



Parkinson's
Progression
Markers
Initiative

PPMI

Operations

Manual

Table of Contents

1.0	GENERAL INFORMATION	4
	Study Management Contacts	4
	Medical Monitor Contact	5
	PPMI Study Core Primary Personnel	6
	Study Personnel	9
	IND SMC Office Closings	10
2.0	OBTAINING INFORMED CONSENT	11
	All PPMI Participants	11
	Designation of Research Proxy	11
	GDPR Addendum	11
3.0	ENROLLMENT	11
	Participant Profile Information	11
	Activities Prior to Enrollment	12
	Protocol Deviations	13
	Protocol Waivers	13
4.0	IMAGING	14
	Ordering DaTscan™ (US Sites)	14
	Order Cancellation (US Sites)	14
	Shipment to Sites (US Sites)	15
	Ordering DaTscan™ (EU/Israel Sites)	15
	Storage of DaTscan™	15
	Administration of DaTscan™	16
	Accountability of DaTscan™	16
	^{99m} Tc-TRODAT-1 (Lagos only)	16
5.0	SOURCE DOCUMENTATION.....	16
	Types of Visits	17
	Assessment and Study Supply Ordering	17
6.0	SIGNIFICANT STUDY EVENTS	18
	Initiation of PD Medication	18
	Adverse Event Reporting.....	18
	Serious Adverse Event Reporting-PPMI002 Clinical Protocol	18
7.0	LABORATORY SPECIMEN MANAGEMENT	20
	Pregnancy Test Kits	20
8.0	SITE MANAGEMENT.....	20
	Site Activation Process	21
9.0	ESSENTIAL DOCUMENTS & ELECTRONIC TRIAL MASTER FILE (eTMF)	
SYSTEM	22	

	Essential Documents	22
	eTMF System	28
	Participant Transfer Process.....	28
	Table of Documents	32
10.0	APPENDICES.....	36
	Appendix A: List of Exclusionary Medications (Generic Name/Brand Names) for PPMI	36
	Appendix B: List of PPMI Exclusionary Conditions.....	38
	Appendix C: PPMI List of Medications to Hold for DaTscan	39
	Appendix D: PPMI Participant Lost to Follow Up Guidance	40
	Appendix E: PPMI Out of Clinic Visit Guidance	41
	Appendix F: Greenphire ClinCard Program Summary.....	43
	Appendix G: Prodromal Participant Change of PPMI Diagnosis	48
	Appendix H: Screening and Baseline Visit Guidance	49

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>Vice President <u>Bridget McMahon</u> Phone: +1 443-695-5220 Email: bmcmahon@indd.org</p> <p>Associate Director <u>Jessica Dimos</u> Phone: +1 203-645-9163 Email: jdimos@indd.org</p> <p>Senior Manager <u>Jillian Ricci</u> Phone: +1 203-430-6160 Email: jricci@indd.org</p> <p>Senior Associate <u>Erin Nichols</u> Phone: +1 765-586-5925 Email: enichols@indd.org</p> <p>Senior Associate <u>Jan Nevy</u> Phone: +1 410-322-9654 Email: jnevy@indd.org</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>Note: If you have any questions about the PPMI study, contact SMC, and they will triage you to the related study core.</p>
<p>Associate II <u>Cari Rainville</u> Phone : +1 203-215-9611 Email: crainville@indd.org</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>
<p>Director, Medical Science Liaison <u>Lynell Lemon</u> Phone: + 1 619-403-6774 Email: llemon@indd.org</p>	<p>SMC-managed PPMI Clinical referrals, SMC Interns, PPMI Publications</p>
<p>Associate II, Publications <u>Tali Cohen</u> Phone: +1 203-513-0120 Email: tcohen@indd.org</p>	<p>PPMI Publications</p>

Medical Monitor Contact

Whom to Connect with	Reason to Contact
<p>PPMI Medical Monitor Andrew Siderowf Phone: +1 215-280-2396 Email : Andrew.Siderowf@pennterms.upenn.edu</p>	<p>Urgent (e.g., after hours) questions about participant safety and enrollment (e.g., SAE reports, eligibility waivers); 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.</p>

Michael J Fox Foundation for Parkinson’s Research Study Personnel

Michael J Fox Foundation for Parkinson’s	Study Responsibilities
<p>Program Director, Clinical Research Tawny Willson</p>	<p>Manages Site Contracts and Study Budgets</p>
<p>Sr. Clinical Operations Specialist, Clinical Research Brandy Fowler</p>	<p>Manages sub-study contracts and budgets</p>
<p>Grants Manager, Research Operations Gabrielle Tran Shelby Parker</p>	<p>Supports site payments (Greenphire) Supports site awards and sub-study contracts</p>
<p>Patient Engagement, Clinical Research Caitlin Kelliher (recruitment), Christina Destro (retention); Courtney Pico (recruitment & retention & IRB/translations)</p>	<p>Manages recruitment and retention efforts across sites. Manages recruitment & retention materials (including translation)</p>

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
Gena Antonopoulos	Project Manager	Pathology
Michelle Totten	Project Manager	Screening
Jan Hamer	Project Manager	Biorepository
Audra Bright	Project Manager	Travel

PPMI IU Cores & Study Personnel	Study Responsibilities
<p>Screening Core Email: ppmi@iu.edu Phone: (888) -830-6299</p> <p>Laura Heathers and Michelle Totten, Project Managers</p>	<p>Manages centralized screening for prodromal participants and referral to PPMI sites, confirms eligibility for genetic cohorts.</p>
<p>Travel Core Email: ppmitravel@iu.edu Phone: (317)-278-9440</p> <p>Laura Heathers and Audra Bright, Project Managers</p>	<p>Coordinates travel for centrally managed PPMI participants/candidates</p>

PPMI IU Cores & Study Personnel	Study Responsibilities
<p>Biorepository Email : ppmibio@iu.edu Phone : 1-317-274-5744</p> <p>Jan Hamer, Project Manager</p>	<p>Supports Biorepository and specimen collection and management</p>
<p>Pathology Core Email: ppmipath@iu.edu Phone: (844)-280-0036</p> <p>Laura Heathers and Gena Antonopoulos, Project Managers</p>	<p>Coordinates brain tissue donations for PPMI participants</p>

PPMI Imaging Core & Study Personnel	Study Responsibilities
<p>Imaging Core</p> <p>Elyse Charlton Project Manager - Imaging Research echarlton@xingimaging.com</p> <p><i>For all questions related to image data transfer or account credentials</i> <i>issues:</i>corelab.support@xingimaging.com</p> <p><i>For all technical questions related to scanner protocol setup or image quality control:</i></p> <p>corelab.support@xingimaging.com</p> <p>Additional Resource Contact: Justin Albani Imaging Operations jalbani@xingimaging.com</p>	<p>Lead project manager for Imaging Core, manages external and internal communications, timelines, deliverables, site questions, site setup processes.</p> <p>Supports transfer of scans and corresponding data, account credentials.</p> <p>Supports technical questions around scanner protocol setup, scanning procedures, or image quality control</p>

PPMI FOUND Study Personnel	Study Responsibilities
<p>FOUND Study (foundinppmi@ucsf.edu) Cheryl Meng, Project Manager</p> <p>Kathleen Comyns, Project Manager</p>	<p>FOUND Study support/management</p>

PPMI Data Management Core Study Personnel	Study Responsibilities
For all technical questions related to the Clinical EDC System: CTSDMC-PPMI@uiowa.edu	Supports Data Management including the EDC and Query System
Dixie Ecklund, Director of Operations dixie-ecklund@uiowa.edu	
Trevis Huff, Lead Data Manager trevis-huff@uiowa.edu	
Christine Kohnen christine-kohnen@uiowa.edu	
Holly Ernst, Lead Project Manager holly-ernst@uiowa.edu	
PPMI Statistics Core Study Personnel Christopher Coffey, PI Statistics Core Email: christopher-coffey@uiowa.edu Dixie Ecklund, Director of Operations Email: dixie-ecklund@uiowa.edu Chelsea Caspell-Garcia, Lead Statistics Manager Email: chelsea-caspell@uiowa.edu	Study Responsibilities Supports statistical analyses that will be performed on the PPMI data and samples

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-Investigator(s), as well as co-coordinator(s) 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 complete 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 (3rd Monday in January)

President's Day (3rd Monday in February)

Spring Holiday (Friday before Easter)

Memorial Day (4th 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 (1st Monday in September)

Columbus Day (2nd Monday in October)

Thanksgiving (4th Thursday and Friday in November)

Christmas (December 25 and possible day before or after)

2.0 OBTAINING INFORMED CONSENT

All PPMI Participants

All newly screened PPMI participants and those requiring re-consent will give informed consent using the main PPMI Clinical protocol consent. Consent may be obtained remotely through an eSignature platform as instructed by SMC.

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 (required for EU sites). 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 per local regulatory requirements.

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

Activities Prior to Enrollment

Participants may be identified to participate in PPMI Clinical through targeted recruitment campaigns, directly from a clinical site, myPPMI, or based on participation in other PPMI related recruitment efforts. These other recruitment efforts obtain information from online questionnaires assessing general health and risk of PD, information from additional remote testing including olfactory testing such as the University of Pennsylvania Smell Identification Test (UPSIT), information based on known PD risk, such as possible REM sleep behavior disorder (RBD) or known genetic variants associated with increased PD risk. Individuals identified through centralized PPMI study recruitment methods, such as ST Direct, completed under separate consent as applicable, will be referred to PPMI clinical sites to consent to participation in PPMI Clinical and undergo the Screening Visit. Prescreening of all participants for smell via completion of an UPSIT will be done for all cohorts outside of the Clinical protocol. For potential genetic variant participants lab results must be reviewed and confirmed for eligibility by the PPMI Screening Core.

All participants:

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 SAA 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 the 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. Also, the appropriate cohort *Inclusion/Exclusion Criteria* eCRF should 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 Deviations

For PPMI 002 Clinical study and all observational/limited risk sub-studies that fall under the PPMI program, protocol deviations are considered any action that deviates from the protocol that puts participants’ safety at risk or compromises the integrity of the study.

Sites will follow their IRB/Ethics board of record’s regulations in reporting the protocol deviation in which participants’ safety is compromised. Such protocol deviations will be documented on a Protocol Deviation Report and filed in the site’s records within the site’s binder in the Florence eTMF (electronic Trial Master File). A Protocol Deviation Log will also be updated to list all deviations reported within the duration of the site’s participation in PPMI Clinical, to be submitted to the IRB/Ethics committee as required (Continuing Annual Review, etc.).

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, ideally prior to screening. 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.

^{99m}Tc-TRODAT-1 (Lagos only)

Refer to the SPECT Imaging Trial Operations Manual (TOM) for details regarding the ^{99m}Tc-TRODAT-1 product (ordering, storage, administration, and accountability).

5.0 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 by the person performing the assessment or collecting the data, 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 (within 72 hours). A full set of current CRFs will be available to the PPMI General Study folder in Florence as well as the EDC system under Study Materials within Case Report Forms. 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 11) 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>.

6.0 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 12 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.

New Clinical Diagnosis

Please refer to the PPMI 002 Clinical Protocol section 12 for guidance on scheduling a "New Clinical Diagnosis" visit.

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. Additionally, sites will email PPMI_SAE@indd.org to notify the SMC of the SAE. 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 (¹²³I-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.

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

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. **Refer to the PPMI Assessments and eCRF Completion Manual for detailed instructions regarding the completion of this eCRF.**

7.0 LABORATORY SPECIMEN MANAGEMENT

Refer to the LabCorp 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, processing and shipment 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™. The result must be confirmed as negative prior to proceeding with the injection. **Sites should use their local lab for supplies and testing as PPMI does not supply or process these tests.**

8.0 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 (all may be on-site or remote)
 - a. Pre-Study Visit to review site interest, capabilities and resources
 - b. Site Initiation Visit
 - c. Interim Site Visits
 - d. Closeout Visit
2. Other 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 oversight and monitoring, via Florence eBinders™ system (Informed Consent review, etc.)
 - e. Centralized data monitoring
 - i. Compliance review PPMI EDC ongoing review and report generation
 - ii. Remote review of data metrics
 - f. Safety Management
 - i. Safety assessments
 - ii. 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. IND staff will work with sites throughout the IRB/Ethics submission process.
 - ii. IND staff will review the site's draft consent(s) for acceptability prior to IRB/Ethics submission.
 - iii. If the site is not able to use the central IRB, the SMC will request the date of the IRB/ethics review to track progress towards approval.
 - 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 into 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.

9.0 ESSENTIAL DOCUMENTS & ELECTRONIC TRIAL MASTER FILE (eTMF) SYSTEM

Essential Documents

PPMI utilizes 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.

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 regulatory document management. Documents required for PPMI will be uploaded into this system. This folder and its subfolders are accessible to trained site members only, along with the SMC, who will have monitoring oversight of and provide support for its use, as well as approve 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 (HubSpot) 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

Sub-Folder	General Description of Contents
04. INFORMED CONSENT	Current and Prior Approved Version Templates Completed ICFs for Monitoring (temporary)
05. PARTICIPANT-FACING ASSESSMENTS	Current and Prior Approved Versions of blank participant assessments (PROs) and the PPMI Cognitive Assessment Bundle (e.g., copies of paper-sourced participant worksheets)
06. RECRUITMENT_RETENTION RESOURCES	Current and Prior Approved Versions of Recruitment and Retention materials (general, site-specific, etc.)
07. CASE REPORT FORM (CRF)	Current and Prior Approved Versions of CRFs (blank set of unique forms)
08. INSTITUTIONAL REVIEW BOARD (IRB)_INDEPENDENT ETHICS COMMITTEE (EC)	<ul style="list-style-type: none"> • PPMI 1.0 Continuing Review and Study Closure Acknowledgment (for 1.0 sites) • IRB_EC Approval Letters; Correspondence; Progress Reports; Correspondence (to/from), Safety Reports • IRB_EC Roster (if not using WCG as IRB)
09. STUDY PERSONNEL	<ul style="list-style-type: none"> • Curriculum Vitae • Delegation of Responsibilities Forms • Licenses
10. IMAGING	<ul style="list-style-type: none"> • Imaging Approvals to scan (MRI and SPECT) • Technical Site Setup Report
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"> • Visit Correspondence • Site Visit and Action Items Logs
13. CLINICAL LABORATORY	<ul style="list-style-type: none"> • Lab Credentials (e.g., CLIA, CAP) • CV lab director • Local lab normal references (e.g., if local lab is utilized, e.g., for PT/PTT at other than Screening visit)
14. BIOLOGICAL RESEARCH SAMPLES	<ul style="list-style-type: none"> • Biological Sample Handling • Shipping Records • Manual
15. SAFETY REPORTS	SAE reports
16. CORRESPONDENCE	Essential Correspondence with IU, MJFF, SMC, Other
17. TABLET	<ul style="list-style-type: none"> • PPMI 2.0 Site Tablet Receipt and Acceptance Form (or note to file if site is using own device)
18. OTHER	<ul style="list-style-type: none"> • Miscellaneous • Nonconformance Reports, related to missing lumbar punctures • Any site related Note to File documents • Any protocol deviation reports & log for site
19. COMMUNICATIONS	This folder is set up as a place to save key communications and documents.
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)

*Note: all studies under PPMI will have similar folder structures to those noted above and may be subjected to change due to the complexity or type of study (investigational vs. observational).

Refer to Florence User Quick Start Guide in the PPMI 002 General Study File > PPMI System Platform User Guides > 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	
1	<p>Contact SMC if a participant transfer is being discussed.</p> <ul style="list-style-type: none"> SMC to provide transferring site with potential site nearest the participant's desired location.
2	<p>Confirm participant wishes to transfer to site provided; notify SMC.</p> <ul style="list-style-type: none"> 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. Obtain written permission from participant to share name and contact information with new site coordinator before providing to new site coordinator. In notification to SMC, include participant's Greenphire reimbursement details: direct deposit or ClinCard user (include last 4 digits of ClinCard, if applicable). Confirm all participant information in EDC is complete.
3	<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>

4

Contact participant to confirm transfer. Provide new site coordinator contact information to participant should they have questions or concerns.

- If applicable, discuss the importance of establishing a clinical care provider (e.g., if relocating).
- Follow up with new site to ensure participant has been successfully contacted by new site and that the transfer will proceed; confirm with SMC.

5

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">• Once consent obtained, new site assumes responsibility for the participant and the originating site is relinquished of these responsibilities.• SMC to transfer participant to new site in EDC.• 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.
2	<p>Add participant ID to site list in the EDC and enter re-consent data in EDC (into <i>Informed Consent Tracking Log eCRF</i>).</p>
3	<p>Schedule participant's next visit if not conducted at the time re-consent obtained.</p>

Instances Where Transfer is not Complete

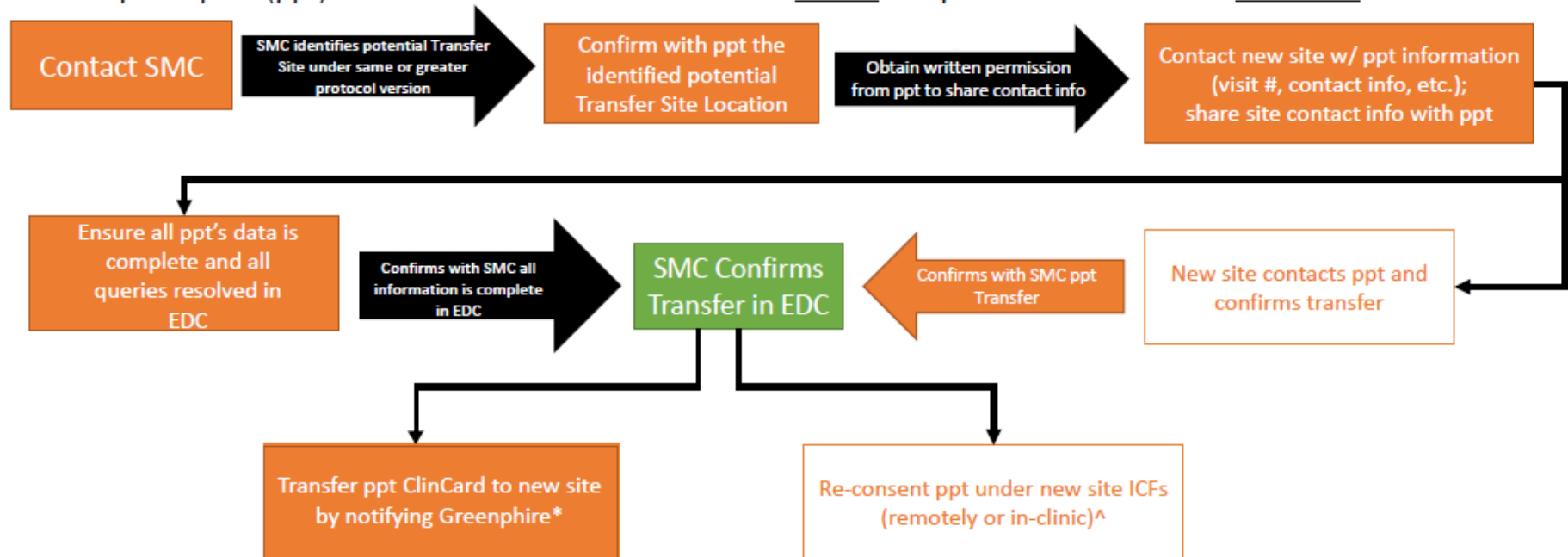
1	<p>Participant unable to be reached by new site.</p> <ul style="list-style-type: none">• Transferring site to follow up with participant to determine continued interest in transferring.
2	<p>Participant changes mind about transfer.</p> <ul style="list-style-type: none">• If participant relays this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

Other

1	<p>Transfer of Participant Greenphire Account</p> <ul style="list-style-type: none">• 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).
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"> • DUPLICATE Template located in Florence General study file • <i>File to be named: PPMI 2.0 Site XXX Contract Location DDMMYYYY Note to file</i> • Fill placeholder and apply Investigator eSignature to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 02 AGREEMENTS > PPMI 2.0 Site XXX Contract Location DDMMYYYY Note to file
Protocol, IRB/Ethics approved	<ul style="list-style-type: none"> • If possible, please rename file to: PPMI 002 Site XXX IRB_EC Approval DDMMYYYY (with date representing date of approval) • Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 03 PROTOCOL > Current Approved Protocol
Informed consent(s), IRB/Ethics approved	<ul style="list-style-type: none"> • If possible, please rename file to: PPMI 002 Site XXX Main/Prodromal ICF_DDMMYYYY (insert version date) Approval DDMMYYYY (with date representing date of approval) • Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 04 INFORMED CONSENT > Current Approved Informed Consents • Advanced directive, HIPAA (if separate) and any other applicable consent documents may be filed here (and named similarly).
Participant-Facing Assessments, IRB/Ethics approved	Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 05 PARTICIPANT-FACING ASSESSMENTS > Current Approved Version(s)
Recruitment Retention Resources, IRB/Ethics approved	Upload to Florence Binders > PPMI 002 > PPMI 002- Site XXX Site Name - Investigator Site File > 06 RECRUITMENT_ RETENTION RESOURCES/Current Approved Version(s)
Case Report Form (CRF), blank unique set download from General Study File	DUPLICATE from Florence Binders > PPMI 002 > PPMI 002 General Study File/ CASE REPORT FORM/Current Version to <u>PPMI 002 - Site xxx Site Name Investigator Site File 07 CASE REPORT FORM (CRF)</u>

Document	Comment
IRB/Ethics Committee (EC) Approval Letter)	Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 08 INSTITUTIONAL REVIEW BOARD (IRB)_INDEPENDENT ETHICS COMMITTEE (EC) > Current Approved Protocol/Approval Letters
Imaging approval to scan	Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 10 IMAGING > IMAGING APPROVALS
Local lab (if using) CLIA, CAP, CV Medical Director, references normal ranges	<ul style="list-style-type: none"> For sites using local labs for Screening. Note <u>all sites</u> will use central lab (LabCorp) Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 13. CLINICAL LABORATORY > Lab_Miscellaneous
Site Tablet Receipt and Acceptance Form (iPad)	Fill placeholder and apply eSignature to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 17 TABLET > PPMI 2.0 Site Tablet Receipt and Acceptance Form (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"> Sample Located in Florence General study file Site to complete contact forms in HubSpot for each team member SMC to place printout of approved contact in this folder for future reference

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"> • DUPLICATE Template located in Florence General study file • Files to be named PPMI 002 Site XXX DR – Last Name_First Initial • Upload and apply eSignatures of staff personnel and PI to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name > 09 STUDY PERSONNEL > Delegation of Responsibilities Forms (may fill placeholders if provided; otherwise, upload into folder)
Curriculum Vitae (includes current role, institution/address)	X	X	X	X	X			<ul style="list-style-type: none"> • File to be named PPMI 002 Site XXX CV_Last Name_First Initial • Upload and apply eSignature to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name > Investigator Site File > 09 STUDY PERSONNEL > Curriculum Vitae • Fill placeholders if applicable; otherwise, upload into folder
Professional License/Renewals (as applicable)	X	X	X	X*	X			<ul style="list-style-type: none"> • Upload to Florence Binders > PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 09 STUDY PERSONNEL/ Licenses_Renewals • Fill placeholders if applicable; otherwise upload into folder
Florence (full or Find & Sign, as applicable)	X	X	X	X	X	X	X	Upload training certification to appropriate folder in Florence, under PPMI 002 > PPMI 002 - Site XXX Site Name - Investigator Site File > 11. TRAINING
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 ¹	

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

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

10.0 APPENDICES

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

(Version 3.0 07Dec2023)

Florence Link:

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 separate guidance document List of Medications to Hold Prior to DaTscan for more information.

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 RLS treatment – contact SMC for medical monitor approval)
- Ropinirole (REQUIP, REQUIP XL) (Exception: Low dose for RLS treatment – contact SMC for medical monitor approval)
- Rotigotine (NEUPRO)

MAO-B Inhibitors:

- Isocarboxazid (MARPLAN)
- Phenelzine (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)
- Butaperazine (REPOISE, TYRYLEN)
- Brexpiprazole (REXULTI)
- 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)

Appendix B: List of PPMI Exclusionary Conditions

(Version 2.0_07Dec2021)

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)

List of Medications to Hold Prior to DaTscan

Drug Class	Hold Time
Methylphenidates	
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
Amphetamine Derivatives	
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
Bupropion (WELLBUTRIN)	24 hrs

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

Appendix D: PPMI Participant Lost to Follow Up Guidance

(Version 1.2_12Jan2023)

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 FOUNDPPI@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 E: PPMI Out of Clinic Visit Guidance (v2.0_20Sep2024)

PPMI 002 Clinical Out of Clinic (OOC) Visits – Planning and Setup Tips for PPMI Sites

When planning to conduct **all or part of** an in-clinic (annual) study visit for PPMI002 Clinical as an Out of Clinic (OOC) visit, 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 the telephone is the only feasible method for the participant, that is also acceptable. Refer to the most current [PPMI Out of Clinic \(OOC\) Schedule of Activities \(SOA\)](#) on the clinical assessments that can be done remotely.

The first step is to schedule 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 and confirm the date and time of the call.
- *Video conference via computer or smartphone (preferred method)* - discussion checklist:
 - High-speed internet?
 - Desktop with webcam, laptop, tablet webcam, laptop, tablet, or smartphone? Is the camera separate, or must the participant position a built-in camera 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 care partner available to join the OOC visit?
 - If possible, conduct a brief test video visit to troubleshoot any connection issues before 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. OOC Visit Review

- Review the schedule of activities with the participant.
- Reassure the participant that it's acceptable 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 aspects are connecting, continuing participant engagement, and seeing***

how they are doing.

- "Out of Clinic" is an option to select in the Visit Status CRF (scroll through the drop-down list in the EDC to select why the visit was conducted outside the clinic). Please select this option if the visit is conducted entirely or as a hybrid visit (i.e., the participant completes part of the visit in person and part of the visit outside the clinic).

The MoCA can also be done via video assessment. The principles of cognitive testing with the MoCA remain the same, with some minor changes:

- Trails: Show the trail and say: "Please tell me where the arrow should go next to follow the pattern, I am showing you."
- Cube: Show the cube and say: "Copy the cube."
- Date: "Look directly at the camera and tell me today's date, day of the week, month, and year."
- Place: "What hospital/clinic/institution am I calling you from?"
- City: "What is the city in which our hospital/clinic/institution is located?"

3. Additional Resources for Successful OOC Visits (*shared with permission)

Out of Clinical (OOC) Annual Visit Schedule of Activities (SOA). Refer to [Florence](#):

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://v2.researchbinders.com/#/app/teams/5e149516d0d359160449be32/binders/5e99cb9659732e0_041903ab8/folders/5ffcc5e22494430033ddfa7a
- *Zoom Troubleshooting Flowchart. Refer to Florence:
https://v2.researchbinders.com/#/app/teams/5e149516d0d359160449be32/binders/5e99cb9659732e0_041903ab8/folders/5ffcc5e22494430033ddfa7a
- *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's disease: *Telemedicine for Parkinson's: a clinician's guide*
(<https://www.youtube.com/watch?v=RGDo0wNAVjk> (Funded by PCORI (Patient-Centered Outcomes Research Institute)

Appendix F: 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.

How to Login to www.clincard.com

- 1) Login to 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, 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
- 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
- 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 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 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 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 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 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 unidentifiable.

- 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 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 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 website
- 2) Directly emailing at support@greenphire.com
- 3) Call 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 G: 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 PPMI ID will be assigned 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 H: Screening and Baseline Visit Guidance

(v1.0_14Nov2024)

PPMI002 Clinical: Timing of Screening 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. Every effort should be made by the site to perform the Baseline visit within 6 months of the Screening visit completion and communication with the participant should emphasize the timing required.

In the event that a Baseline visit cannot occur within 6 months of the Screening visit completion, inform the SMC of the planned Baseline date.