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Metformin in Alzheimer's dementia Prevention

MRI & PET

Technical Procedures Manual

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1. GENERAL INFORMATION

The purpose of this manual is to further explain the MRI and PET imaging components of the MAP protocol. Standard procedures are needed to ensure consistency of data collection in this longitudinal study. This manual contains information for study site clinical staff involved with the care of study subjects during the imaging procedure and those involved with the processing and transfer of MRI and PET imaging data.

Contents include:

- Core Image Lab, Core MRI Lab, and Core PET Lab Imaging Workflow
- MRI Acquisition Guidance
- PET Acquisition Guidance
- DICOM File and Data Upload Instructions

2. CONTACT INFORMATION

General Image Workflow Questions

Contact Nathan Walborn (nwalbor1@jhmi.edu) for questions or concerns regarding general image workflow, scan upload, and PET upload form completion.

MRI Technical/QC Questions

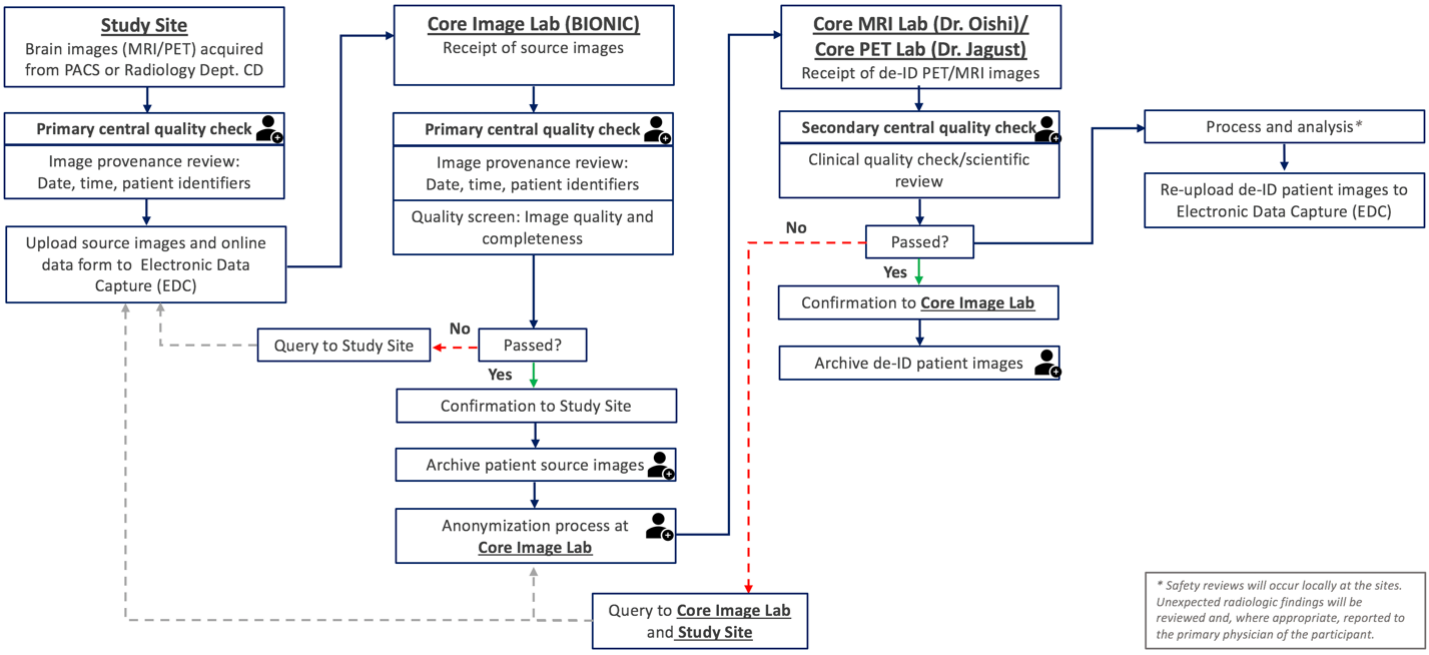
Contact Kenichi Oishi (koisihi2@jhu.edu) for questions or concerns regarding MRI technical issues and MRI scanner-specific acquisition.

PET Technical/QC questions

Contact Suzanne Baker (slbaker@lbl.gov) for questions or concerns regarding PET technical issues, PET scanner-specific acquisition, and reconstruction parameters.

3. MAP IMAGING WORKFLOW

The imaging workflow is outlined below (top of page 3).



3.1. Study Site

The study site coordinator will obtain the appropriate source brain image (MRI/PET) from their institution's Picture Archiving and Communication System (PACS) or Radiology Department CD, complete a local quality check, and upload the source brain images and MRI- or PET-related information to the electronic data capture (EDC) system.

In addition to uploading the MRI and PET scans, the coordinators will create and complete the appropriate MRI and PET forms in the EDC.

3.2. Core Image Lab (BIONIC)

BIONIC research assistant

A BIONIC research assistant will download the source brain image onto their local computer and complete a primary central quality check, including an image provenance review for image date, time, and other subject identifiers, in addition to a quality screen for image quality and completeness.

- If the source brain image does not pass the primary central quality check, the research assistant will submit a query via the EDC to the study site coordinator, and the study site coordinator will need to re-upload the current source brain images.

This will be repeated until the source brain images passes the primary central quality check.

- When the source brain image passes the primary central quality check, the research assistant will give confirmation to the study site and will move forward with the workflow:
    - A BIONIC research assistant will archive the brain source image in the Core Image Lab's shared drive that hosts the repository of trial images.
    - A BIONIC research assistant will complete the standardized, full anonymization of the brain source image locally, and re-upload the de-identified brain image to the EDC.

3.3. Core MRI Lab (Dr. Oishi)

The Core MRI Lab will download the de-identified MRI image and complete a secondary central quality check, including a clinical check and scientific review.

- If the de-identified brain image does not pass the secondary central quality check, a BIONIC research assistant will determine which party needs to address the issue and will submit a query via the EDC intended for either the study site coordinator or the Core Image Lab.
    - If the issue is related to image acquisition and/or reconstruction, the study site coordinator will need to communicate with the site MRI technician and provide the subject's source brain image with correct data elements and continue the workflow from there.
    - If the issue is related to de-identification, the BIONIC research assistant will need to redo the anonymization process of the image and continue the workflow from there.

This will be repeated until the de-identified brain image passes the secondary central quality check.

- When the de-identified brain image passes the secondary central quality check, the Core MRI Lab will give confirmation to the Core Image Lab and the workflow will proceed:
    - A BIONIC research assistant will archive the de-identified MRI image in the Core Image Lab's shared drive.
    - The Core MRI Lab will complete necessary analysis of the MRI image and will upload necessary data/images to the EDC.

3.4. Core PET Lab (Dr. Jagust)

The Core PET Lab will download the de-identified PET (and MRI for comparison) image and complete a secondary central quality check, including a clinical check and scientific review.

- If the de-identified brain image does not pass the secondary central quality check, the Core PET Lab will submit a query via the EDC to either the study site coordinator or the core image lab.
    - If the issue is related to image acquisition and/or reconstruction, the study site coordinator will need to communicate with the site PET technician and provide the subject's source brain image with correct data elements and continue the workflow from there.
    - If the issue is related to de-identification, the BIONIC research assistant will need to redo the anonymization process of the image and continue the workflow from there.

This will be repeated until the de-identified brain images passes the secondary central quality check.

- When the de-identified brain image passes the secondary central quality check, Dr. Jagust's lab will give confirmation to the Core Image Lab and the workflow will proceed:
    - A BIONIC research assistant will archive the de-identified PET image in the Core Image Lab's shared drive.
    - The Core PET Lab will complete necessary processing and analysis of the PET image locally.
- The Core PET Lab will re-upload the final processed de-identified PET image, in addition to

analysis data, to the EDC.

- A BIONIC research assistant will archive the final processed de-identified PET image in the Core Image Lab's shared drive.
- Note: The Core PET Lab will upload a comprehensive spreadsheet with PET results analysis data at the "Project Level" in the EDC at a pre-specified frequency.

All archiving activities will be logged as complete and with date completed.

4. MRI ACQUISITION GUIDANCE

4.1. Site Qualification

Overview

Only one MRI scanner is qualified for the MAP study at your site and must be used for ALL subsequent subject scans during the study. If the same MRI scanner is not used, the scan will not be reimbursed, and the subject will need to be re-scanned on the MAP qualified scanner. Central QC will be done by BIONIC and the MRI Core Lab.

MRI Subject Scan Protocol

There is one section to the human protocol: Core

- 3 Plane/Tri-Planar Scout/Calibration Scan
- Sagittal 3D Accelerated MPRAGE/IRSPGR
- Sagittal 3D FLAIR
- Axial T2 Star/GRE
- Axial DTI

The MAP study uses the MRI scan protocol identical to the ADNI-3, but with several exceptions listed below.

1. Core scan sequences include sagittal 3D MPRAGE/IRSPGR, sagittal 3D FLAIR, axial T2 Star/GRE, and axial DTI, in addition to the scout view (3 place/tri-planar).
    a. Please use a basic b=1000 DTI without multi-band protocol acquisition, a minimum denominator, for the DTI scan. This is critical for data harmonization, although some of the scanners have multi-band capability, others do not, and using different b-values affects the diffusivity measures.
2. The phantom scan will be used for the local QC purpose, not for the central QC.
3. A human volunteer scan is required for the central QC. If the MAP MRI scanner was previously qualified for the ADNI-3 study, please send the QC team a human volunteer scan OR one of the ADNI-3 images. There are two reasons for this:
    a. If updates in scanner/software occur during the MAP study, central QC needs to evaluate the MRI's quality after the upgrade based on the quality before the upgrade.
    b. Each scanner/software has its own DICOM form. The central QC staff needs to be trained to become familiar with these DICOM forms.
4. A fiducial marker (e.g., vitamin E capsule) must be attached to the subject's right temple.

Human Volunteer Scan Instructions

NOTE: IRB approval is required prior to conducting a volunteer scan.

A standardized naming convention is not required for the human volunteer scan.

Data Transfer of Certification Scans

After each scanning session, please upload all sequences acquired for site certification in the DICOM file format to the site-specific OneDrive folder sent to your team (for human volunteer scans only).

Site Certification Scan Results

The QC team (BIONIC and the MRI Core Lab) will perform a quality control check on the phantom and/or volunteer scan data. QC team will determine if the correct parameters have been met and assure there are no other underlying problems seen during the scanning of these sessions. After successful qualification scanning, an official Site Certification e-mail will be sent to the selected contacts for your site and the ADNI-3 Study contacts notifying them your site has been approved and is ready to scan subjects.

4.2. MRI Subject Pre-Scan Procedures

Subject Pre-screening

All subjects should have been screened by the study coordinator for standard MRI contraindications. However, subjects must be screened for MRI contraindications immediately before the MRI scan using your local standard protocol. Contraindications include, but are not limited to:

- The presence of non-removable ferrous metal objects
- Aneurysm clips
- Pacemakers
- Other contraindications such as defibrillators, etc.

Subject Safety and Monitoring

- All sites should follow the standard subject consent protocols as approved by your local IRB.
- Explain the scan procedure to the subject so that they know what to expect during the MRI.
- Provide the subject with the opportunity to use the restroom before the scan begins.
- Please use universal MRI safety precautions. Make sure the subject does not have any large ferrous metal on or inside of him/her such as shrapnel, a metal fragment in the eye, aneurysm clips, ear implants, spinal nerve stimulators, permanent makeup, or a pacemaker. Make sure that all loose metal objects are removed.
- Subjects are allowed to take their medications on the day of the scan.
- Offer the subject hearing protection.
- Please use standard local practice for monitoring the subject during the scan. These may include MRI safe devices to monitor pulse and oxygen levels.

Subject Positioning

1. Proper subject positioning is crucial for successful reproduction of serial MRI exams. Therefore, it is important that each subject is positioned in the same manner for each and every MRI exam.

2. Please follow the procedures below for positioning the subject in the head coil:
    - Place clean sheet on scanner table and coil cradle.
    - Besides standard room exclusions ensure the subject has removed their dentures as well as any hair clips, combs, earrings, necklaces, etc.
    - Remove all upper body clothing with metallic trim, such as zippers, buttons or embroideries that may cause artifacts in the MRI images.
    - Provide each subject with ear protection.
    - Position the subject so their head and neck are relaxed, but without rotation in either plane. Proper placement in the head coil is crucial because scans are acquired straight, not in an oblique orientation. The subject should also be well supported in the head coil to minimize movement. Motion artifacts may result in data rejection and request for a re-scan in many cases.
    - Support under the back and/or legs can help to decrease strain on the knees and back as well as assisting in the stabilization of motion in the lower body.
    - Once the subject has been positioned, place sponges along the sides of head and a Velcro strap across forehead (if available) for stabilizing support and reduction of motion.
    - Align the centering crosshairs on the subject's nasion *(directly between the eyebrows)* at every scanning session.
    - Center the head coil over the subject's head, making sure the subject is high enough in the coil to prevent signal loss at the inferior aspect of the brain.
    - Offer each subject a panic button in case of emergencies or claustrophobia if common local practice at your facility (for example, a squeeze ball alarm.)
    - Remind subject to hold as still as possible and advance subject to the iso-center of the scanning bore.

    NOTE

    - It is extremely important that the subject is positioned in the same manner, at the nasion, for the Baseline MRI exam and for the second MRI visit.
    - It is imperative that the subject positioning procedures are followed exactly for the follow-up exam for a particular subject to ensure consistent imaging of the brain.
    - If a deviation from these instructions is required to accommodate a subject, the MRI technician must note this on the MRI Scan Information Form and refer to these notes during the follow-up exam.

4.3. MRI Example Images - Human Core Scan Sequences

The following pages are example images or what will be acquired for the MAP study, as well as positioning recommendations.

3 Plane/Tri-Planar Scout

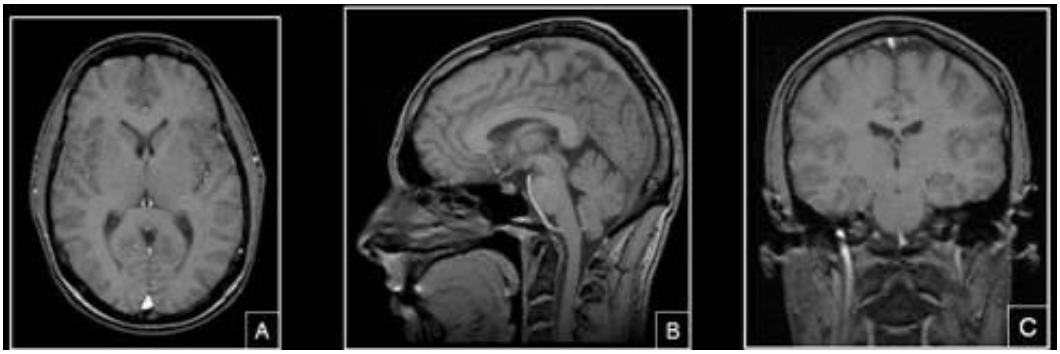


Figure 1. Example of 3 Plane/Tri-Planar Scout

1. A quick acquisition in 3 orthogonal planes for anatomical orientation. One slice acquired in the middle of each plane (sagittal, coronal, transverse). The head should be centered laterally along the inter-hemispheric fissure and centered on the thalamus for the anterior/posterior and superior/inferior planes. Please use the images below as reference when determining if the subject is positioned properly.
2. Proper placement of the subject's head inside the head coil is crucial because scans are acquired straight, not in an oblique orientation. <u>The head should be as straight as possible in the coil.</u>
3. If the subject is not positioned properly, please adjust the subject in the head coil and re-scout. Continue repositioning and scouting until the subject is correctly centered in the head coil.

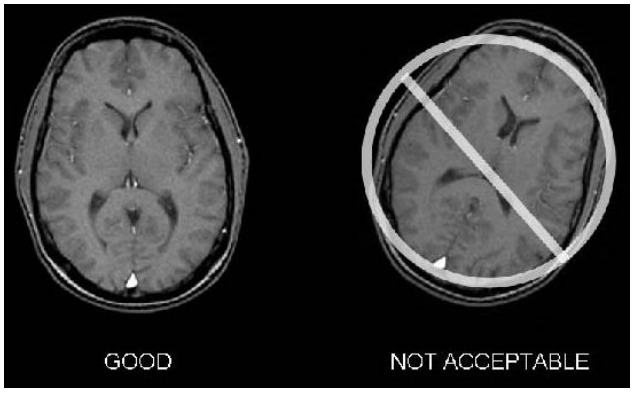


Figure 2. Example of Proper Head Positioning

4. Pre-scan Adjustments/Calibration Scans: most modern MRI scanners provide automated adjustment procedures for radiofrequency coil tuning and frequency adjustments after the subject is positioned in the magnet. Follow the adjustment procedures provided by the manufacturers.
5. Positioning for all Axial Scans:
   a. Orientation: straight axial. Prescribe slices inferior to superior. DO NOT oblique the scanning field of view (FOV).
   b. Positioning: position on mid-sagittal slice from tri-planar scout. Make sure to get full BRAIN

coverage whenever possible. The acquisition stack should be placed just above the most superior point in the brain and should fully cover the cerebellum as well as all brain in the lateral and the anterior to posterior planes. If extra transverse slices are required to achieve this coverage, please acquire those slices.

Sagittal 3D Accelerated MPRAGE/IRSPGR

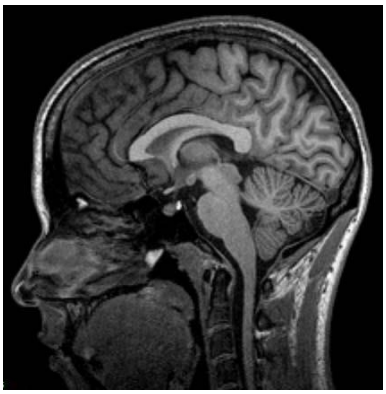


Figure 3. Example of Sagittal 3D Accelerated MPRAGE/IRSPGR

1. Orientation: straight sagittal. Slices will be prescribed from left to right. DO NOT oblique the scanning FOV to compensate for subject head tilt.
2. Positioning: use the tri-planar scout to position the acquisition box. Make sure to get full head coverage. Studies that do not contain the whole brain and skull cannot be processed. The skull must be fully included superiorly and laterally. The entire cerebellum should be included inferiorly. In the anterior/posterior plane, the nose should also be included otherwise image folding into the back of the brain will result and the exam may not be usable for the study. Please see the images below to use as a guide to correctly position the acquisition box.

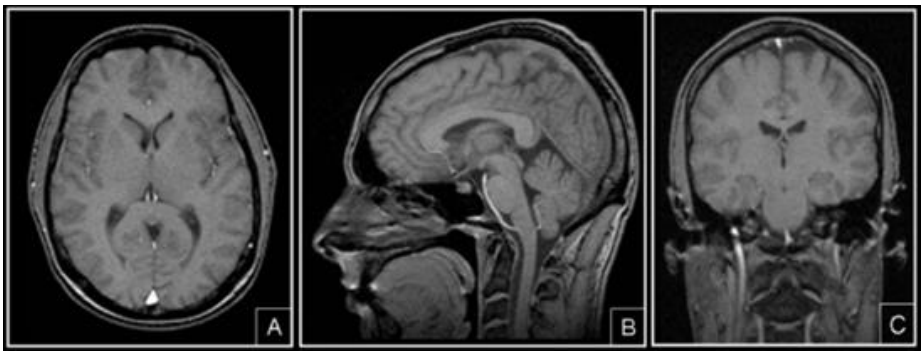


Figure 4. Example of 3 Plane Localizer for MPRAGE/IRSPGR FOV Placements

Box A - Axial image: FOV placed in center to avoid side-to-side wrap.

Box B - Sagittal image: FOV placed anterior to avoid nose wrap.

Box C - Coronal image: FOV placed to assure top of the brain is covered.

Sagittal 3D FLAIR [straight, no oblique]

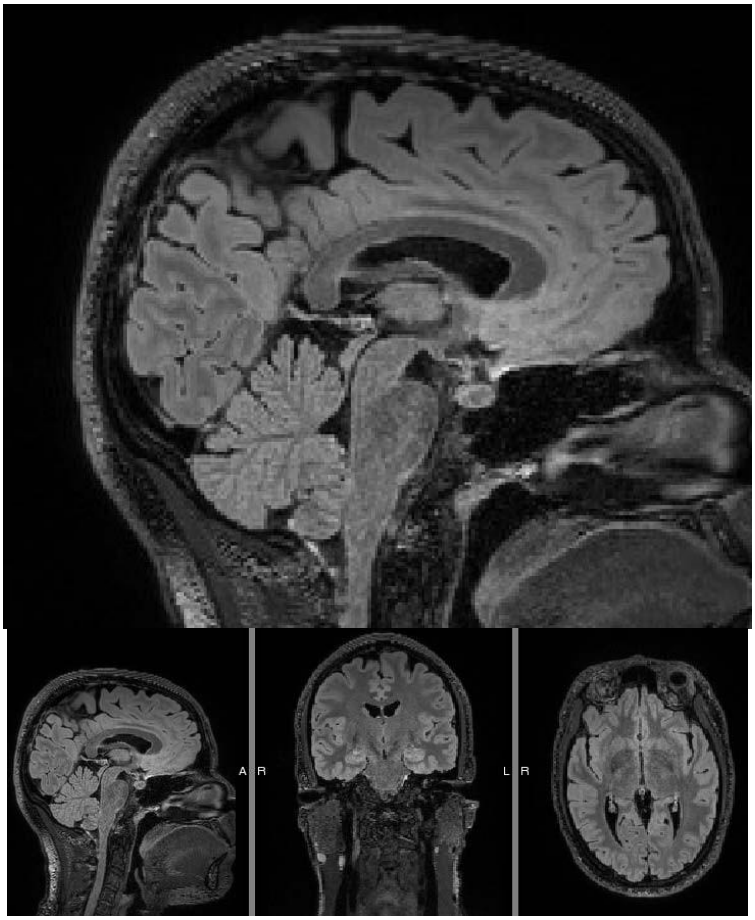


Figure 5. Example of 3D FLAIR

Axial T2 Star/GRE

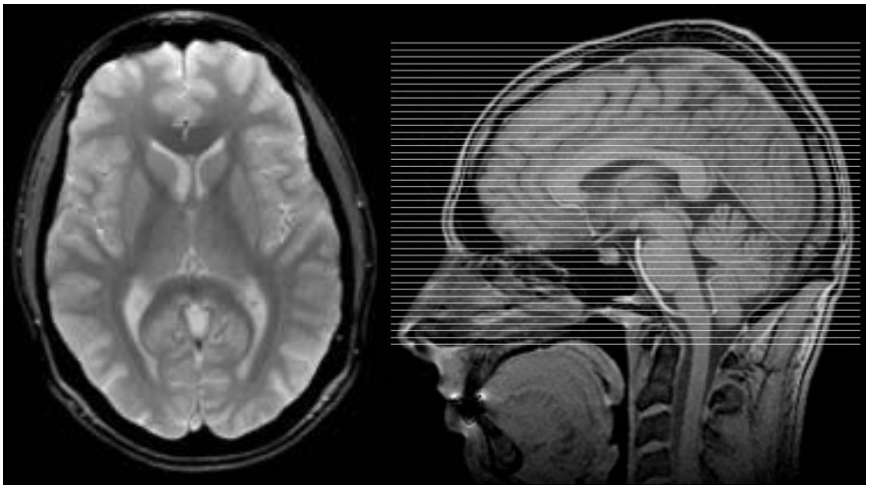


Figure 6. Example of Axial T2 star / GRE

Axial Diffusion Weighted Image (DTI) [straight axial, no oblique]

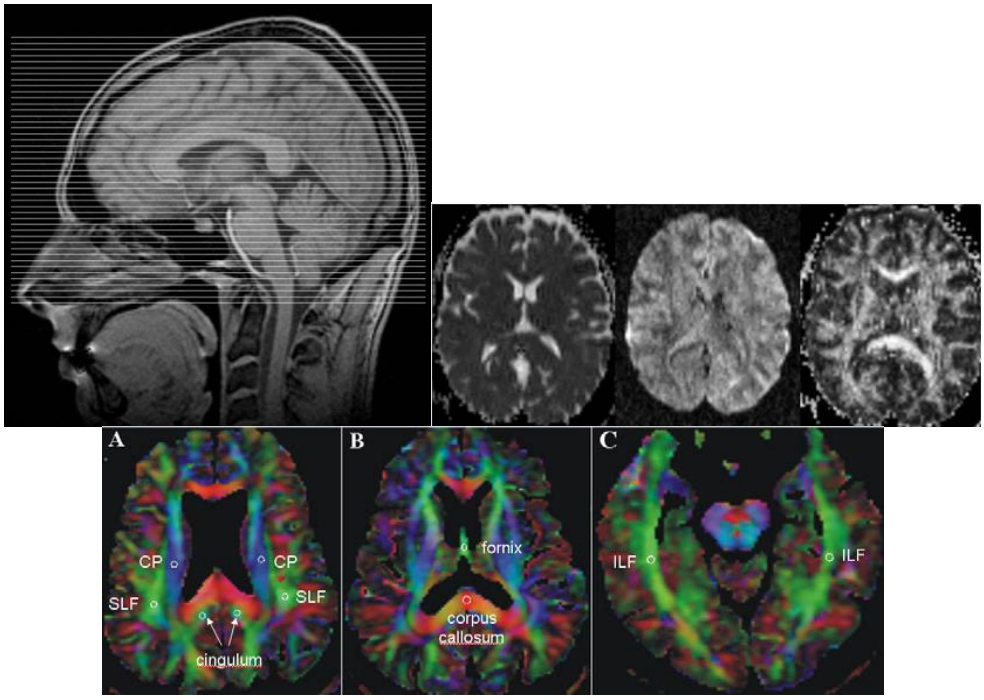


Figure 7. Example of Axial Diffusion Weighted Image (DTI)

1. Orientation: straight axial; DO NOT oblique scans.
2. Positioning: position on mid-sagittal slice from tri-planar scout. Make sure to get full BRAIN coverage. The acquisition stack should be placed just above the most superior point in the brain and should fully cover the cerebellum as well as all brain in the lateral and the anterior to posterior planes. If extra transverse slices are required to achieve this coverage, please acquire those slices.

4.4. MRI Subject Scan Procedures

MRI Scan Information Form

1. The "MRI Scan Information Form" should be completed at the time of acquisition for every MAP subject.
2. The study coordinator at the referral site should complete the top section of the MRI Scan Information Form. If this section is incomplete, please contact the study coordinator for the information.
3. The MRI technician should complete the remainder of the form during the scan. Please be sure to indicate if each sequence has been completed and note any problems or modifications to the protocol in the appropriate sections. This enables the QC team to closely follow each scanning session and note if data transfer and archive have been completed.
4. Please complete the form in full and transfer to the study coordinator at the referral site. The study coordinator will enter the information into the EDC, and this will be linked with the subjects' MRI data. Please keep a copy on site for your records.

To report an incident regarding the MRI sequences please email: Kenichi Oishi (koisihi2@jhu.edu) and

Nathan Walborn (nwalbor1@jhmi.edu). To report an incident about a specific subject, please contact your study coordinator.

Entering Subject Information into the Scanner

Although the scan header will be de-identified and rendered HIPAA compliant when data is entered in the EDC, your site is requested to use the MAP subject naming convention below when entering the subject information into the scanner.

Naming Convention

A MAP subject's enrollment ID is in the format of AAA-BBB, where AAA is a three-digit site ID and BBB is a three-digit consecutive number. It is assigned by the EDC when a subject is randomized. Please note that each subject also has a screening ID that is different from the enrollment ID.

Scan Discontinuation

If the subject elects to discontinue the MRI because of discomfort every effort should be made to adjust the table, head coil, etc. and finish acquiring the scan. However, if the subject still does not want to complete the scan, then the MRI should be abandoned and noted as incomplete on the ADNI-3 MRI Scan Information Form. The comments section should include the reason the subject was unable to complete the MRI.

Archive Procedures

Every MRI scan for the MAP Study must be archived at the MRI facility following standard local practice. Additional data transfers or copies may be requested in the event that a data transfer is interrupted or incomplete. Possible MRI archive mediums include:

- optical disk
- PACS
- CD or DVD

Data Transfer

Each site will upload the MRI scan and subject data to the EDC within 24 hours after the completion of the scan as detailed in the DICOM File and Data Upload Instructions Section.

Request for Repeat MRI Scans

- Reasons for MRI Repeats

A request for a repeat MRI may be required if the scans are found to be unacceptable due to subject motion or an incomplete/incorrect MRI acquisition. Your site will be asked to schedule a repeat study.

QC team will check all MAP MRI scans to be sure that the exam was conducted on the one scanner qualified for MAP at your site was used, and that the correct, electronically loaded sequences have been used to scan each subject. Repeat exams may also be required if the incorrect scan sequence, orientation, or angulations are used. It is imperative to use the MAP approved acquisition sequence with every MAP subject. Scans with image degradation due to the incorrect scan sequence, orientation, or angulations will NOT be reimbursed nor will scans acquired on any scanner other than the one qualified for MAP. Re-scans will be reimbursed if the correct scan sequence, orientation, and angulations were used.

- Procedures for MRI Repeats

Repeat MRI scans should be performed as quickly as possible. The QC team will contact the referral site as well as the MRI facility requesting a repeat MRI. Detailed information regarding the reason for the

repeat as well as suggestions for improvement will be communicated to both sites.

4.5. Quality Control

Sites will only be required to scan the human volunteer scan at initial site certification, software/hardware updates, or when significant maintenance is performed.

Hardware and Software Updates

To avoid any delays or mistakes in scanning, the QC team requires notification at least 2 weeks ***PRIOR*** to any software and/or hardware updates for any scanner involved in the MAP imaging study so they can provide your site the correct upgraded protocols if needed.

At the time of your site's MRI scanner upgrade, the MRI staff will be required to scan a human volunteer (depending on the nature of the upgrade) prior to continuing scanning subjects.

IMPORTANT: If a site fails to perform these human scans and/or they have not been performed within 2 weeks of the upgrade, MAP may not accept or reimburse the subsequent subject scans. The study coordinator and the principal investigator at each site will be notified if a human volunteer scan has not been received within that time frame.

Data Transfer

Each site will upload the phantom data to the OneDrive folder within 24 hours after the completion of the scan.

Human Scan Results and Site Notification

The QC team will examine each human volunteer scan to ensure that the image quality is good enough for the downstream analysis. When finished, if there is an issue that needs to be addressed, an email will be sent to your site notifying you of the problem.

5. PET ACQUISITION GUIDANCE

5.1. Site Qualification

It is preferable for sites to use existing qualified TRC-PAD, ADNI, LEADS, DIAN, DIAN-TU, Pointer, or NiAD scanners for PET imaging. If you are using a scanner that has not been qualified for one of these projects by Bob Koeppe, it will need to be qualified before imaging can be performed. Please contact Suzanne Baker (slbaker@lbl.gov) regarding scanning a Hoffman phantom to qualify your PET scanner for this study.

You should make every attempt to acquire MAP data on the same scanner. If you need to change scanners, again, please contact Suzanne Baker. You will need to perform two Hoffman phantom scans and send images to Suzanne Baker prior to scanning any subjects on the new PET scanner.

Do you need to perform Hoffman phantom scans?

Phantom scans will be performed during the site qualification process, to set up MAP PET acquisition and reconstruction protocols and to validate their quality. It will also be required after a major hardware upgrade of your PET system, to detect any potential deviation due to the upgrade. Once the system is up and running again, please check the potential impact of the upgrade on the acquisition parameters and communicate with Suzanne Baker to find out what change is considered acceptable.

NOTE: If you are using a new scanner that is not listed in Section 7, the PET core quality assurance team will provide you with scanner specific instructions for your site's PET scanner.

Instructions on Hoffman phantom scans:

1. Filling the Hoffman phantom:

Radioactivity: ~0.6 mCi F-18 at time of scan start.

Fill the phantom carefully to prevent air bubbles as much as possible. Mix thoroughly.

Tips for successful filling:

a. Withdraw ~50 mL from a filled phantom, BEFORE inserting the radioactivity. It works best to use a spinal needle to inject the radioactivity. Be careful not to "stab" the plastic with the tip of the needle as this often creates a "hot spot" in the scan.

b. Next, fill the phantom with all but ~10 mL, and mix thoroughly.

c. Then inject all but the last ~1 mL and mix again.

d. Finally, inject the remaining ~1 mL as carefully as possible to prevent air bubbles and mix one last time.

NOTE: for mixing, it works well to put down absorbent pads and have two people roll the phantom back and forth from half a minute to a minute, thereby decreasing each person's exposure to the phantom. (One can even use the floor and one's feet.)

2. Scanning the Hoffman phantom:

Acquisition: The acquisition time for the Hoffman phantom scan should be four 5-minute frames, for a total of 20 minutes.

Reconstruction: The same reconstruction parameters should be used as the human scans.

3. Upload Hoffman phantom reconstruction files:

After each scanning session, please upload the Hoffman phantom reconstruction files in the DICOM file format to the site-specific OneDrive folder sent to your team (for Hoffman phantom scans only).

Please email Suzanne Baker (slbaker@lbl.gov) and Nathan Walborn (nwalbor1@jhmi.edu) with any questions or concerns regarding reconstructed Hoffman phantom scan upload.

4. Phantom scan evaluation and result:

PET core QC will examine the phantom data and determine if the correct parameters have been met and ensure there are no other underlying problems with the scanning session. Your site will be notified by email if the phantom scans pass or fail, and whether your PET system has been certified for MAP.

Regulatory

Sites must be appropriately licensed through appropriate state or federal agencies to receive and use all radiotracers prior to imaging.

Sites must also receive both **IRB** approval and **radiation safety committee (RSC) or similar** approval before scanning any subjects.

5.2. Continued Quality Monitoring of PET Scanner

To ensure scanner/ancillary equipment stability and quality, each site is required to perform ongoing

quality control procedures.

PET-only Scanner:

- The PET scanner should have an up-to-date calibration and normalization on the date of each imaging session.
- A daily QC/blank scan should be done at the beginning of the day the scanning is to be completed. This scan should be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the quality of the PET scan the study should be rescheduled.

PET/CT Scanner:

- The PET/CT scanner should have an up-to-date calibration and normalization on the date of the imaging session.
- A daily QC check should be done at the beginning of the day the scanning is to be completed. This scan should be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the quality of the PET scan the study should be rescheduled.
- Daily CT should be performed as recommended by the specific vendor, but typically should include a "checkup/calibration" procedure and a water phantom scan. The checkup/calibration procedure guarantees optimum image quality by warming up the x-ray tube and should be performed at startup and within 1 hour prior to any scan. The water phantom provides quality measurements of 3 parameters. The parameters are the CRT value of water calculated in Hounsfield units (HU), the pixel noise of images calculated as a standard deviation, and the tube voltages measured directly on the x-ray tubes. These three measurements should be determined for all available kVp values.

PET/MR Scanner:

- The PET/MR scanner should have an up-to-date calibration and normalization on the date of the imaging session.
- On the day of a scan, a daily normalization and detector setup should be completed before any subject scanning is performed. This scan should be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the quality of the PET scan the study should be rescheduled.
- Daily MR QC should be performed as recommended by the specific vendor.

Ancillary Equipment:

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

5.3. PET General Information

Ambient Conditions

Standardization of the environment during the uptake period following tracer administration is not essential.

Naming Convention

MAP subjects' enrollment ID is in the format of AAA-BBB, where AAA is a three-digit site ID and BBB is a three-digit consecutive number. It is assigned by the EDC when a subject is randomized. Please note that each subject also has a screening ID which is different from the enrollment ID.

The tracer should be included in the Series Description.

In the PET scan Series Description, include PET radiotracer used as follows:

- amyloid_florbetaben
- tau_MK6240

PET DICOM and Upload Form Instructions

Please see Section 6. DICOM File and Data Upload Instructions.

5.4. PET Procedures

Be sure to have the PET scan upload form and fill out accordingly during the procedure.

Radiotracer Doses

Using aseptic technique and radiation shielding, draw off the radiotracer and assay with a dose calibrator. Record the assay time to the nearest minute. Do not add saline to the dose prior to administration. Adding saline could potentially lead to precipitation out of solution form.

Suggested radiotracer doses and acquisition start-stop times:

Tracer	Suggested Target Dose ± 10%		Minimum injectable dose		Acquisition start-stop time post-injection (min)
	mCi	MBq	mCi	MBq	
Florbetaben	8	295	5	185	90-110
MK6240	5	185	4	150	90-110

The above are suggested target doses +/-10%. We will accept data scanned with the above tracers as long as the amount injected does not fall below the minimum injectable dose and scans are acquired using the start-stop times listed under Acquisition time post-injection.

Position the subject with sufficient time so that the scan can be started precisely 90 minutes post-injection.

Prepare Subject

- Have the subject use the restroom and empty their bladder.
- Allow them to lie comfortably in a bed or reclining chair in a room. Supply them with blankets/pillows as needed to maximize their comfort.
- Obtain intravenous access using a small angiocath.

Drawing up, Assaying, and Injection Dose

- Draw up sufficient tracer to achieve the target dose and assay with a dose calibrator.
- Record the assay time to the nearest minute. Do not q.s. (add saline) to the dose prior to administration. Adding saline could potentially lead to precipitation out of solution form.
- Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter or is discolored.
- Inject the radiotracer and follow the injection with an intravenous flush of 0.9% sterile sodium chloride. Record the injection time to the nearest minute. The intravenous line can be discontinued at this time.

- Re-assay the dose syringe. If the residual activity is 0.1 mCi or greater, record the amount and correct the amount of the injected dose for the residual activity.
- Allow the subject to rest comfortably in the room during the incorporation period until about 10-15 minutes prior to the start time for the particular radiotracer.
- 10-15 minutes before scanning, have the subject use the restroom and empty their bladder.
- For PET/CT scanners, the subject should be placed on the scanning table early enough to obtain a CT scan prior to the emission scan, and still be able to begin the emission acquisition at the appropriate start time. PET-only systems will acquire a transmission scan following the emission acquisition, so preparation of the subject can begin a few minutes later than if on a PET/CT system.

5.5. Subject Positioning

Proper subject positioning is a key aspect of the successful completion of the PET exams. It is important to take the time necessary to ensure not only that the subject is properly positioned but also can **comfortably** maintain that position throughout the duration of the scanning session. **Excessive motion and in particular a difference in the subjects' position between the emission scan and the transmission or CT scan used for attenuation correction is the single most common cause of failed studies.**

- Have the subject remove any bulky items from their pockets such as billfolds, keys, etc.
- In addition, they should remove eyeglasses, earrings, and hair clips/combs if present. If possible, they should try and remove hearing aids also.
- Position the subject so that their head and neck are relaxed. It may be necessary to add additional pads beneath the neck to provide sufficient support. Use the lasers to ensure there is little or no rotation in either plane. The head should be approximately positioned such that the PET scanning planes are parallel to the imaginary line between the external canthus of the eye and the external auditory meatus (orbitomeatal plane), and the head is centered in the sagittal plane. Ultimately, if the subject is comfortable, this should translate to less subject motion during the scan.
- Alignment marks should be put on the subject using the laser system, which can then be subsequently used to check alignment and reposition the subject as necessary.
- Use support devices under the back and/or legs to help decrease the strain on these regions. This will also assist in stabilizing the lower body thus reducing motion.
- Once the subject has been positioned, foam pads can be placed alongside the head for additional support. Velcro straps and/or tape should also be used to secure the head position. Vacuum beanbags can also be used in this process.
- The subjects should be offered a "panic button" or be reassured that someone is watching or able to hear them at all times.
- Proper positioning of the subject to get the entire head in the field of view is critical to the success of the project.

Checking the subject positioning and readjusting (if possible) the position of the subject's head should be done often throughout the study.

5.6. Attenuation Correction Procedures

PET/CT Scanner:

- Standard CT acquisition parameters, but low effective mAs (~30 is typical).
- The subject must undergo the CT scan about 5 minutes prior to starting the PET scan. Be sure to prepare the subject so that you are ready to press “start” for the PET emission scan at the required time.

PET-only Scanner:

- Acquire an attenuation correction scan using rod sources for 5-6 minutes after the acquisition of the standard emission scan. The subject should be repositioned “on their marks” prior to acquiring the transmission scan.
- Segmentation and re-projection routines will be applied for attenuation correction.

5.7. Emission Acquisition Procedures

- Scans should never be started prior to the acquisition start time, and every effort must be made to start the scan on time. Scheduling scans very close in time following a clinical study (which could run late) is not an acceptable reason for starting a scan late.
- It is crucial that the subject’s position be checked several times throughout the PET scan. A good idea is to check the subject’s marks using the laser system at the end of each 5-minute scan frame. The subject’s position should be returned as closely as possible to the original position just at the beginning of the next scan frame.

5.8. Post PET Scan

- Reconstruct images using parameters specific to your site’s scanner. The same reconstruction parameters should be used for all emission scans. Upon completion of the reconstruction, review all the images to assess for artifacts.
- Archive ALL raw and processed study data including copies of the normalization and blank scans. It is necessary to archive and store raw and processed data at the imaging site for the duration of the project and local guidelines (approximately 5 years).

6. DICOM FILE AND DATA UPLOAD INSTRUCTIONS

Steps for study site coordinators to upload DICOM source files are outlined below. Please note, the steps for MRI DICOM file and PET DICOM file upload are identical.

Method 1: open PACS system and login.

1. Locate the MRI/PET and export to DICOM files:
    a. Export DICOM files directly from the PACS system to a folder on your computer;
    b. Save in folder labeled as “subject ID_image date/time”;
        i. Zip folder into a compressed file (Windows):

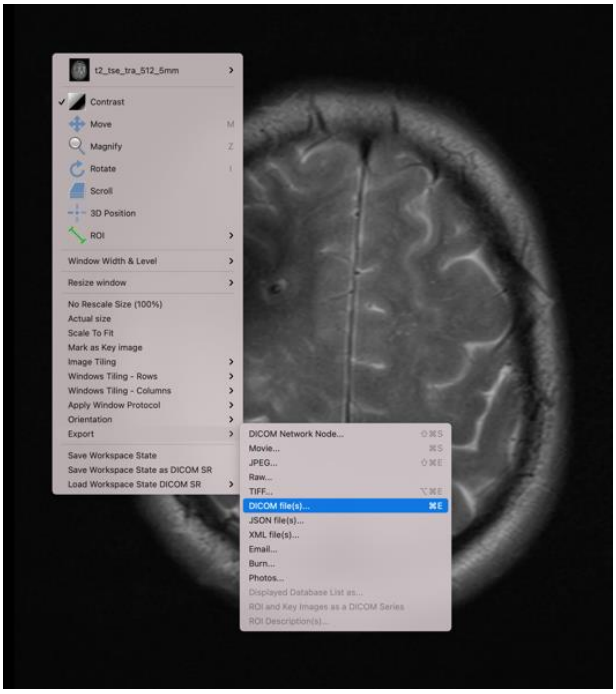
        - Right click on the file that you just created and select “Send to,” then “Compressed (zipped) folder”;

        - Locate the ‘zipped’ folder in the same location (notice the zipper on the folder) – this is the file you will upload to the source docs page of the EDC.

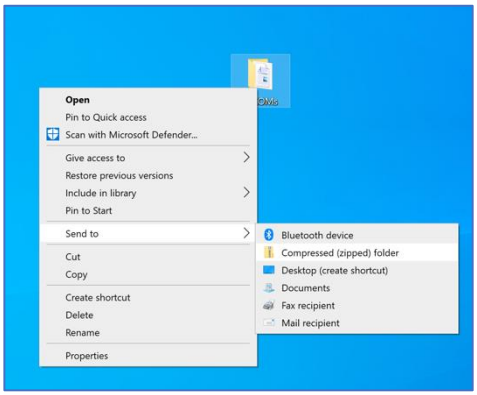
        ii. Zip folder into a compressed file (macOS):

        - Right-click on the file that you just created and select “Compress ‘Folder Name’”;

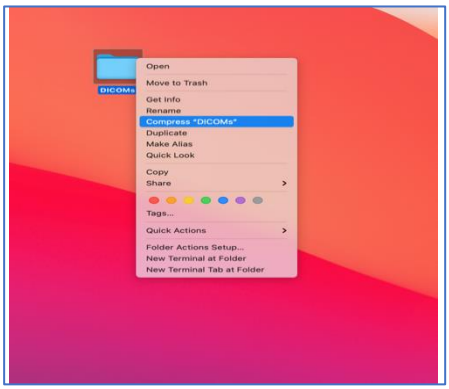
        - Locate the ‘zipped’ file in the same location (notice the zipper on the folder) – this is the file you will upload to the source docs page of the EDC.



Compressing a file (Windows)

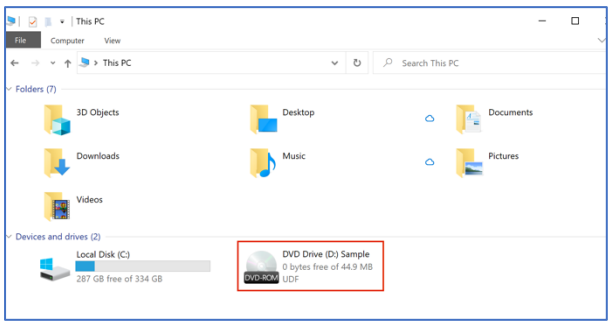


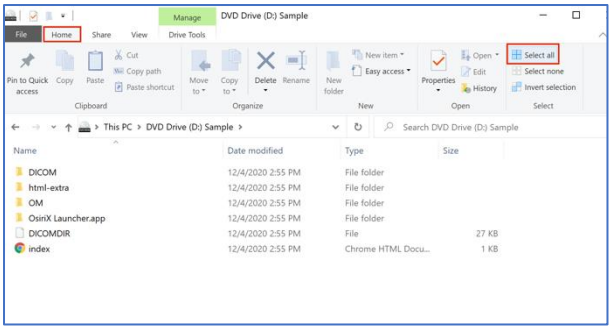
Compressing a file (macOS)



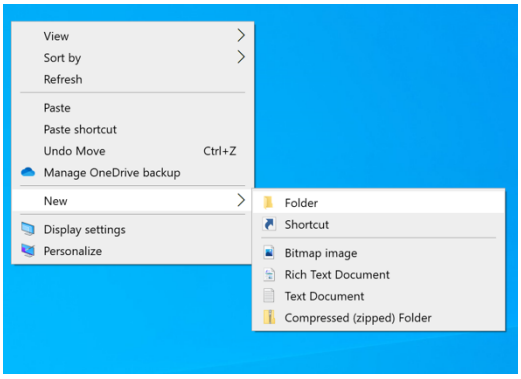
Method 2 (Windows): Request a CD from radiology with the scans that you want burned onto it:

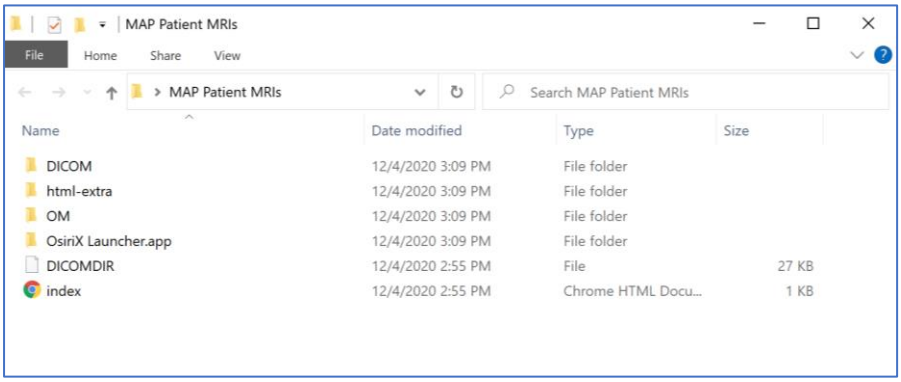
1. Select all files on the CD and copy.
2. Copy files to a local folder:
   a. Create a new folder on your computer (ex. “MAP Subject MRIs”);
   b. Open this folder;





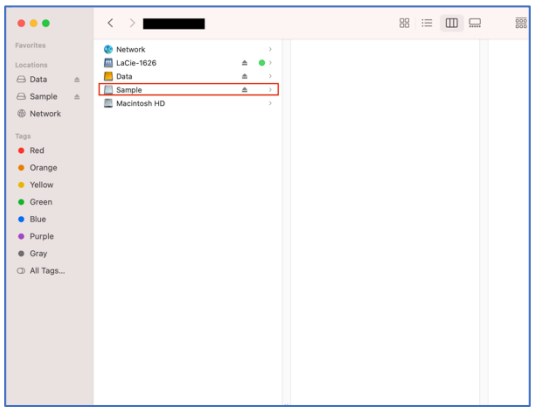
   c. Right-click and paste.

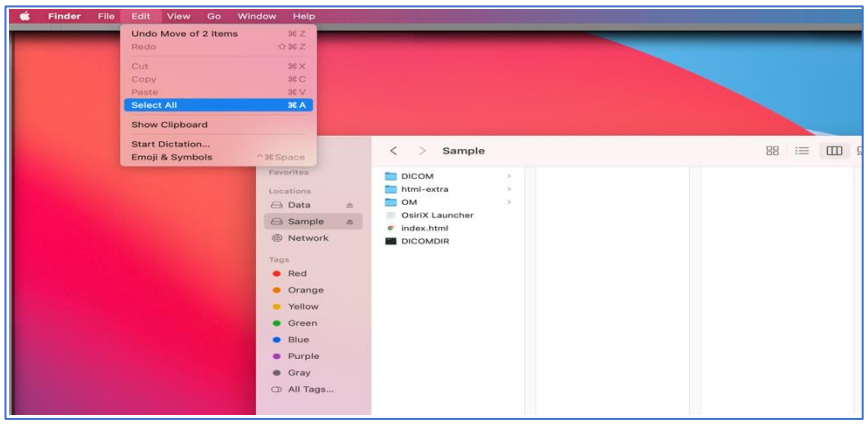




3. Zip folder into a compressed file (see reference photos above):
   a. Right-click on the file that you just created and select “Send to,” then “Compressed (zipped) folder”;
   b. Locate the ‘zipped’ file in the same location (notice the zipper on the folder) – this is the file that you will upload to the source docs page of the EDC.

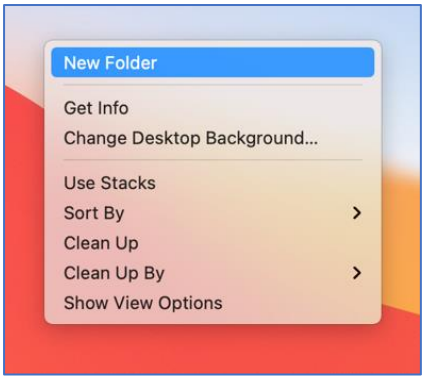
Method 3 (macOS): Request a CD from radiology with the scans that you want burned onto it.

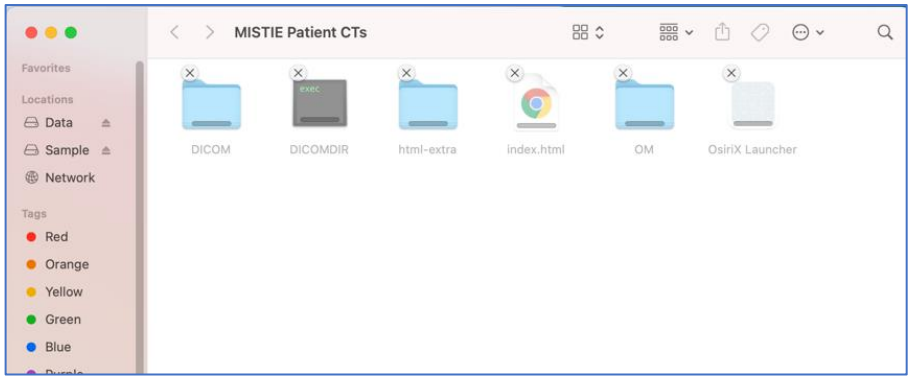




Locate the CD on your computer, select all files and "Copy".

1. Copy files to a local folder:
   a. Create a new folder on your computer (ex. "MAP Subject MRIs");
   b. Open this folder;





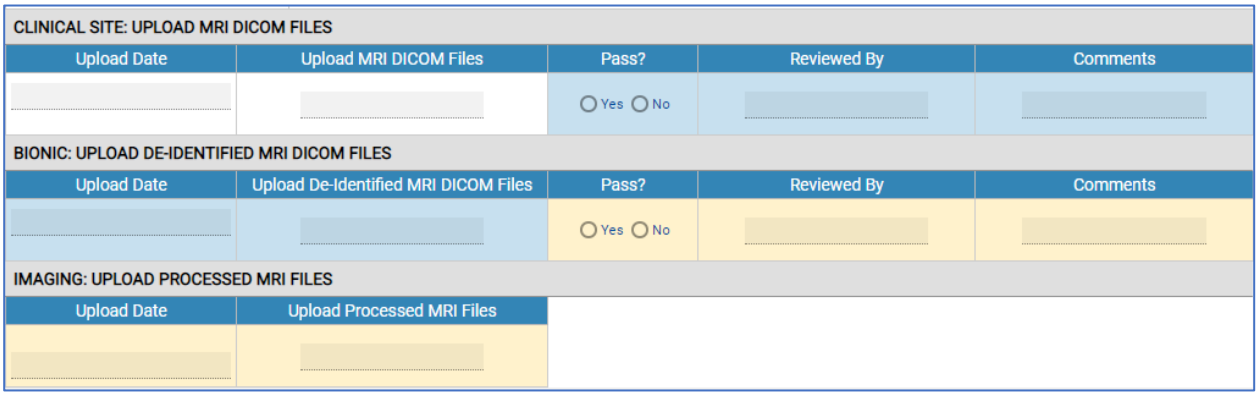
   c. Right-click and paste.
2. Zip folder into a compressed file (see reference photos above):
   a. Right-click on the file that you just created and select "Compress 'Folder Name'";
   b. Locate the zipped file in the same location (notice the zipper on the folder) – this is the file you will upload to the source docs page of the EDC.

Upload to the EDC

MRI and PET scans will be taken at baseline and end of study. Please upload any additional imaging taken during the study.

In the EDC upload sections, the white sections are completed by the site, the blue sections will be completed by BIONIC, and the yellow sections will be completed by the Core MRI and Core PET labs.

MRI and PET Upload Sections



CLINICAL SITE: UPLOAD MRI DICOM FILES

Upload Date	Upload MRI DICOM Files	Pass?	Reviewed By	Comments
		○ Yes ○ No		

BIONIC: UPLOAD DE-IDENTIFIED MRI DICOM FILES

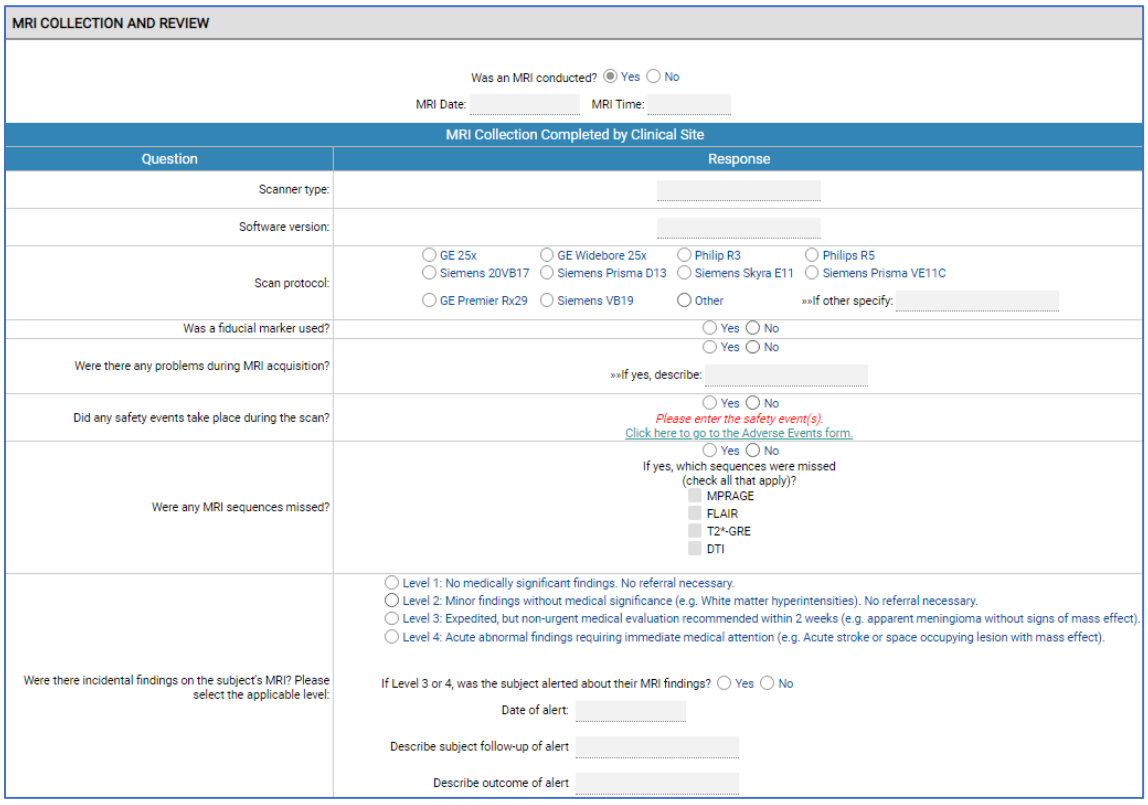
Upload Date	Upload De-Identified MRI DICOM Files	Pass?	Reviewed By	Comments
		○ Yes ○ No		

IMAGING: UPLOAD PROCESSED MRI FILES

Upload Date	Upload Processed MRI Files

In addition to uploading the MRIs and PET scans, the study site coordinators will create and complete the appropriate MRI or PET form in the EDC. These upload forms must be filled out for the scan to be analyzed and for the site to be credited for performing the scan.

MRI Form



MRI COLLECTION AND REVIEW

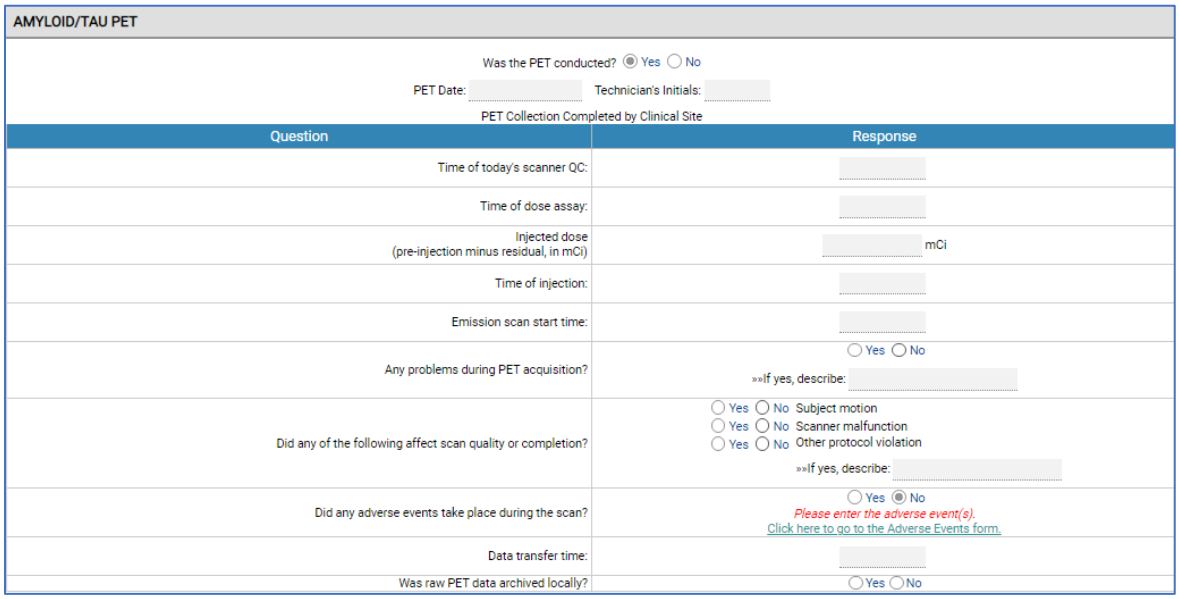
Was an MRI conducted? ◉ Yes ○ No

MRI Date: MRI Time:

MRI Collection Completed by Clinical Site

Question	Response
Scanner type:	
Software version:	
Scan protocol:	○ GE 25x ○ GE Widebore 25x ○ Philip R3 ○ Philips R5 ○ Siemens 20VB17 ○ Siemens Prisma D13 ○ Siemens Skyra E11 ○ Siemens Prisma VE11C ○ GE Premier Rx29 ○ Siemens VB19 ○ Other »»If other specify:
Was a fiducial marker used?	○ Yes ○ No
Were there any problems during MRI acquisition?	○ Yes ○ No »»If yes, describe:
Did any safety events take place during the scan?	○ Yes ○ No *Please enter the safety event(s).* Click here to go to the Adverse Events form.
Were any MRI sequences missed?	○ Yes ○ No If yes, which sequences were missed (check all that apply)? ☐ MPRAGE ☐ FLAIR ☐ T2*-GRE ☐ DTI
Were there incidental findings on the subject's MRI? Please select the applicable level:	○ Level 1: No medically significant findings. No referral necessary. ◯ Level 2: Minor findings without medical significance (e.g. White matter hyperintensities). No referral necessary. ○ Level 3: Expedited, but non-urgent medical evaluation recommended within 2 weeks (e.g. apparent meningioma without signs of mass effect). ○ Level 4: Acute abnormal findings requiring immediate medical attention (e.g. Acute stroke or space occupying lesion with mass effect). If Level 3 or 4, was the subject alerted about their MRI findings? ○ Yes ○ No Date of alert: Describe subject follow-up of alert Describe outcome of alert

PET Form



AMYLOID/TAU PET

Was the PET conducted? (•) Yes ( ) No

PET Date: _____ Technician's Initials: _____

PET Collection Completed by Clinical Site

Question	Response
Time of today's scanner QC:	_____
Time of dose assay:	_____
Injected dose (pre-injection minus residual, in mCi)	_____ mCi
Time of injection:	_____
Emission scan start time:	_____
Any problems during PET acquisition?	( ) Yes ( ) No »»If yes, describe: _____
Did any of the following affect scan quality or completion?	( ) Yes ( ) No Subject motion ( ) Yes ( ) No Scanner malfunction ( ) Yes ( ) No Other protocol violation »»If yes, describe: _____
Did any adverse events take place during the scan?	( ) Yes (•) No *Please enter the adverse event(s).* Click here to go to the Adverse Events form.
Data transfer time:	_____
Was raw PET data archived locally?	( ) Yes ( ) No

7. SCANNER PARAMETERS FOR IMAGE ACQUISITION AND RECONSTRUCTION

7.1. MRI

Manufacturer	Model	Software	ADNI-3 Protocol
GE	Discovery MR750W	25.1_R02	GE MR750w 25.1
GE	Premier	RX27	GE 25x/Widebore 25x
Philips	Ingenia Elition	R5	Philips R3/R5
Siemens	Prisma 3T	VG62A	Siemens Prisma
Siemens	Skyra	E11C	Siemens Skyra E11
Siemens	Tesla Trio	VB17	Siemens Prisma
Siemens	Trio	VB17	Siemens VB-17
Siemens	Verio	Syngo MR B19	Siemens

7.2. PET

- **GE DISCOVERY 600, 610, 690, 710, AND MI DR - PET/CT SCANNERS**
- **GE DISCOVERY MI – PET/CT SCANNER**
- **GE DISCOVERY STE – PET/CT SCANNER**
- **PHILIPS GEMINI TF – PET/CT SCANNER**
- **SIEMENS BIOGRAPH MCT – MCT TRUEV PET/CT SCANNER**
- **SIEMENS BIOGRAPH VISION – PET/CT SCANNER**
- **SIEMENS HRRT 207-SLICE PET-ONLY SCANNER**

GE DISCOVERY 600, 610, 690, 710, AND MI DR - PET/CT SCANNERS

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Randoms Correction:

Singles: (not 'real-time subtraction' or 'delays')
Reconstruction Parameters:

Reconstruction Method: **VPHD or VPFX**, whichever your site normally uses. (**NOT** VPHD**S** or VPFX**S**).

4 iterations; 24 subsets (or as close to 24 subsets as the software allows)

Grid: 192 x **192** x **47**

FOV: 256 mm (results in voxel size of 1.333 mm)

Slice Thickness: 3.27 mm

Smoothing Filter: NONE or 0.0 (for all filter options: loop filter, post-filter and z-axis filter)

All corrections '**On**'

Note: Reconstruction offsets should be used to assure the head is fully in the in-plane FoV.

GE DISCOVERY MI – PET/CT SCANNER

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Randoms Correction:

Singles: (not 'real-time subtraction' or 'delays')

Reconstruction Parameters:

Reconstruction Method: VPHD or VPFX, whichever your site normally uses (**NOT** VPHDS or VPFXS). .

6 iterations; 16 subsets

Grid: 192 x 192 x (53, 71, or 89) (depending on the Disc-MI model)

FOV: 256 mm (results in voxel size of 1.333 mm)

Slice Thickness: 2.79 mm

Smoothing Filter: NONE or 0.0 (for all filter options: loop filter, post-filter and z-axis filter)

All corrections '**On**'

Note: Reconstruction offsets should be used to assure the head is fully in the in-plane FoV.

GE DISCOVERY STE – PET/CT SCANNER

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Randoms Correction:

Singles: (not real-time subtraction)

Reconstruction Parameters:

Reconstruction Method: 3D Iterative (fully 3D Iter; not 3D FORE IR)**:**

4 iterations; 20 subsets

Grid: 128 x **128**

FOV: 256 mm (results in voxel size of 2.0 mm)

Slice Thickness: 3.27 mm

Smoothing Filter: NONE or 0.0 (for all filter options: loop filter, post-filter and z-axis filter)

All corrections '**On**'

Note: Reconstruction offsets should be used to assure the head is fully in the in-plane FoV.

PHILIPS GEMINI TF – PET/CT SCANNER

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Acquisition Protocol: Brain Protocol

Reconstruction Parameters:

Reconstruction Method: Iterative: LOR-RAMLA

Grid: 128 x **128** x **90**

FOV: 256 mm (results in voxel size of 2.0 mm)

Slice Thickness: 2.0 mm

Smoothing: Set SMOOTHING parameter to '**SHARP**'

All other parameters should be set to defaults for the "**Brain**" protocol. All corrections '**On**'

For LOR-RAMLA reconstruction: The attenuation field should indicate "CTAC-SG" and the scatter field should indication "SS-Simul".

SIEMENS BIOGRAPH MCT – MCT TRUEV PET/CT SCANNER

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Scans and scan duration:

LIST-MODE: If your scanner has list-mode capability.

NO LIST-MODE: **ONLY** If your scanner does not have list-mode capability.

*****Note that to reduce motion artifacts, two separate emission scans will be acquired as closely together as possible. Do not repeat CT scan.

Reconstruction Parameters:

Method: Iterative: OSEM-3D (do NOT use TrueX or ToF reconstruction)

4 iterations; 24 subsets

Grid: 400 x **400** x **81 (or 109 for TrueV model)**

Zoom: 2.0 (results in voxel size of ~1.018 mm)

Smoothing Filter: NONE (All-pass or '0.0')

Match CT slices: 'Off' or 'No' (results in PET slice thickness of ~2.027 mm)

All corrections **'On'**

SIEMENS BIOGRAPH VISION – PET/CT SCANNER

Acquisition Parameters:

CT scan:

Low mAs scan acquired shortly before emission. Leave enough time to start emission acquisition promptly at start time given in the table in Section 5.4. Scans should never be started early.

Reconstruction Parameters:

Method: Iterative: OSEM-3D (do NOT use TrueX reconstruction)

8 iterations; 5 subsets with ToF (time-of-flight)

Grid: 400 x **400** x **159**

Zoom: 2.0 (results in voxel size of 0.825 mm)

Smoothing Filter: NONE (All-pass or '0.0')

Match CT slices: 'Off' or 'No' (results in PET slice thickness of ~1.645 mm)

All corrections **'On'**

SIEMENS HRRT 207-SLICE PET-ONLY SCANNER

Acquisition Parameters:

Transmission scan: Five- or six-min scan acquired immediately post-emission scan.

Reconstruction Parameters:

Method: Iterative: (OP OSEM-3D) 6 iterations; 16 subsets

Grid*:* 256 x 256 x 207 Voxel size: 1.219 mm^3

Smoothing Filter: 2 mm Gaussian

All corrections '**On**'