferred to enable the most data collection, if telephone is the only feasible method for the participant, that is also acceptable.

The first step is to set up a call with the participant in advance to discuss the topics below and confirm the best way to connect for the visit.

#### 1. Technology Review

- *Telephone only without video*– discuss the activities that will be completed, confirm the date and time of the call.
- *Video conference via computer or smartphone (preferred method)* - discussion checklist:
  - High speed internet?
  - Desktop with web cam, laptop, tablet or smartphone? Is the camera separate or does the participant have to position a built-in camera in order to be seen?
  - How is the sound, lighting and space?
  - Can the participant be seen up close, mid-range and full-body view?
  - Is the chair appropriate for the assessments? Any adjustments needed (e.g., arms on the chair for MDS-UPDRS)?
  - Does the participant need assistance? Is the study partner available to join the OOC visit?
  - If possible, conduct a brief test video visit in advance to troubleshoot any connection issues prior to the OOC visit.
  - Email the participant a few days ahead to confirm the day/time of the test visit and to provide all relevant information needed to join the test video visit (e.g., link to join conference, name of app to download if applicable, dial-in number, meeting ID, password if required, etc.).

- On the day of the test visit, call the participant on the phone to guide them through the video call if needed.
  - On computers, instruct the participant to click on the link in your email.
  - On tablets and smartphones, instruct the participant to download the app and guide them to join the call.

## 2. OOB Visit Review

- Review the schedule of activities with the participant.
- Reassure participant it's OK if things don't go 100%, especially the first time; it's OK if some of the visit activities are not possible (depending on the available access); whatever information is gathered is good information and valued!
- ***The most important aspect is connecting, continuing participant engagement, and seeing how they are doing.***
- "Out of Clinic" is now an option to select in the Visit Status CRF (just scroll through the drop-down list in the EDC to select the reason the visit was conducted out of clinic). Please select this option if the visit is conducted fully or in part out of clinic (i.e., participant completes part of the visit in person and part of the visit out of clinic).

## 3. Additional Resources for Successful OOB Visits (\*shared with permission)

- PPMI Supplement to Protocol Out of Clinic Assessment Guidance (lists assessments that can be done out of clinic) Refer to Florence: <https://us.v2.researchbinders.com/#/app/teams/5e149516d0d359160449be32/documents/5ffcc9f73f89bd0033baf3e2/versions/1>

Your site or institution may also have helpful resources and specific instructions for using its web conferencing platforms for telehealth/telemedicine visits.

*\*A Guide for Conducting Virtual Research Activities (University of Rochester Center for Health & Technology © Copyright 2020).*

Includes tips for setup, testing and conducting virtual research visits, troubleshooting guidance, and information about conducting MoCA and MDS-UPDRS remotely. Refer to Florence:

<https://us.v2.researchbinders.com/#/app/teams/5e149516d0d359160449be32/documents/5ffcc623af324c003a510e1e/versions/1>

- \*Zoom Troubleshooting Flowchart. Refer to Florence: <https://us.v2.researchbinders.com/#/app/teams/5e149516d0d359160449be32/documents/5ffcc61e14c6e100354d8669/versions/1>
- \*Educational video put together by Christopher Tarolli MD MHPE and Alistair Glidden, at the University of Rochester, to train

clinicians to deliver care remotely to individuals with Parkinson disease: [Telemedicine for Parkinson's: a clinician's guide](https://www.youtube.com/watch?v=RGDo0wNAVjk)  
(<https://www.youtube.com/watch?v=RGDo0wNAVjk>) (Funded by PCORI (Patient-Centered Outcomes Research Institute))

## Appendix G: Greenphire ClinCard Program Summary

( v1.0\_06Jul2023)

Florence Location: PPMI General Study Folder -> Protocol, Operations Manual and Procedure Guidance -> Guidance Documents ->

### Greenphire ClinCard Program Summary:

PPMI will be using the Greenphire ClinCard solution to deliver participant stipends for their participation in the PPMI program. Participants have the option to set up their bank accounts for direct deposit or be issued a ClinCard, which is a specially designed debit card for clinical research. The study coordinators will set up **either** the direct deposit or ClinCard option for the participant in the ClinCard portal into which study coordinators will load participant site visit payments as appropriate. Additionally, the participant will have the option to receive study related messages and updates via text and/or email.

**Participants should only have one registration either under the direct deposit or ClinCard option.**

Access to the ClinCard portal must be granted by the Site Management Core (SMC). If access is needed, please contact your site's SMC representative or [ppmi\\_smc@indd.org](mailto:ppmi_smc@indd.org).

### How to Login to [www.clincard.com](http://www.clincard.com)

- 1) Login to [www.clincard.com](http://www.clincard.com).
- 2) Enter your login and password as provided to you. Keep in mind that your login and password are case sensitive so make sure to use capital letters as necessary.
- 3) If you have difficulty logging into [www.clincard.com](http://www.clincard.com), please click on the "Forgot username and password?" link, enter your email address, and click "Reset my password." This will instantly send you an email with a link allowing you to reset your password.

**Note: You can also call our site support team at 215-609-4378.**

### How to Register a Participant:

- 1) Login to [www.clincard.com](http://www.clincard.com)
- 2) Click on "Register Subject"
- 3) Select Study, if applicable
  - a. PPMI DD: direct deposit option

b. PPMI ClinCard/CC: debit card option

4) Enter the required information into the brief form.

a. Subject id field – the required subject id format is 4, 5 or 6 numeric digits (e.g. PPMI ID).

**Note:** If you would like the participant to receive payment confirmations or appointment reminders, be sure the “Email (Enable)” and/or “Text Messaging (Enable)” checkboxes are selected.

5) Click on the “Register” button.

6) You will be brought to the “Subject Information” screen where you can set up a bank account or ClinCard, make a payment, or edit a participant’s information.

7) If you have difficulty making a payment for the first time please call the ClinCard site support team at 215-609-4378 and they will be happy to walk you through it

### **How to Look Up a Participant Who Has Already Been Registered:**

1) Login to [www.clincard.com](http://www.clincard.com)

2) Click on “Look Up Subject”

3) Search for the participant you want to pay by entering one of the following pieces of information and click on “Search.”

a. First name and/or last name

b. Subject ID

c. Subject’s initials

d. Participant Email

e. Last 4 digits of ClinCard

4) Click on the underlined name of the participant.

5) You will be brought to the “Subject Information” screen where you can perform any of the actions required for the participant, e.g., issue payment.

### **Option #1: Direct Deposit**

#### **How to Setup a Bank Account for a Participant:**

Once you have selected an existing participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen, you will see options that represent all of the actions you can perform on the participant.

1) Click on “Add Bank Account” and a pop-up screen will appear.

- 2) Enter the account number, routing number, and bank name.
- 3) Click on the “Submit” button.
- 4) Once the bank account has successfully been set up, you will receive a confirmation message at the top of the “Subject Information” screen.

## **Option #2: ClinCard**

### **How to Assign a ClinCard to a Participant:**

Once you have selected an existing participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen, you will see options that represent all of the actions you can perform on the participant.

- 1) Click on “Assign ClinCard” and a pop-up screen will appear.
- 2) In the “New Card” field, enter the 16-digit number visible through the window of one of the ClinCard card packages you received.

**Note:** There is no need to open the envelope prior to providing to the participant

- 3) Click on the “Assign” button.
- 4) Once the card has successfully been assigned, you will receive a confirmation message at the top of the “Subject Information” screen.
- 5) Now an option to “Replace ClinCard” appears. In the event that a participant loses their card, you can replace that card for them by clicking on “Replace ClinCard,” and follow the steps above, using a card number from a new ClinCard card package.

**Note:** This will inactivate the lost card and automatically transfer any available/pending balance to the newly assigned ClinCard

### **How to Make a Site Visit Payment:**

Once you have selected a participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen, you will see options that represent all the actions you can perform on the participant.

- 1) Click on “Request Payment” and a pop-up screen will appear.
- 2) Select from the dropdown box which milestone the participant is being paid, e.g., Screening, Baseline, Visit 1, etc.
- 3) Click on the “Pay” button.
- 4) Once the payment has successfully been submitted, this will be reflected in your “Recent Activity” on the left-hand side of the screen as well as on the Audit History tab.
- 5) If the participant has opted to receive email and/or text messages, the participant will receive a payment initiation communication when the payment has been submitted.

## How to Make a Travel Payment:

Once you have selected an existing participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen, you will see options that represent all of the actions you can perform on the participant.

- 1) Click on “Request Reimbursement” and you will be brought to a new page that will give you three travel reimbursement options:
  - a. Add Flight
  - b. Add Other (this travel bucket is to include all of the payments that are to be reimbursed for Hotel, Meal, Parking and Transportation, and Mileage and Tolls)

2) Enter the required information into the fields that will appear in the pop-up window.

**Note: For flight payments to be approved, documentation is required to be uploaded.**

3) Click on the “Save” button.

4) You will also have the option to upload a receipt by clicking on the “Add Receipt” button at the far right of the screen.

**VERY IMPORTANT: Receipts uploaded that contain identifiable information for PPMI study participants is to be unidentified.**

5) When you are finished making payment requests click on the “Submit Request” button

6) Once the payment has successfully been submitted, this will be reflected in your “Recent Activity” on the left-hand side of the screen as well as on the Audit History tab.

7) If the participant has opted to receive email and/or text messages, the participant will receive a payment initiation communication when the payment has been submitted and approved.

**Note:** Travel payments over a certain amount will require sponsor approval in the ClinCard Portal prior to payment being initiated.

Approvers are automatically alerted by email each time a travel reimbursement request is made.

## How to Make a Manual Participant Payment:

Manual participant payments are any payments which are not site or travel payments. Namely, these are adverse event-related payments.

Occasionally, a participant may experience an adverse event that his or her insurance is unable to cover. Should this happen, you can use the manual participant payment feature to reimburse the participant for their medical bills.



Once you have selected an existing participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen you will see options that represent all of the actions you can perform on the participant.

- 1) Click on “Request Reimbursement” and a pop-up screen will appear.
- 2) Enter the payment value that you want to pay the participant in the “Amount” field.
- 3) Add an appropriate comment in the “Note” field.
- 4) You will also have the option to upload a receipt by clicking on “Browse” under the Receipt section to upload a receipt.

**VERY IMPORTANT: Receipts uploaded that contain identifiable information for PPMI study participants is to be unidentified.**

- 5) Once the payment has successfully been submitted, this will be reflected in your “Recent Activity” on the left-hand side of the screen as well as on the Audit History tab.
- 6) If the participant has opted to receive email and/or text messages, the participant will receive a payment initiation communication when the payment has been submitted and approved.

**Note:** All “manual” payments will require sponsor approval in the ClinCard Portal prior to payment being initiated. Approvers are automatically alerted by email each time a travel reimbursement request is made.

### **How to Setup an Appointment Reminder:**

Once you have selected an existing participant or registered a new participant, you will be brought to the “Subject Information” screen. On the right-hand side of the screen, you will see options that represent all of the actions you can perform on the participant.

- 1) Click on the “Schedule Appointment” button and a pop-up menu will appear.
- 2) Using the dropdowns, enter the correct date and time of the participant’s next appointment.
- 3) Click on the “Schedule” button.
- 4) The appointment has been stored and will appear at the bottom of the “Subject Information” screen under the header “Appointments.”
- 5) If the participant has opted to receive email and/or text messages, the participant will receive a reminder communication 3 days and 1 day prior to the participant’s next appointment.

### **How to Request Assistance:**

If you have questions or comments about using the [www.clincard.com](http://www.clincard.com) Admin Portal, you may reach the ClinCard site support team by:

- 1) Submitting an email request through the “Support” link within the [www.clincard.com](http://www.clincard.com) website
- 2) Directly emailing at [support@greenphire.com](mailto:support@greenphire.com)
- 3) Calling the site support team directly at 215-609-4378 or (+44) 208 150 6470 between the hours of 8:00 am and 10:00 pm Eastern Time (Monday through Friday) in order to speak with a ClinCard team member.

**If Fraudulent Activity is Detected:**

- 1) Participant identifies unauthorized transaction(s)
- 2) Participant contacts Greenphire Support within 60 days.
  - a. United States/Canada Toll Number:+1 215-609-4378
  - b. International Toll Number:+44 208 150 6470
- 3) If past 60-day window, dispute may be declined.
- 4) Participant reviews transaction history and confirms if unauthorized transactions occurred.
- 5) Greenphire Support freezes the participant’s ClinCard and provides dispute form to the participant (Greenphire Support can also replace the card upon request)
- 6) Participant completes dispute form and returns it to the details provided on the form.
- 7) Greenphire completes investigation within 90 days from the time the dispute form is submitted.

## Appendix H: Prodromal Participant Change of PPMI Diagnosis

( v1.0\_13Jul2022)

### Change of Diagnosis for the Prodromal Participants between Screening and Baseline

This guidance provides instruction as to how to manage a Prodromal participant's change in clinical or research diagnosis to Parkinson's disease (PD) between the start of the Screening visit through completion of the Baseline visit (i.e., between time of consent to enrollment).

A site investigator (or sub-investigator) may encounter a scenario where a Prodromal participant receives a clinical diagnosis of PD, or there is a change in research diagnosis to PD, before or at the Baseline visit. However, the consented participant should continue to be assessed under the Prodromal protocol eligibility criteria. As such, it is advised to:

- **Maintain participant assignment in the Prodromal cohort** but indicate *the new diagnosis of PD on the Primary Clinical Diagnosis CRF*.
  - If the participant received a clinical diagnosis of PD outside of the context of PPMI research assessments, this also should be documented on the *Primary Clinical Diagnosis CRF*.
- Notify the SMC.
- The participant will remain in the Prodromal cohort and continue to follow the Prodromal cohort Schedule of Activities.
- *The Consensus Committee* will review all cases with a change in diagnosis and assign a Research tag that will then exclude these participants from the Prodromal analytic dataset analysis and include them in the PD analytic dataset.
- Disclosure to the participant regarding this change in primary clinical diagnosis is left to the discretion of the investigator.

If a participant receives a clinical diagnosis of PD *and started treatment prior to completion of Baseline visit* (and Investigator agrees with the diagnosis):

- Participant should be screen failed.
- **If participant is willing to go off treatment** (and agrees to remain off treatment for 6 months after Baseline), then they will be permitted to re-screen for the PD cohort as a new participant.
- Notify the SMC to properly document re-screening.

## Appendix I: SPECT and Baseline Visit Guidance

(v1.0\_07Aug2023)

### PPMI002 Clinical SPECT and Baseline Visit Guidance

Per protocol, the Screening and Baseline visits should be within 60 days of each other. However, due to scheduling conflicts, participant hesitation and other various reasons, the Baseline visit may occur past the 60-day window. This is not a reportable protocol deviation. The guideline is that the Baseline visit should occur within 6 months of the SPECT scan date. Every effort should be made by the site to perform the Baseline visit by this time and communication with the participant should emphasize the timing required.

In the event that a Baseline visit cannot occur within 6 months of the SPECT scan **the SPECT must be repeated and eligibility reconfirmed** in order for the participant to continue their participation and enroll into PPMI. To ensure eligibility is returned in a timely manner, **inform your SMC site representative of the scheduled date of the repeat SPECT scan**. The site must have received the SPECT eligibility for this repeat scan before proceeding with the Baseline visit. If the participant agrees to have the SPECT repeated, the guidance is as follows:

- The participant must be re-consented.
  - Within the EDC, under the Event Driven tab, the *Documentation of Informed Consent* CRF must be completed with the date of the re-consent. The re-consent details are to be documented within the *Informed Consent Tracking Log*.
- Review the participant's eligibility.
  - Within the EDC, delete and complete the *Inclusion Exclusion Criteria* CRF
- For participants of childbearing potential, the pregnancy test must be repeated prior to the SPECT scan.
  - Within the EDC, add and complete an additional *Pregnancy Test* CRF
- Schedule and perform a repeated SPECT scan and upload to Invicro under the Screening timepoint.
  - Within the EDC, add and complete an additional *Dopamine Imaging* CRF
- Complete an assessment for AEs the day of the SPECT as well as the Telephone AE assessment within 2-3 business days.
  - Within the EDC, add and complete an additional *Adverse Event In-Clinic Assessment* CRF
  - Within the EDC, add and complete an additional *Adverse Event Telephone Assessment* CRF
- Following receipt of SPECT eligibility:
  - Complete the *Inclusion Exclusion Criteria* CRF based on eligibility.
  - Delete and complete the Visit Status CRF

To note, the research blood sample at Screening for a Prodromal participant does not have to be collected as part of this rescreening process.