



MRI Technical Operations Manual

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1 Overview

The imaging core lab is Invicro based in New Haven, Connecticut, USA. In conjunction with the study sponsor, Invicro will provide the imaging center with any technical support necessary to ensure optimal imaging is achieved. Invicro will be responsible for imaging center evaluation, qualification, and training as well as, receipt, quality control (QC), query, and data management of magnetic resonance imaging (MRI) data.

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

1.1 Purpose of the Technical Operations Manual

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

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

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

1.2 Trial Design

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

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

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

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

During the PPMI Clinical study, participants will receive up to 6 MRI scans, depending on the cohort designation. MRI scans will be used to evaluate the imaging biomarkers for disease progression.

1.3 General Requirements

1.3.1 Imaging Center Compliance

- **Responsibilities:** Each imaging center is responsible for the following activities.
 - Always ensure consistent scan parameters and that the approved scanner is used for all participant assessments. Ideally, the same scanner is used for all assessments within and across all participants.
 - Acquire images according to the trial-specific process standards within and according to the protocol's schedule of assessments. Image acquisition and documentation should not deviate from the clinical trial protocol; however, the TOM may provide expanded information and processes.
 - **All scans must be submitted to Invicro within 24 hours.**
 - Respond promptly to queries generated by Invicro within 5 days.
 - Confirm that all technologists or other personnel who will be performing scans for this protocol are properly trained on the study-specific acquisition and reconstruction parameters, as well as, data submission and query handling procedures.
- **Regulatory compliance:** All site personnel must comply with the International Council for Harmonization E6(R2) guidelines on Good Clinical Practice (GCP) when documenting acquisition, archiving images, and submitting image data to Invicro.
- **Confidentiality:** Follow regional privacy practices to de-identify (ie, redact) all participant information (name, medical record number, etc) before submitting image data to Invicro. Image data submitted to Invicro via the iPACS system will automatically undergo de-identification.

1.3.2 Required Modalities

- **T1-weighted (T1), three-dimensional (3D) volumetric sequence** (Section 5.3) – to detect any significant structural abnormalities and to be used for accurate measurements of brain structures
- **Resting state functional MRI (rsfMRI)** (Section 5.4) — to evaluate cerebral activity
- **T2-star gradient recalled echo (T2* GRE) neuromelanin magnetization transfer (NM-MT) sequence** (Section 5.5) - to evaluate the substantia nigra region and assess hemorrhages,

microhemorrhages, and stroke

- **Diffusion tensor imaging (DTI) sequence** (Section 5.6) – to assess stroke
- **T2-weighted (T2) Fluid Attenuated Inversion Recovery (FLAIR) sequence** (Section 5.7) – to assess vasogenic edema or white matter hypersensitivities

1.3.3 Schedule of Assessments

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

Table 1: Schedule of MRI Assessments

Scan	Healthy Control ^a	PD ^a	Prodromal ^a
Baseline Scan ^b	X	X	X
Visit 04 (12 months) ^c	-	X	X
Visit 06 (24 months) ^c	-	X	X
Visit 10 (48 months) ^c	-	X	X
Withdrawal Visit ^d	-	X	X
New Clinical Diagnosis Visit ^e	-	X	X

^a Cohorts include participants newly enrolled in PPMI Clinical and participants transitioning from PPMI 001. Newly enrolled participants in PPMI Clinical will start with the Baseline Visit. Participants transitioning from PPMI 001 to PPMI Clinical will not have a baseline MRI, and these participants will start at the equivalent visit in PPMI Clinical from the PPMI 001 schedule.

^b Baseline MRI imaging must occur within 60 days of the Screening Visit.

^c Follow up MRI imaging will occur within ± 45 days of the scheduled visit.

^d If a participant withdraws from the study and agrees to attend one more visit, follow the Clinical protocol Event Drive Modification of Scheduled Visits for withdrawal from study to determine if imaging should be completed.

^e Follow the Clinical protocol Event Driven Modification of Scheduled Visits to determine if imaging should be completed. Annual visits are nested within the “Other MRI Timepoint” selection option when submitting the data to Invicro in iPACS.

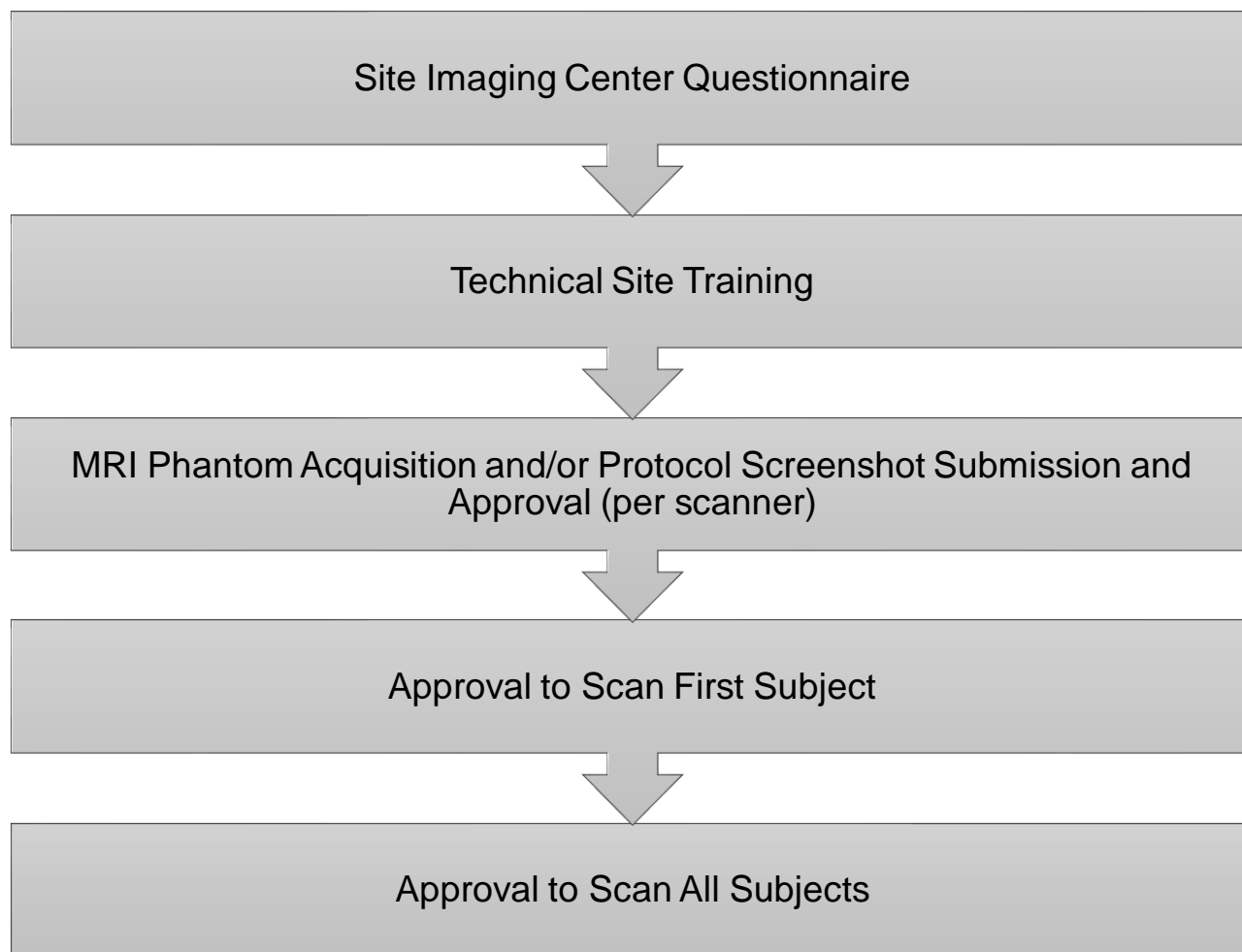
1.3.4 MRI Image Data Submission Timelines

MRI scans and corresponding imaging documents must be submitted to Invicro within 24 hours of image acquisition.

2 Imaging Center Set-up

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

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



2.1 Technical Assessment Questionnaire

The initial step in the set-up process is the center's completion of a technical assessment questionnaire. This form provides Invicro with contact information for key individuals, address information, specific scanner and computer system capabilities, and other specifications necessary for

satisfactory completion of the study. Invicro will provide a brief overview of the set-up process to the site and imaging center at the time of sending the questionnaire.

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

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

2.2 MRI Technical Site Training

2.2.1 Remote Technical Set-up

Imaging center training and MRI scanner qualification will occur via remote set-up procedures

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

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

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

2.3 Acquiring and Submitting Phantom Images

As part of Invicro's qualification process, a phantom acquisition will be required of each imaging center. The phantom submission provides a measure of scanner performance, confirms an appropriate standardized protocol has been established, and serves as a control to assist with review and assessment of future study participant acquisitions. This phantom acquisition will be performed using an American College of Radiology (ACR) phantom approved for use by Invicro. Phantoms must be acquired using each of the sequences listed below.

- **ACR single slice Sagittal Spin Echo** (Section [2.3.2](#))
- **ACR 11 slice Axial T1-weighted Spin Echo** (run twice, back-to-back) (Section [2.3.3](#))

- **3D Volumetric T1-weighted (MP-RAGE, IR-FSPGR)** (Section 5.3)
- **rsfMRI** (Section 5.4)
- **NM-MT** (Section 5.5)
 - Please note, the 16 slices of the NM-MT sequence should be centered on the array of squares located in the middle of the ACR phantom
- **DTI** (Section 5.6)
- **3D T2 FLAIR** (Section 5.7)

Additionally, submission of the phantom data serves as a test of the transfer pathway to be used for study participant imaging data. Each imaging center will be provided with a username and password to access Invicro's web submission platform with detailed instructions on how to electronically transfer images.

Please note: In instances where an imaging center has worked or is currently working with Invicro on a recent or concurrent trial, a phantom acquisition may not be necessary. In such cases, in lieu of the phantom acquisition, the imaging staff will be asked to establish the imaging protocol and provide a PDF printout and/or screenshots for Invicro to review for verification that the scanner was properly set-up in accordance with the imaging protocol.

2.3.1 Positioning Considerations

- Ensure that the phantom is at room temperature before scanning.
- Align the phantom as a head would be aligned. On the phantom, the words "NOSE" and "CHIN" should be positioned where the nose and chin would be for a head study.
- Use the crossed black lines on the phantoms anterior side as a landmark to line up the phantom in the center of the head coil. Level to ensure that the phantom is horizontal and that the plastic bar on the "CHIN" side is horizontal.
- Ensure that the crosshairs engraved on the phantom are placed at the magnet's isocenter.
- Use padding to secure the phantom to reduce motion induced artifact.

2.3.2 ACR Single Slice Sagittal Echo Sequence

The ACR Single Slice Sagittal Spin Echo sequence must be acquired utilizing the parameters detailed in Table 2.

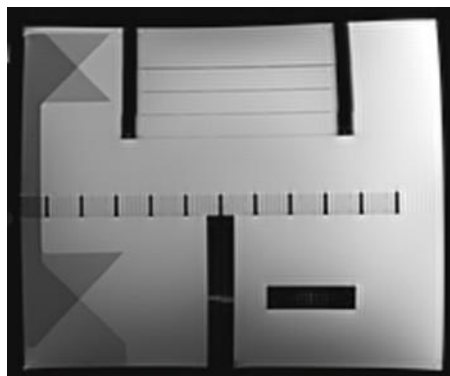
Table 2: ACR Single Slice Sagittal Echo Parameters

Study	Pulse Sequence	TR (ms)	TE (ms)	FOV (cm)	Number of Slices	Slice Thickness (mm)	Slice Gap (mm)	NEX	Matrix	Scan Time (min:sec)
ACR Sagittal Locator	Spin Echo	200	20	25	1	20	N/A	1	256x256	0:56

Please note: Intensity, uniformity and distortion corrections must be applied. Phantoms are likely to fail analysis without the proper corrections applied.

For GE scanners, please use PURE (Phased Array Uniformity Enhancement); for Siemens scanners, please ensure Prescan Normalize is applied; for Philips scanners, please use CLEAR (Constant LEvel AppeaRance); for Hitachi scanners, please use NATURAL (Natural Uniformity Realization Algorithm).

Figure 1: ACR Sagittal Locator (Single Slice)



The ACR Sagittal Locator acquisition ([Figure 1](#)) should appear as pictured in the image to the left. Notice that the 45° crossed wedges on the left of this image appear with equal intensity.

Please note: If the image you acquire does not appear like this, the phantom must be re-centered, re-leveled and re-imaged.

2.3.3 ACR Slice Axial T1-weighted Spin Echo Sequence

The ACR 11 Slice Axial T1-weighted Spin Echo sequence must be acquired utilizing the parameters detailed in the [Table 3](#). Two acquisitions for this sequence are required. Both should be identical scans, with the repeat immediately following the first.

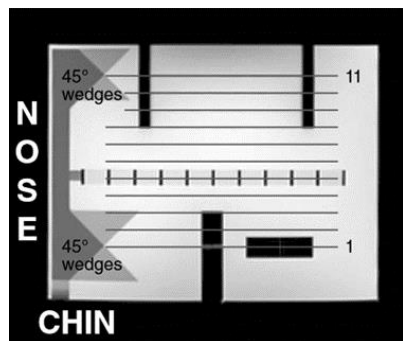
Table 3: ACR Slice Axial T1-weighted Spin Echo Parameters

Study	Pulse Sequence	TR (ms)	TE (ms)	FOV (cm)	Number of Slices	Slice Thickness (mm)	Slice Gap (mm)	NEX	Matrix	Scan Time (min:sec)
ACR Axial T1	Spin Echo	500	20	25	11	5	5	1	256x256	2:16

Please note: Intensity, uniformity and distortion corrections must be applied. Phantoms are likely to fail analysis without the proper corrections applied.

For GE scanners, please use PURE (Phased Array Uniformity Enhancement); for Siemens scanners, please ensure Prescan Normalize is applied; for Philips scanners, please use CLEAR (Constant LEvel AppeaRance); for Hitachi scanners, please use NATURAL (Natural Uniformity Realization Algorithm).

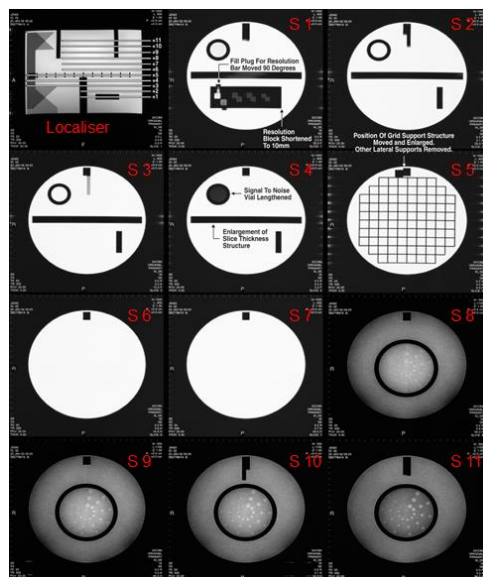
Figure 2: ACR Sagittal Locator (11-Slice Axial)



The 11-slice ACR Axial T1 series must be prescribed on the ACR Sagittal Locator as pictured in [Figure 2](#).

This image illustrates the correct alignment of the slices of the ACR Axial T1 sequences on the ACR Sagittal Spin Echo.

Figure 3: 11-Slice ACR Axial T1 Series



The collection of images in [Figure 3](#) shows the correctly positioned 11 slices of the ACR Axial T1 sequence (S1 to S11).

Please examine all 11 images and verify that all are present, properly positioned and free of image artifacts.

Please note: If during the review of the phantom acquisition, artifacts or improper positioning is noticed, the phantom must be reacquired to achieve optimal image quality.

Please note: This sequence must be run twice back-to-back.

2.4 Approval to Scan First Participant

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

Please note, this 'Approval to Scan' notification indicates that the imaging center is now ready to scan their first study participant only.

2.5 Approval to Scan All Subsequent Participants

After the first study participant has been imaged, the imaging center will be instructed to transfer the images to Invicro within 24 hours of acquisition for QC review. Once the participant images have

passed QC, the imaging center and clinical coordinator will receive email notification of the QC approval signifying that they may continue imaging additional participants. Sites will be notified within approximately 3 business days of receipt of the first participant data (barring no queries). Should the first participant scan not pass QC review, Invicro will communicate with the imaging and clinical personnel regarding how to resolve the issue prior to moving forward with additional participant imaging.

Please note: The clinical coordinator should NOT schedule a second participant for imaging until Invicro has reviewed the first participant and it has passed QC.

3 Technical Binder

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

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

4 Scan Identification (Naming Convention)

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

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

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

5 MRI Imaging Overview & Procedures

5.1 MRI Scanners

It is a study requirement that the MRI scanner to be used for study acquisitions have a magnetic field strength of 3 Tesla.

All scans for each participant must be acquired on the same scanner using the approved scanning protocol. In the event the scanner is not available, or is in need of service, you must contact Invicro/Sponsor/Clinical Research Associate (CRA) *prior* to performing any scan on a different scanner. Additionally, it is also important to communicate any anticipated software or hardware, upgrades, including coils and/or gradients, to Invicro in advance. If the approved scanner is planned to be replaced at any time during this clinical trial, please notify Invicro/Sponsor/CRA as soon as possible.

5.2 Participant Positioning

Participants should be positioned comfortably and correctly to minimize motion during the scan. Please adhere to the following:

- The participant should be informed about the total acquisition time and positioned for maximum comfort.
- Participants must be positioned comfortably and supine in the head coil to minimize any motion during the scan.
- Proper back support, and support under the knees will ensure greater comfort, and lead to less motion in the scan.
- There should be no left-right or ear-to-shoulder head tilt, and the participant's neck should not be hyper- extended or retracted.
- The participant's head should be centered in the head coil using the nasion (see example to the right) as an anatomical landmark. Ensure the participant is high enough in the coil to avoid loss of signal at the inferior aspects of the brain.
- Use immobilization devices, such as velcro straps, or foam padding to reduce motion.
- Use the positioning lasers to send the nasion to the magnets isocenter.

If a participant's neck length is such that it does not permit proper positioning in the head coil, please document this on the MRI Acquisition Document along with any other pertinent information regarding the participants scanning session. Use of immobilization devices, such as straps or padding on each side of the head may be used to minimize motion.

Please note: It is very important that the position of the participant's head with respect to the magnet's isocenter does not vary between exams of the same participant.

Parallel imaging may be utilized to reduce scan time. Please adhere to manufacturer recommendations when incorporating this scan technique.

Please review for motion and other image artifacts. Per internal standard procedures, repeat the sequences as needed in order to obtain a high-quality image suitable for analysis. Imaging centers may be asked to repeat the scanning of a participant if excessive movement is noticed during QC review.

5.3 T1 3D Volumetric Sequence

For accurate quantitative measurements of brain structures and detection of structural abnormalities, you will acquire a high-resolution T1-weighted, 3D volumetric sequence (eg MP-RAGE, IR-FSPGR) in the sagittal plane, with a slice thickness of 1.2 mm or less. Additional required parameters are listed in [Table 4](#).

Table 4: T1 3D Volumetric Sequence

T1-weighted, 3D volumetric sequence (eg MP-RAGE, IR-FSPGR)	
Series Description	3D T1-weighted
Plane	Sagittal
Slice thickness (mm)	1.0 (slice thickness must remain consistent across timepoints)
Number of slices	192 (Please adjust slice thickness up to 1.2 mm to cover brain, if absolutely necessary. Please do not adjust the number of slices)
Voxel size (mm)	1.0*1.0 mm in plane resolution
Phase encode dir.	Anterior-Posterior (AP)
Matrix	256 x 256 (the use of interpolation, zero-filling or a ZIP factor is not permitted)
TR/TE/FA/other parameters	Will be defined by Invicro according to the scanner
FOV	256 mm (full FOV required, no rectangular FOV)
Scan Time	~ 7 minutes
Note: Phantoms and participant study scans will use the parameters detailed in this table.	

The FOV must include the entire brain anatomy including the vertex, cerebellum and pons. Slices should be oblique sagittal, angled along the longitudinal fissure on both the axial and coronal localizers. To avoid artifacts, position the participant such that there is sufficient empty space around the head: approximately 1.5 cm of air or more above the top of the head, and leave 3 - 4 blank slices on either side of the head. Avoid nose ghosting.

Please note: Parallel imaging may be utilized to reduce scan time. Please adhere to manufacturer recommendations when incorporating this scan technique (GRAPPA for Siemens and ASSET for GE).

Please note: Exact parameters for the sequence may differ slightly by site and will be decided as part of site set-up.

5.4 Resting state functional MRI (rsfMRI) Sequence

Please instruct the participant to keep their eyes open during the entire scan. You can instruct them to focus on a point on the mirror or scanner. Check with the participant immediately after the scan to verify they kept their eyes open and did not fall asleep. No audio or video presentation should be made during the scan.

Position the axial resting state fMRI slices along the AC-PC plane with care that there is one slice above the vertex, and then cover the rest of the brain and as much of the cerebellum as possible with the remaining slices. The slices should be centered in the axial plane to prevent aliasing in the Anterior/Posterior direction (see [Figure 4](#)).

Requested imaging parameters for the initial and repeat resting state fMRI sequence can be referenced in [Table 5](#). Invicro will work with the imaging center to establish the appropriate multiband (MB)/simultaneous multislice sequence (SMS) to be used depending on scanner and software capabilities. The repeat scan will have the reversed phase encoding direction, and number of measurements updated to “10.” All other parameters should be held constant.

Please note: Two Axial Resting State fMRI (BOLD) sequences must be acquired. The initial sequence, and a repeat sequence with the reverse phase encode direction to correct for distortion.

Figure 4: Resting State fMRI Slices

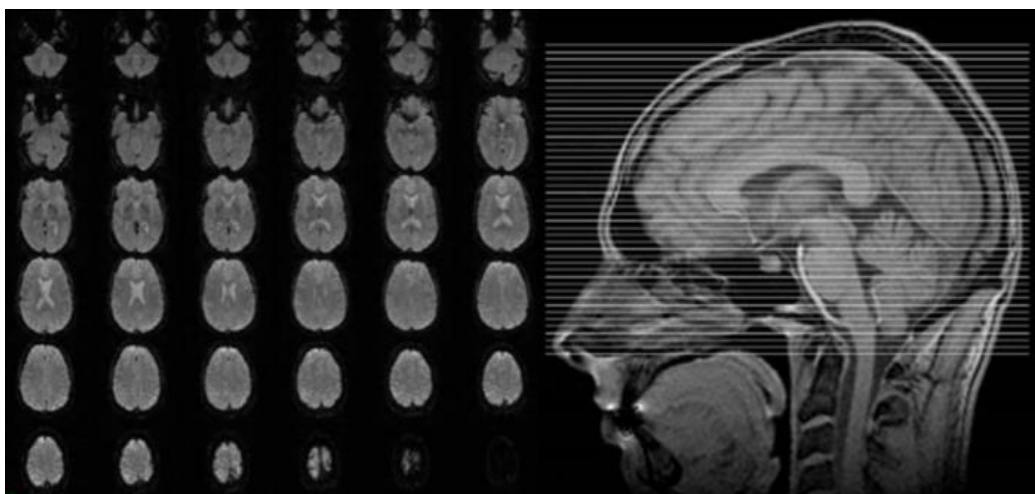


Table 5: Multiband resting state fMRI sequence parameters

	Multiband 2D Gradient-echo T2*-weighted EPI	Multiband REPEAT 2D Gradient-echo T2*-weighted EPI
Series Description	rsfMRI_PA	rsfMRI_AP
Plane	Axial Oblique, plane parallel to AC-PC line	Axial Oblique, plane parallel to AC-PC line
Slice thickness (mm)	3.0 with no gap	3.0 with no gap
Number of Slices	52	52
Phase encode dir.	P >> A	A >> P
Matrix	66x66 (target voxel size 3.045x3.045mm)	66x66 (target voxel size 3.045x3.045mm)
FOV	201 x 201 mm	201 x 201 mm
Repetition Time (ms)	1000	1000
Echo Time (ms)	30	30
Flip angle	58	58
Slice order	Interleaved	Interleaved
Number of measurements	600	10
In-plane acceleration	1 (no acceleration in-plane)	1 (no acceleration in-plane)
Through slice acceleration	4 (Multiband/Hyperband factor)	4 (Multiband/Hyperband factor)
Instructions	Keep the eyes open and remain still	Keep the eyes open and remain still
Scan Time	~ 10 minutes	~ 25 seconds
Distortion Correction	Disabled	Disabled
Intensity correction filters	Enabled (Prescan Normalise, SCIC or PURE, CLEAR)	Enabled (Prescan Normalise, SCIC or PURE, CLEAR)
Note: Phantoms and participant study scans will use the parameters detailed in this table.		

Please note: Exact parameters for each sequence may differ slightly by site and will be decided as part of site set-up. Alternative sequence parameters for scanners without access to MB/SMS sequences is outlined in [Appendix 1](#) and/or [Table 10](#).

5.5 NM-MT Sequence

A specialized MRI sequence sensitive to neuromelanin (neuromelanin NM: NM-MRI) will be acquired, providing high-contrast between the substantia nigra and surrounding tissue. Coverage will be limited to select midbrain coverage, making careful positioning of the slices critical. See [Figure 5](#) for step by step instruction on selecting the FOV. See [Figure 6](#) for final FOV placement and example

image for NM-MRI.¹

- Step 1: Select the sagittal plane that shows the largest gap between Thalamus and Midbrain (either Figure 5b or 5c works in this example).
- Step 2: Place the cross-hair so that the coronal plane (f) goes through the most anterior point of the midbrain and the axial plane is 3 mm superior to the bottom of the third ventricle (see the inset of Figure 5f). The axial plane (yellow line in Figure 5e) denoting the superior boundary of the NM-MRI volume. The plane should be parallel to the AC-PC line.

Figure 5: Instructions for placement of slices for NM Scanning

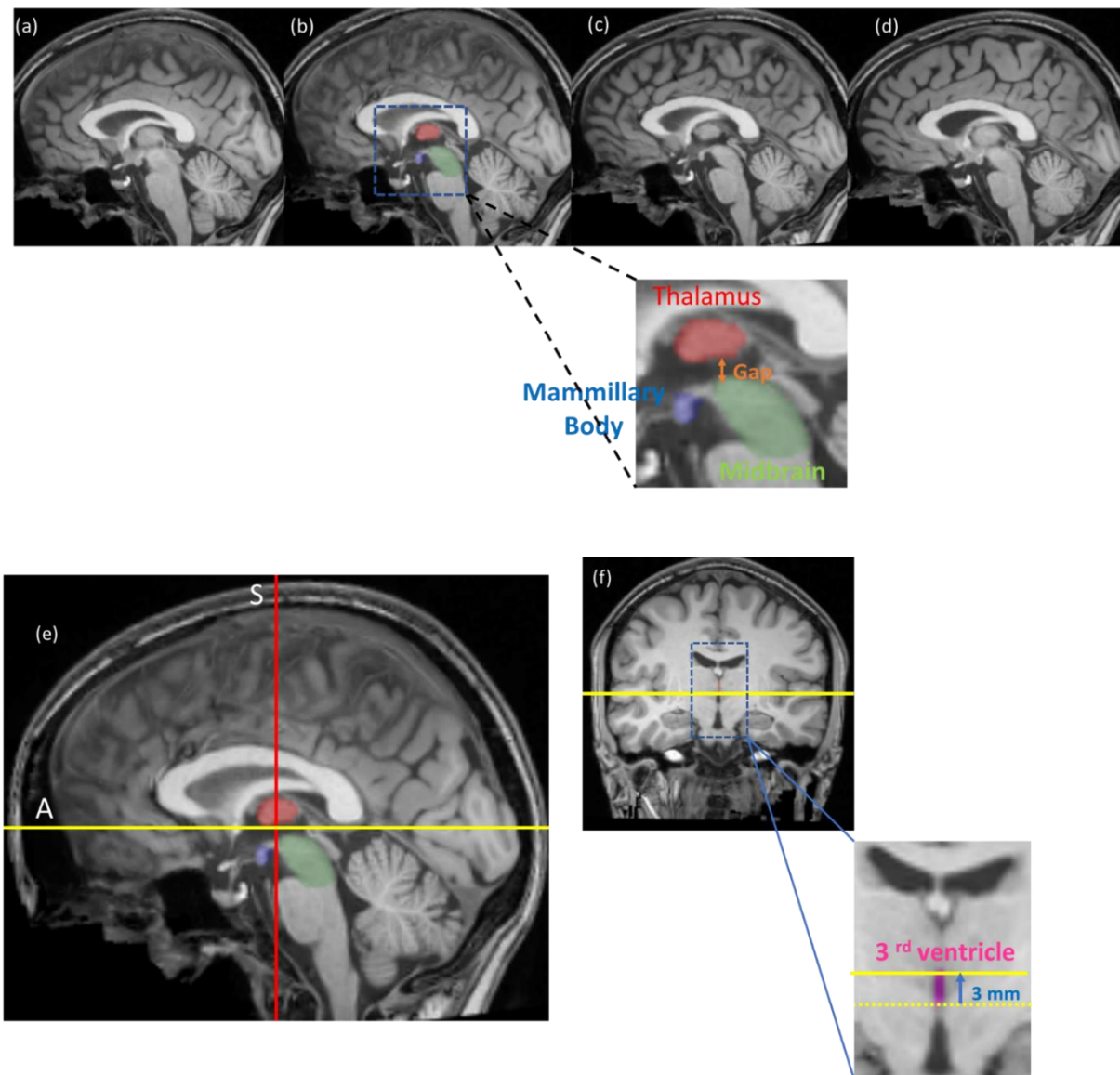


Figure 6: Final FOV placement (a) and Sample slice through the substantia nigra (b) (bright tissue

in the midbrain (Chen et al. 2014)

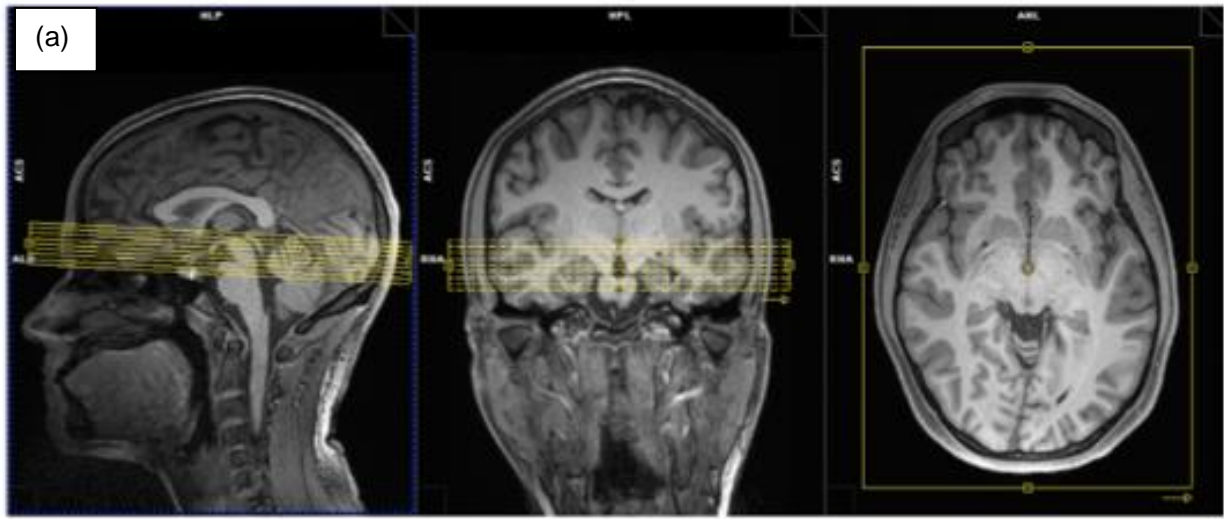


Table 6: NM-MT Sequence

2D Gradient recalled echo with MT preparation	
Series Description	2D GRE-MT
Plane	Oblique, follow instructions
Slice thickness (mm)	1.5 mm
Number of slices	16
Phase encode dir.	Right-Left (RL)
Matrix	440x440
FOV (mm)	220x220
Voxel Size (mm)	0.5 x 0.5 x 1.5
Repetition Time (ms)	~ 465 ms
TE	Minimum (< 5 ms)
Flip angle	40
MT Pulse FA	300°
MT offset Frequency	1.5 kHz (3.0 T)
MT pulse duration	10 ms
Measurements	5
Scan Time	~ 10 minutes
Receive Band Width	<500 Hz/Pixel

Please note: Exact parameters for the sequence may differ slightly by site and will be decided as part of site set-up.

5.6 DTI Sequence

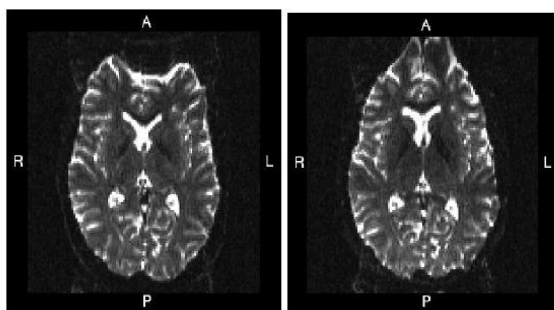
Please instruct the participant to keep still during the entire scan. Slices should cover top of the brain down to base of cerebellum. Two sequences with reversed phase encoding direction should be acquired in full to correct for susceptibility induced distortions.

Requested imaging parameters for the DTI sequences can be referenced in [Table 7](#). Invicro will work with the imaging center to establish the appropriate MB/SMS to be used depending on scanner and software capabilities. The number of sequences to be setup will be dependent on the sequence type available, number of b-values, directions and phase encode direction. All other parameters should be held constant.

Table 7: Multi-shell Diffusion Tensor Imaging

Multiband 2D Diffusion-weighted EPI	
Series Description*	DTI_B0_PA; DTI_revB0_AP; DTI_B700_64dir_PA; DTI_B1000_64dir_PA; DTI_B2000_64dir_PA
Plane	Straight Axial
Slice thickness (mm)	2.0 with no gap
Number of Slices	72
Phase encode dir.	P >> A (b0 images to be acquired both P/A and A/P directions)
Matrix	116x116** (target voxel size 1.98x1.98mm)
FOV	230x230 mm
Repetition Time (ms)	~3800 (minimum allowed)
Echo Time (ms)	~90-100
In-plane acceleration	1 (no acceleration in-plane)
Through slice acceleration	3 (Multiband/Hyperband factor)
Flip angle	90
Fat Suppression	on
Slice order	Interleaved
Number of directions	64 per shell
B-Values	0, 700, 1000, 2000 s/mm2 ***
Instructions	Keep still
Distortion Correction	Disabled
Intensity correction filter	Enabled (Prescan Normalise, SCIC or PURE, CLEAR)
<p>Note: Phantoms and participant study scans will use the parameters detailed in this table.</p> <p>* Scan series description will vary dependent on sequence type, number of b-values, directions and phase encode direction. Additional guidance to be provided.</p> <p>**On GE systems, to prevent interpolation for 116x116 matrix, set USER CVs : rhrcyres = 116, rhrcxres=116, rhimsize=116</p> <p>***number of b-values to be acquired will be dependent on scanner capability. Multiple b0 images to be acquired. Additional guidance on order of sequences to be provided.</p>	

Figure 7: Example of DTI acquisition with different phase encoding direction



Phase enc. dir. A>>P Phase enc. dir. P>>A

Note the differences in the distortion pattern in [Figure 7](#).

Please note: Exact parameters for the DTI sequences may differ slightly by site and will be decided as part of site set-up. Alternative sequence parameters for scanners without access to MB/SMS sequences is outlined in [Appendix 1](#) and/or [Table 11](#).

5.7 3D T2 FLAIR Sequence

A high-resolution 3D T2 FLAIR sequence will be acquired in the sagittal plane, with a slice thickness of 1.2 mm or less, for assessment of white matter disease, and other pathology. Additional required parameters are listed See [Table 8](#) for parameters.

Table 8: 3D T2 FLAIR Sequence

3D T2 FLAIR Sequence	
Series Description	3D T2 FLAIR
Plane	Sagittal
Slice thickness (mm)	1.0 – 1.2 (slice thickness must remain consistent)
Number of slices	192 (please adjust slice thickness up to 1.2 mm to cover brain, not the number of slices)
Voxel size (mm)	1.0*1.0 mm in plane resolution
Phase encode dir.	Anterior-Posterior (AP)
Matrix	256 x 256 (the use of interpolation, zero-filling or a ZIP factor is not permitted)
TR/TE/FA/other parameters	Will be defined by Invicro according to the scanner
FOV	256 mm (full FOV required, no rectangular FOV)
Scan Time	~ 7 minutes
Note: Phantoms and participant study scans will use the parameters detailed in this table.	

The FOV must include the entire brain anatomy including the vertex, cerebellum and pons. To avoid artifacts, position the participant such that there is sufficient empty space around the head: approximately 1.5 cm of air or more above the top of the head, and leave 1 - 2 blank slices on top of the head. Avoid nose ghosting.

Please note: Parallel imaging may be utilized to reduce scan time. Please adhere to manufacturer recommendations when incorporating this scan technique (GRAPPA for Siemens and ASSET for GE).

Please note: Exact parameters for the sequence may differ slightly by site and will be decided as part of site set-up.

5.8 MRI Series Description

The Series Description for each sequence should be labeled as described in [Table 9](#).

Table 9: MRI Series Description

Sequence Name	Series Description
T1-weighted, 3D volumetric sequence	3D T1-weighted
rsfMRI	rsfMRI_PA
Repeat rsfMRI	rsfMRI_PA
NM-MT	2D GRE-MT
DTI	see Table 7
3D T2 FLAIR	3D T2 FLAIR

6 Image Data Archiving and Submission

6.1 Data Submission Checklist

All imaging metadata and data files should be sent through iPACS. Modality specific electronic submission forms are required to be completed within iPACS for each data submission. Please reference Section [1.3.3](#) of this document, and the clinical protocol for details on the schedule of assessments.

- Image data for uploading into the submission form
- Imaging procedure and participant visit information for entry into the submission form (an example of the electronic submission forms utilized for this study is provided in the appendices of this manual).

6.2 Image Data Submission



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

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

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

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

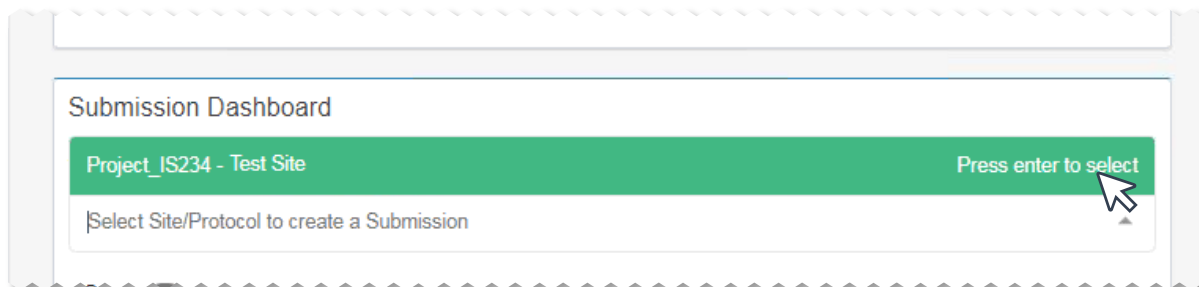
- 2 Log in:** a unique username and password is provided to personnel responsible for data submission.

A screenshot of the 'iPACS sub' login page. At the top is the 'iPACS sub' logo and the text 'Please sign in to continue.' Below this are two input fields: 'Username' and 'Password'. The 'Password' field has a small eye icon to its right. Below the fields is a blue 'Sign in' button. At the bottom left is a link 'DropZone' and at the bottom right is a link 'Need Help?'.

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

A screenshot of the 'iPACS Submission' dashboard. The top navigation bar includes the 'iPACS Submission' logo and links for 'Submissions' and 'Help'. The main content area is titled 'Submission Tasks'. On the left is a sidebar with a blue 'Add Submission' button at the top, followed by a list of tasks: 'Conversation' with a count of 0, 'Query Tasks' with a count of 6, and 'Submission Tasks' with a count of 8. To the right of the sidebar are two dropdown menus labeled 'Patient Name' and 'Patient ID'.

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

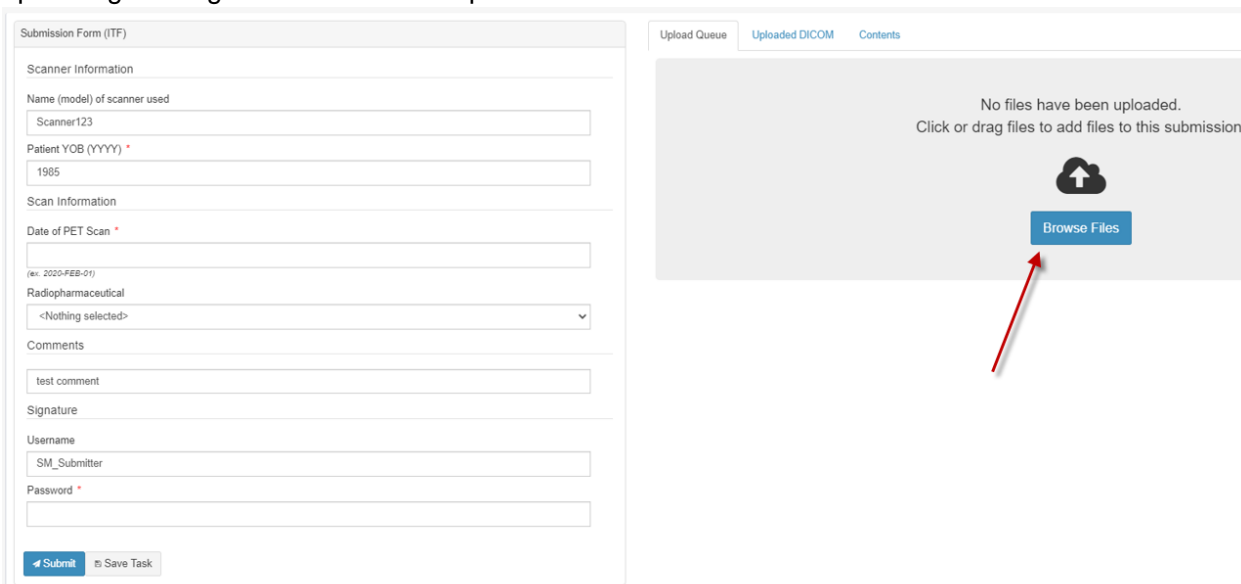


Submission Dashboard

Project_IS234 - Test Site Press enter to select

Select Site/Protocol to create a Submission

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



Submission Form (ITF)

Scanner Information

Name (model) of scanner used
Scanner123

Patient YOB (YYYY) *
1985

Scan Information

Date of PET Scan *
(ex. 2020-FEB-01)

Radiopharmaceutical
<Nothing selected>

Comments
test comment

Signature

Username
SM_Submitter

Password *

Submit Save Task

Upload Queue Uploaded DICOM Contents

No files have been uploaded.
Click or drag files to add files to this submission.

Browse Files

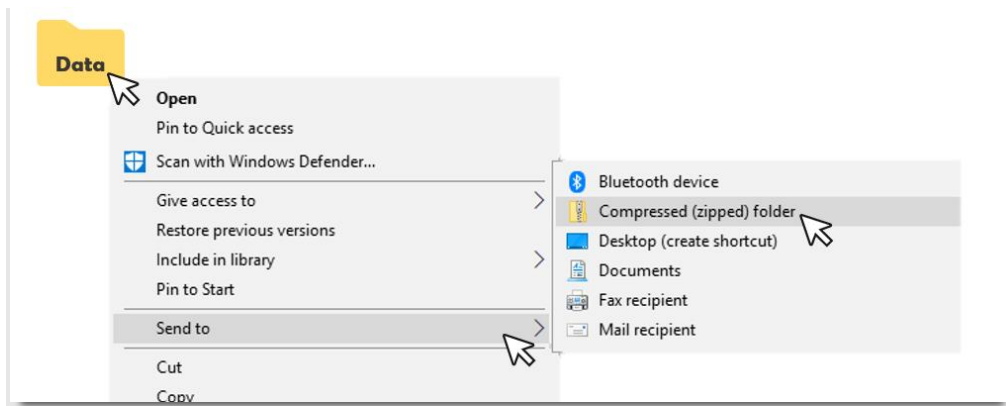
- 6 Fill in the submission form with the requested study-specific and modality information. Use the free text *Comments* field to provide any explanatory notes related to the data submission and acquisition procedures.

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

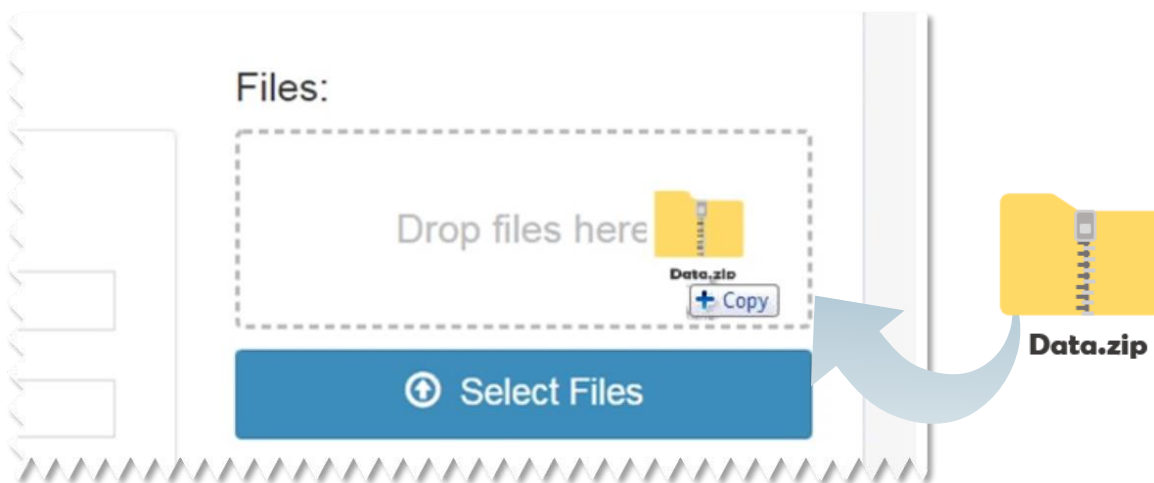
- Current PPMI 001 participants will be divided into the following:
 - Healthy Control
 - PD

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

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



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



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

Signature _____

Username _____

SM_Submitter

Password * _____

Submit Save Task

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



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

If you do not receive an email notification following submission, contact: Corelab_Support@invicro.com

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

Corelab_Support@Invicro.com

6.3 iPACS Submission Form Comments Section

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

6.4 Scanner QC & Maintenance Documentation

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

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

6.5 QC and Query Resolution Process

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

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

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

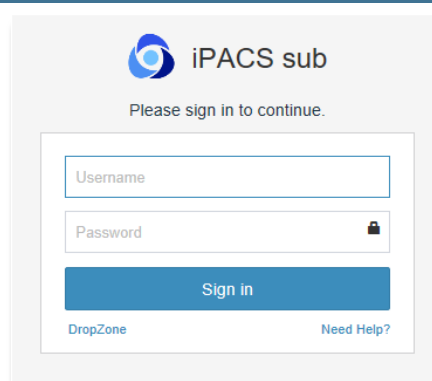
Respond to the queries promptly within 24 hours of receipt.

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

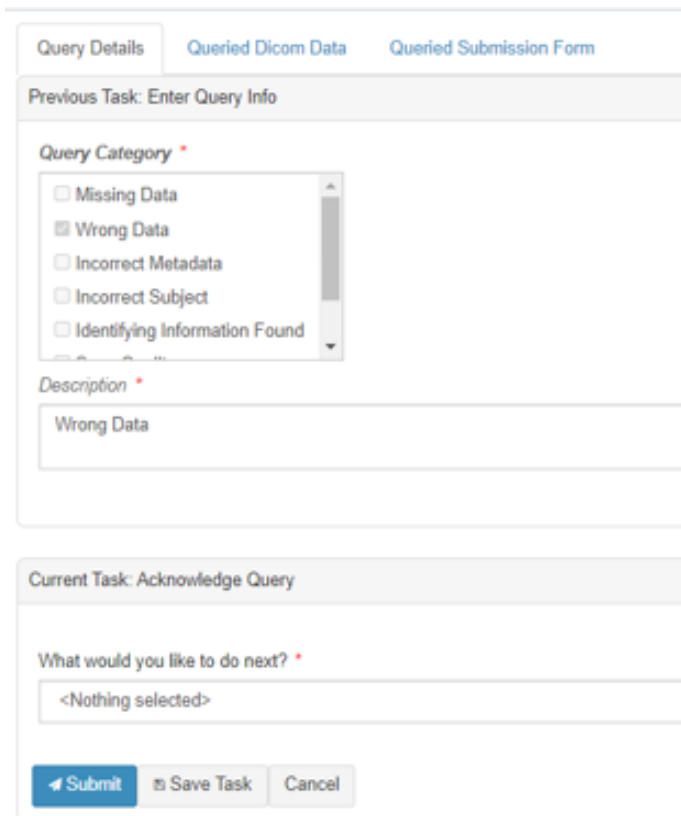
To resolve any issues that arise, Invicro will employ the query resolution process outlined below:

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

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

The image shows the login page for the iPACS sub portal. At the top, there is a logo for 'iPACS sub' and the text 'Please sign in to continue.' Below this, there are two input fields: 'Username' and 'Password'. The 'Password' field has a small lock icon on the right. A blue 'Sign in' button is positioned below the password field. At the bottom of the form, there are two links: 'DropZone' on the left and 'Need Help?' on the right.

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

The image shows the 'Respond to Query' page in the iPACS sub portal. The page has three tabs: 'Query Details' (selected), 'Queried Dicom Data', and 'Queried Submission Form'. Below the tabs, there is a section titled 'Previous Task: Enter Query Info'. This section contains a 'Query Category' dropdown menu with the following options: 'Missing Data', 'Wrong Data' (selected), 'Incorrect Metadata', 'Incorrect Subject', and 'Identifying Information Found'. Below the dropdown is a 'Description' text area containing the text 'Wrong Data'. Below this section, there is a section titled 'Current Task: Acknowledge Query'. This section contains a 'What would you like to do next?' dropdown menu with the text '<Nothing selected>'. At the bottom of the page, there are three buttons: 'Submit' (blue), 'Save Task' (grey), and 'Cancel' (grey).

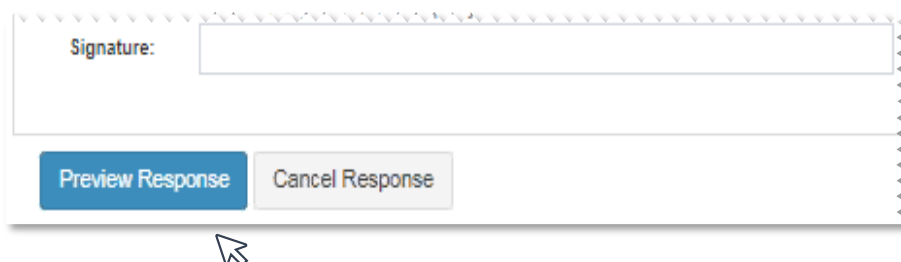
4 Navigate to the bottom section with the heading, **Current Task: Acknowledge Query**. Under the **What would you like to do next?** section, choose **Edit Submission** to respond to the query from the drop-down list and then click **Submit**.

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

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

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

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

A screenshot of a web form interface. At the top, there is a label "Signature:" followed by a large, empty rectangular text input field. Below the input field, there are two buttons: a blue button labeled "Preview Response" and a grey button labeled "Cancel Response". A mouse cursor is visible pointing at the bottom of the form area.

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

6.6 Archiving Instructions

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



Retain the archived image data for 25 years after completion or discontinuation of the trial or per institutional guidelines, whichever is longer. Only after this period may data be destroyed per local regulations.

7 QC & Calibrations

QC measures are to be performed according to the center and scanner manufacturer standard procedures as implemented in the center's QC program for the MRI scanner.

7.1 QC Procedures

Participating MRI facilities must have a quality control program in place that outlines standard QC procedures. The QC program must include MRI safety policies and a preventative maintenance program. QC procedures, calibrations, preventative maintenance, or service that has been performed on the scanner should also be documented within the scanner QC section of the iPACS submission form.

7.2 Phantom Data

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

8 MRI Scanner Replacement or Upgrades

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

9 Supporting Information

9.1 Invicro Contacts

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

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

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

corelab_support@invicro.com

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

Andrea Perez

Sr. Manager II, Imaging QC & Processing
+1-203-401-4315 voice
aperez@invicro.com

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

Andrew Serrano

Project Manager II
+1-203-990-1638 voice
+1-203-789-8037
aserrano@invicro.com

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

9.2 TOM Amendment History

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

Version Number	Version Date	Summary of Changes
Final v1.0	11-May-2020	Original
Final v2.0	07-Aug-2020	<ul style="list-style-type: none"> • Updated to add premature withdrawal visit Section 1.3.2 and Section 10 (Appendix 1) • Updated data submission process (Section 6) • Editorial changes (global)
Final v3.0	27-Jul-2021	<ul style="list-style-type: none"> • Updates made to Table 1 (Section 1.3.3) • Updated the iPACS MRI Submission form (Section 11.1) • Updated based on Protocol 002 Version 1.2 (global) • Editorial changes (global)
Final v4.0	18-Nov-2022	<ul style="list-style-type: none"> • Updated rsfMRI sequence parameters (Section 5.4) • Updated DTI sequences (Section 5.6) • Updated to New Clinical Diagnosis Visit (Section 1.3.2) • Updated for consistency with protocol Version 2.0 dated 09-Aug-2022 (global) • Editorial updates (global)

9.3 Abbreviations

ACR	American College of Radiology
3D	3-dimensional
ASL	Arterial Spin Labeling
BOLD	Blood oxygenation level dependent
cm	Centimeter
CRA	Clinical Research Associate
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion Tensor Imaging
EPI	Echo-planar imaging
FLAIR	Fluid attenuate inversion recovery
FOV	Field of view
GCP	Good Clinical Practices
GRE	Gradient recalled echo
iPACS	Invicro's iPACS system
MB	Multiband
mm	Millimeter
MRI	Magnetic Resonance Imaging
MT	Magnetization transfer
NM	Neuromelanin
PD	Parkinson's Disease
QC	Quality control
rsfMRI	Resting state functional Magnetic Resonance Imaging
SMS	Simultaneous multislice sequence
T	Tesla
T1	T1-weighted
T2	T2-weighted
TOM	Technical Operations Manual

10 References

1. Wengler K, He X, Abi-Dargham A, Horga G. Reproducibility assessment of neuromelanin-sensitive magnetic resonance imaging protocols for region-of-interest and voxelwise analyses. *Neuroimage*. 2020;208:116457.

11 Appendices

11.1 Appendix 1 : Alternate rsfMRI and DTI sequence parameters

Table 10: Resting state fMRI sequence (alternate parameters)


	2D Gradient-echo T2*-weighted EPI	REPEAT 2D Gradient-echo T2*-weighted EPI
Series Description	rsfMRI_RL	rsfMRI_LR
Plane	Axial Oblique, plane parallel to AC-PC line	Axial Oblique, plane parallel to AC-PC line
Slice thickness (mm)	3.5 with no gap	3.5 with no gap
Number of Slices	~ 40	~ 40
Phase encode dir.	R >> L	L >> R
Matrix	64x64	64x64
FOV	224 x 224 mm	224 x 224 mm
Repetition Time (ms)	2500	2500
Echo Time (ms)	30	30
Flip angle	80	80
Slice order	Interleaved	Interleaved
Number of measurements	240	10
In-plane acceleration	GRAPPA or SENSE (factor of 2)	GRAPPA or SENSE (factor of 2)
Instructions	Keep the eyes open and remain still	Keep the eyes open and remain still
Scan Time	~ 10 minutes	~30 seconds

Note: Phantoms and participant study scans will use the parameters detailed in this table.

Table 11: Diffusion Tensor Imaging sequences (alternate parameters)

2D Diffusion-weighted EPI	
Series Description	DTI_RL (and DTI_LR for the repeated scan with reverse PE)
Plane	Straight Axial
Slice thickness (mm)	2.0 with no gap
Number of Slices	~ 80
Phase encode dir.	R >> L (L>>R for repeated scan)
Matrix	128x128*
FOV	256x256 mm
Repetition Time (ms)	~10000
Echo Time (ms)	~80
Flip angle	90
Slice order	Interleaved
Number of directions	32
B-VALUE	0 and 1000 s/mm ² (B=0 images interleaved throughout if possible in product sequence)
Instructions	Keep still
Scan Time	~ 8 minutes
<p>Note: Phantoms and participant study scans will use the parameters detailed in this table.</p> <p>*On GE systems reconstructed final images will be 256x256 – to prevent interpolation for 128x128 matrix, set USER CVs: rhrcyres = 128, rhrcxres=128, rhimsize=128</p>	

11.2 Appendix 2: iPACS Submission Form (Example)



MRI Submission Form

Clinical Site ID:

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

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

Modality: ☐ MRI

Cohort: ☐ Healthy
☐ PD
☐ Prodromal

MRI Imaging Timepoint: ☐ Baseline
☐ Month 12/V04
☐ Month 24/V06
☐ Month 48/V10
☐ Other MRI Timepoint

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

Sequences: ☐ T1-weighted
☐ T2-weighted (T2) Fluid Attenuated Inversion Recovery (FLAIR)
☐ Neuromelanin (NM-MT)
☐ DTI
☐ rs-fMRI (2D T2 EPI BOLD)

Scanner (Manufacturer/Model):

Comments:

Scanner Event Information:

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

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

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PPMI 2.0_MRI_V7.0_15APR2021