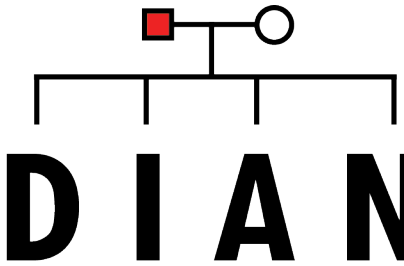


Dominantly Inherited Alzheimer Network Observational Study (DIAN-Obs)

PET Technical Procedures Manual v4.0

January 17, 2022

Responsibilities and Approvals

Function	*Name and Title*	*Signature/Date*
ICL Director Approval	Tammie Benzinger, Executive Management	
ICL Project Manager Approval	Russ Hornbeck, Management	

Revision History

Version	*Issue Date*	*Description of Revision*
1.0	February 01, 2008	Initial version of document
2.0	February 11,2010	Version 2.0 (Amendment 2.0)
A3	March 23, 2011	Version A3 (Amendment 3.0)
2.0	March 12, 2013	Added Batch Record #, Redacted Tracer Information
2.1	March 19, 2013	Corrected Pregnancy Test timeline to match protocol
2.2	April 09, 2013	Added language to ensure PET scans are not uploaded to local clinical Picture Archiving and Communication Systems (PACS) for Medical Review
2.3	June 26, 2013	Added question to Metadata forms to directly address whether female participants are of childbearing potential
2.4	July 08, 2013	Added 3D Filtered Back-projection (3DFBP) reconstruction option to PiB forms to accommodate ongoing scans.
2.5	July 30, 2013	Revised Uploader Section to reflect CNDA upgrade to XNAT 1.6
2.6	November 08, 2013	Added new PET Scanner Type information
2.7	August 29, 2014	Changed subset specifications for GE Discovery 690, 710. Changed FOV for 600, 690, 710 models to 25.6 cm. Added PICO scanner, HRRT 4mm smoothing for PiB, Biograph (1093/1094) and MCT scanners zoom changed to 2.0. Removed Radiotracer log requirement and forms.
2.8	October 01, 2014	Reinserted AV45(florbetapir F 18) Protocol. Added alternative pagination for metadata forms.
2.9	May 20, 2015	Added AV1451 (T807 / Tau Tracer) protocols and forms. Changed study from “DIAN-longitudinal” to “DIAN-Observational”
3.0	June 05, 2015	Added range for T807 (6.5-10mCi).Removed Avid scanner qualification Added diagrams for sequential PiB / T807 sessions (same day)
3.1	July 14, 2015	Added reconstruction frames for T807 reconstructions.
3.2	October 07, 2019	New forms to match TU study, replaced CNDA with DCA, added Siemens Vision, GE Discovery MI, GE Signa PET/MR scanners, added PI-2620, MK-6240 tau tracers
3.3	January 02, 2020	Updated PI-2620 protocol to harmonize with first in human studies. Moved metadata forms to end of manual
3.4	January 13, 2020	Removed references to AV45/Florbetapir
3.5	April 07, 2020	Removed references to MK-6240, Added instructions for no electronic media or phones during FDG uptake.
3.6	April 13, 2020	Added deviation language to FDG, corrected range for PI-26202, Added Siemens 1080 Scanner, PI-2620-Approved Order form
3.7	April 21, 2020	Updated Language for GE PET scanners, Formatting
3.8	July 02, 2021	Re-added MK-6240 scanning protocol, ordering information
3.9	October 22, 2021	Removed long scan option from MK-6240 protocol
4.0	January 17, 2022	Removed Siemens HRRT scanner. Added Siemens Horizon Scanner

Table of Contents

Imaging Overview:

We hypothesize that Alzheimer disease (AD) has a preclinical stage in which elevated levels of brain amyloid protein and accumulation of beta-amyloid deposits foreshadow the gradual onset of neuronal dysfunction, cell loss and dementia. While the exact role of amyloid in the initiation of brain damage is still unclear, we suggest that clarifying the temporal relationships between amyloid deposition, neural dysfunction and loss, and the onset of dementia would be extremely helpful in understanding the biological origins of AD and in designing appropriate interventions. Brain imaging provides a window into many of the hypothesized biochemical, functional and anatomic changes in AD. With positron emission tomography (PET) using [^{11}C]PiB it is possible to estimate the density of beta-amyloid (Aβ) plaques by imaging the PiB binding sites. With [^{18}F]FDG PET it is possible to estimate neuronal function from measures of metabolic activity. Depending on approval and local availability, many trial sites will also examine the presence and severity of tau pathology using [^{18}F]AV-1451 or [^{18}F]PI-2620. Finally, with magnetic resonance imaging (MRI) loss of brain tissue over time can be quantified in regional and global brain volume measures. It is our premise that by examining the temporal and spatial interrelationships between these three measures important insights will be gained into the pathophysiology of AD. The value of the imaging measures is further amplified when combined with the complimentary data of CSF biomarkers and clinical and psychometric evaluations.

PET

Sites collecting PET scans must use a PET scanner that has been qualified to scan DIAN-Obs subjects. After images are uploaded into the DIAN Central Archive (DCA), quality control will be done by the Imaging Core team at the University of Michigan (headed by Dr. Robert Koeppe) and processing will be done by the Imaging Core team at Washington University (headed by Dr. Tammie Benzinger).

To ensure standardization across sites all tracer activity shall be converted and recorded in millicuries (mCi).

PET PiB

Scan Acquisition: Participant preparation consists of intravenous catheterization followed by the bolus injection (over 10-60 sec) of **PiB 8-18 mCi** (296-666 MBq). There are two acceptable procedures for obtaining the PiB PET scans. In one approach, the subject will rest quietly for approximately 30 minutes after injection and then be positioned in the scanner for scanning which will start 40 minutes after injection, acquiring 6 x 5 minute frames for a total acquisition time of 30 additional minutes. In the second approach the subject will be positioned in the scanner at the time of injection and a full 70 minute scan will be obtained starting at the time of injection. The first approach consists of the minimum dataset needed for analysis, while the second approach will allow more complex data analysis and modeling of the kinetic properties of the tracer. The site PI will have complete flexibility as to which approach to use for each PET PiB scanning session.

Specifically, in the first approach the PET scan will be acquired in dynamic, 3D imaging mode for 30 min (consisting of 6 x 5 min frames) beginning 40 min (+/- 30 seconds) after injection of PiB. In the second approach PET scan will be acquired in dynamic, 3D imaging mode for 70 min (consisting of 4 x 15 sec frames, 8 x 30 sec frames, 9 x 60 sec frames, 2 x 180 sec frames, 10 x 300 sec frames) beginning at the time of injection. No blood sampling will be performed for the PiB PET study. A standard brain transmission scan (or CT transmission scan for PET/CT scanners) will be obtained for attenuation correction after the emission data acquisition, or prior to acquisition if obtaining a CT transmission. Subjects will be removed from the scanner following the completion of the transmission scan (See PET Protocol below).

PET FDG

NOTE: **FDG doses administered within 10% of the protocol-required dose per standard clinical practice will not be considered a protocol deviation**

Scan Acquisition: Subjects to receive a PET FDG scan in the morning are asked to omit all food and fluids (except water) from midnight the night before the FDG scan (or FDG and PiB if done on the same day) until after the imaging is completed. Subjects scanned later in the day are asked to omit food and fluids (except water) for at least 4 hours prior to FDG injection. Upon arrival to the imaging center, compliance to the dietary requirements should be confirmed and blood glucose level should be checked. Blood glucose level should be < 140 mg/dL (7.8 mmol/L). If BGL $\geq$140 mg/dL, rescheduling the subject should be considered. If this is not an option, the scan should continue and a note should be made on the metadata form in the appropriate comment box following the blood glucose record.

Typically, the PiB scans will be followed closely by the FDG scans on the same day; however, this arrangement is for convenience to the subject and coordinators but is not a requirement (see Appendix A for schema). After completion of PiB scanning, subjects will be moved to a dimly lighted, quiet room and **FDG 5 mCi** (185MBq) will be injected as a bolus. Recent research shows electronic media influences FDG uptake and distribution, therefore **no electronic media or portable devices may be used by the subject during the uptake period.** About 20 min later, subjects will be repositioned in the PET scanner, and FDG PET scans will be acquired in dynamic, 3D mode beginning 30 min (+/- 30 seconds) after injection of FDG for 30 min (consisting of 6 x 5 min frames). A standard brain transmission scan (or CT transmission scan for PET/CT scanners) will be obtained for attenuation correction after the emission data acquisition, or prior to acquisition if obtaining a CT transmission. (The transmission scan for the PiB scan cannot be used for the PET FDG scan.) Subjects will be removed from the scanner following the completion of the transmission scan.

Note: The injection of the FDG should be timed so that a minimum of 120 minutes (about 6 half-lives of C-11) will elapse from the time of injection of PiB to the start of the FDG scan. This means that a minimum of 90 minutes should elapse between the time of injection of PiB and the time of injection of FDG to provide for the nearly complete decay of C-11. Subjects may drink water (in moderation) between the PiB and FDG scans, but no food intake will be permitted (in compliance with the recommended 4 hour fast prior to the FDG scan).

PET Tau Imaging Tracer [^{18}F]AV-1451 (Avid Compound: T807)

NOTE: **Site participation for T807 (^{18}F-AV-1451) imaging is limited. Availability of this radiotracer will be based on location, local regulation, and site performance criteria specified by Avid and the DIAN Imaging Core. T807 doses administered within 10% of the protocol-required dose per standard clinical practice will not be considered a protocol deviation.**

Scan Acquisition: Participant preparation consists of intravenous catheterization followed by the bolus injection of **10 mCi (370 MBq)** of T807**.** The primary outcome measures for the tau study will be standardized uptake value ratios (SUVRs) generated using the last 30 minutes of the acquisition. However, as this tracer has not previously been tested in autosomal dominant population, full kinetic modeling with binding potentials in a subset of the participants will be performed in order to provide further validation of this approach. Thus the participants will have the option of either resting in a chair after injection (short protocol) or resting on the PET table for the full time from injection to end of scan, with collection of a full dynamic PET dataset. There are two acceptable procedures for obtaining the T807 PET scans:

1) The first (preferred) option is to start scanning at the time of injection and continue for 105 minutes. If needed, the subject may take up to a 15 minute break after the first 60 minutes of scanning, and scanning should resume immediately after the break. The PET scan will be acquired in dynamic, 3D imaging mode for 105 min (consisting of 10 x 6 sec frames, 6 x 20 sec frames, 4 x 30 sec frames, 5 x 60 sec frames, 5 x 120 sec frames, and 17 x 300 sec frames) beginning at the time of injection. If a 15 minute break is taken a 1200 sec (60 minutes) then the last part of acquisition shall be 14 x 300 sec frames.

2) The second option; at approximately 75 minutes following injection (note the temporal difference to other imaging tracers), a continuous 30-min brain scan (6 acquisitions x 5 minutes duration) will be performed.

For either procedure a standard brain transmission scan (or CT transmission scan for PET/CT scanners) will be obtained for attenuation correction after the emission data acquisition, or prior to acquisition if obtaining a CT transmission. Subjects will be removed from the scanner following the completion of the transmission scan (See PET Imaging Protocol section).

Note: Image acquisition of T807 must occur at least 160 minutes after injection of PiB (8 half-lives)
T807 must be injected 12 hours or more before PiB.

PET Tau Imaging Tracer [^{18}F]MK-6240 (Cerveau)

NOTE: Site participation for [18F]MK-6240 imaging is limited. Availability of this radiotracer will be based on location, local regulation, and site performance criteria specified by Cerveau and the DIAN Imaging Core. MK-6240 doses administered within 20% of the protocol-required dose (5 mCi / 185 MBq) per standard clinical practice will not be considered a protocol deviation.

The primary outcome measures for this tau study will be standardized uptake value ratios (SUVRs) generated using the last 30 minutes of the acquisition.

[^{18}F]MK-6240 Administration: Subjects will receive a single intravenous bolus injection of 185 MBq (5 mCi). Injected activity will not be less than 159.1 MBq (4.3 mCi) and no more than 222 MBq (6 mCi). Total injected volume will not be more than 10 mL followed by a 10 mL normal saline (0.9% NaCl) flush.

Scan Acquisition: Participants will receive the [18F]MK-6240 injection and rest quietly in an uptake room. At exactly 80 minutes following the injection, participants will undergo a continuous 30-minute brain scan consisting of 6 x 300 sec frames.

PET Tau Imaging Tracer [^{18}F]PI-2620 (Life Molecular Imaging, LMI)

NOTE: Site participation for [^{18}F]PI-2620 imaging is limited. Availability of this radiotracer will be based on location, local regulation, and site performance criteria specified by LMI and the DIAN Imaging Core. [^{18}F]PI-2620 doses administered within 10% of the protocol-required dose per standard clinical practice will not be considered a protocol deviation

The primary outcome measures for this tau study will be standardized uptake value ratios (SUVRs) generated with a 30-minute acquisition (6 x 300 sec frames) from 45-minutes to 75-minutes post injection. However, as this tracer has not previously been tested in autosomal dominant population, full kinetic modeling with

binding potentials in a subset of the participants will be performed in order to provide further validation of this approach. Thus, participants will have the option of resting on the PET table for the full time from injection to end of scan, 0-90 minutes.

[18F]PI-2620 Administration: Subjects will receive a single intravenous bolus injection of **185 MBq (5 mCi).** Injected activity will not be less than 166.5 MBq (4.5 mCi) and no more than 203.5 MBq (5.5 mCi) or ±10%. Total injected volume will not be more than 10 mL followed by a 10 mL normal saline (0.9% NaCl) flush.

Scan Acquisition: There are two acceptable procedures for obtaining the [18F]PI-2620 PET imaging scans:

1) Long protocol (the preferred option): Image acquisition will begin immediately after participants receive the [18F]PI-2620 injection. Scanning will continue for a total of 90 minutes. The PET scan will be acquired in dynamic, 3D imaging mode for 90 min (consisting of 10 x 6 sec frames, 6 x 20 sec frames, 4 x 30 sec frames, 5 x 60 sec frames, 5 x 120 sec frames, and 14 x 300 sec frames) beginning at the time of injection.

2) Short protocol: For participants unable to tolerate the full-length scan, participants will receive the [18F]PI-2620 injection and rest quietly in an uptake room. At exactly 45 minutes to 75 minutes following the injection, participants will undergo a continuous 30-minute brain scan consisting of 6 x 300 sec frames.

General Information

The purpose of this manual is to explain the PET imaging component of the DIAN-Obs protocol. Standard procedures are needed to ensure consistency of data collection in this longitudinal study.

This manual contains information for study-site staff involved with the care of the study participants during the imaging procedures and those involved with scanning the study participants

Contact Information

If you have any questions or concerns regarding PET imaging study please contact:

DIAN-PET@DIAN-info.org

If you have question regarding the scan uploading to the DCA please contact:

dca-helpdesk@radiologics.com

Site Qualification

Your institution must obtain human research approval that specifically includes the use of radioactive tracers prior to enrolling participants for the PiB protocol. Separate IRB approval may be required for PET centers not under the governance of the main imaging site.

Scanner qualification:
All PET performance sites will be required to obtain scanner qualification by the University of Michigan team and Robert Koeppe, PhD (koeppe@umich.edu) before conducting scans. This procedure will require the scanning of a radioactive (<1 mCi 18F activity) Hoffman 3-D brain phantom on two separate days using the

specified DIAN-Obs PET protocol. If needed, this phantom may be provided, on a temporary basis, to the performance site by the DIAN-Obs Imaging Core. The PET protocol will be provided to the performance site and will be specific to the PET scanner make and model. Subsequently, the acquisition and reconstruction parameters for the human subjects must be the same as used in the phantom scanning (with specific scans for both the human PiB and FDG PET acquisitions). Reconstructed resolution will be using the equivalent of a ramp filter (i.e., near the intrinsic resolution of the scanner) as this allows maximum flexibility during processing and analysis. Scanner specific qualifications will come from Dr. Robert Koeppe.

After acquisition and reconstruction, phantom image data will be uploaded to the DIAN-Obs Central Archive (DCA), retrieved by the University of Michigan team, and reviewed. If problems are identified with the phantom scans, the site will be contacted directly by Dr. Koeppe's team, the relevant issues will be discussed, and specific changes suggested. Qualification scans and review will be repeated (and iterated) until the site is qualified. Once the site is qualified the Hoffman 3-D brain phantom is then returned as directed by the University of Michigan team.

PiB [^{11}C]2-(4'-methylamino-phenyl)-6-hydroxy-benzothiazole qualification) Prior to conducting PET PiB studies, each site will be qualified for PiB production by Scott Mason, PhD., (masonns@upmc.edu) at the University of Pittsburgh. If the site is not yet producing PiB for human use, Dr. Mason will provide preclinical toxicology, evidence for lack of human pharmacologic actions, and a sample PiB Drug Master File (DMF). It is expected that each site will need to adapt the DMF to their local environment. Dr. Mason will be available for consultation during this phase.

[^{18}F]AV-1451/T807 (Avid). Prior to conducting studies using T807 (^{18}F-AV-1451), approval from Avid Radiopharmaceuticals and the DIAN-Obs Imaging Core must be obtained for participating sites.
[^{18}F]MK-6240 (Cerveau). Prior to conducting studies using ^{18}F-MK-6240, approval from Cerveau and the DIAN-Obs Imaging Core must be obtained for participating sites.

[^{18}F]PI-2620/Piramal (LMI). Prior to conducting studies using ^{18}F-PI-2620, approval from Life Molecular Imaging and the DIAN-Obs Imaging Core must be obtained for participating sites.

Once your institution has received human research approvals that specifically include the use of radioactive tracers, AND your site has passed the phantom QC imaging from University of Michigan, your site is ready to scan DIAN subjects. If your site is doing PiB, production approval must also be obtained before scanning DIAN subjects, see above.

Depending on tracer availability, site location, and local regulation not all sites will be able to choose their sites tau tracer protocol. Suitability for inclusion will be reviewed by DIAN Imaging Core.

Once your institution has received human research approvals that specifically include the use of radioactive tracer approval, AND your site has passed the phantom QC imaging, your site is ready to scan DIAN-Obs subjects. If your site is doing PiB, production approval must also be obtained before scanning DIAN-Obs subjects, see above.

Continued Quality Monitoring During Execution Phase

All MRI and PET image data sets uploaded from any site will be quarantined in the DIAN Central Archive (DCA) until the data is passed by the appropriate image QC team. As described above all review of images should occur within two working days and the performance site will be contacted if a study does not meet criteria.

PET Imaging Protocol

Scanner Parameters and Reconstruction

DIAN-Obs PET Acquisition Parameters

With the exception of the Siemens 1023/1024 Pico and HiRes 1080 (detailed below), please use following acquisition framing for Siemens, GE Discovery, and Philips PET scanners

The following parameters will be used for PiB, AV-1451, PI-2620, and FDG human protocols

Scan: emission:

PiB: Sites can choose between two PET protocols to be administered for PiB; one protocol is a 70 minute [(4 x 15s)(8 x 30s)(9 x 60s)(2 x 180s)(10 x 300s) frames] 3-D dynamic PiB acquisition scan starting at the time of injection and the other is a ***40 minute uptake*** followed by a ***30 minute*** (6 x 300 sec frames) 3-D dynamic PiB acquisition.

AV-1451: Sites can choose between two PET protocols to be administered for T807 protocol
The preferred protocol is to begin scan at time of injection and continue for ***105 minutes***. If needed, the subject may take ***up to a 15 minute break after the first 60 minutes*** and scanning should resume immediately after the break. (10 x 6s)(6 x 20s)(4 x 30s)(5 x 60s)(5 x 120s)(17 x 300s)
Note: If 15 minute break taken at 1200 secs (60 minutes) then final frames are 14 x 300s.
The second protocol is acquired as a ***75 minute uptake*** followed by a dynamic 3-D acquisition for ***30 minutes***, acquired as 6 x 300 sec frames.

Note: Do not rinse syringe after ^{18}F-AV-1451 injection.

MK-6240: Scan is acquired as a ***80 minute uptake*** followed by a dynamic 3-D acquisition for ***30 minutes***, acquired as 6 x 300 sec frames

PI-2620: Sites can choose between two PET protocols to be administered for PI-2620.
The preferred protocol is to begin scan at time of injection and continue for ***90 minutes***. Frames are as follows: [(10 x 6s) (6 x 20s) (4 x 30s) (5 x 60s) (5 x 120s) (14 x 300s)]. The second protocol is acquired as a ***45 minute uptake*** followed by a dynamic 3-D acquisition for ***30 minutes***, acquired as 6 x 300 sec frames

FDG: The FDG protocol will be acquired as a 30-minute uptake followed by a dynamic 3-D acquisition for 30 min, acquired as 6 x 300 sec frames. See Appendix A.

Siemens BioGraph Vision PET/CT scanner:

Scan: transmission: CT scan
Scan: emission: DIAN-Obs PET Acquisition Parameters

Reconstruction: 3D-OSEM+TOF (time of flight) turned on, no smoothing (no PSF, TrueX off), 8 iterations, 5 subsets. Reconstruct into 440 matrix. Zoom = 2.0. The button saying “Match CT slices” must be turned OFF. With this button on, PET gets interpolated onto the CT slice spacing.

Siemens HR+ scanner:

Scan: emission: DIAN-Obs Scanner Acquisition Parameters

Scan: transmission: 5 min 2-D scan post-emission scan. Process with segmentation and re-projection.

Reconstruction: FORE followed by 2D-OSEM, 4 iterations, 16 subsets, no smoothing, zoom=2.0. Reconstruct into 128x128 grid. Brain mode must be set to "ON".

Siemens BioGraph TruePoint PET/CT scanner (Models 1093/1094):

Scan: transmission: CT scan
Scan: emission: DIAN-Obs PET Acquisition Parameters

Reconstruction: 3D-OSEM, 4 iterations, 16 subsets (or 14 subsets, if the option of 16 is not available, which depends on the software version), no smoothing. Reconstruct into 336x336 grid if software no longer allows "TRIM" to be used. For software still allowing "TRIM", reconstruction into a 168x168 grid is okay.
The button saying "Match CT slices" must be OFF so image will not be interpolated onto the CT slice spacing. Switching "Match CT slices" OFF results in either 81 or 109 PET slices for the standard 3-ring and extended FOV 4-ring (TrueV) systems, respectively.

Siemens BioGraph mCT PET/CT scanner:

Scan: transmission: CT scan
Scan: emission: DIAN-Obs PET Acquisition Parameters

Reconstruction: 3D-OSEM (Iterative), 4 iterations, 24 subsets. Do NOT use *TrueX*. Reconstruct into 400x400 grid.
The button saying "Match CT slices" must be OFF so the image will not be interpolated onto the CT slice spacing. Switching "Match CT slices" OFF results in either 81 or 109 PET slices for the standard 3-ring and extended FOV 4-ring (TrueV) systems, respectively. **Zoom must be set to 2.0.**

Siemens BioGraph mMR (PETMR) scanner:

Scan: emission: DIAN-Obs PET Acquisition Parameters

Reconstruction: 3D-OSEM, 4 iterations, 21 subsets. Reconstruct into 344x344x127 grid (344 mtx).
Filter turned OFF (AllPass). Zoom should be set to 2.

Siemens BioGraph Horizon PET/CT scanner:

Scan: transmission: CT scan
Scan: emission: DIAN-TU PET Acquisition Parameters
Reconstruction: 3D-OSEM (Iterative) Do NOT use *TrueX*. 4 iterations; 20 subsets
Grid: 360x360x81 (or 109 for the extended FoV model)
Smoothing Filter: **NONE** (All-pass or '0.0')
Match CT slices: '**OFF**' or '**No**' (results in PET slice thickness of ~2.027 mm).
Zoom must be set to 2.0.

Siemens BioGraph 1023/1024 (PICO) scanner:

To reduce motion artifact for this scanner, ***two separate emission scans*** will be acquired as closely together as possible. The first is to be started at the beginning of the tracer scan. If your scanner software version does not allow a repeat emission acquisition unless you perform a second CT scan, please contact Robert Koeppe (Koeppe@umich.edu) prior to scanning.

Scan: transmission: CT scan(s)
Scan: emission:

PiB: The PiB protocol will be acquired with a ***40 minute uptake*** followed by two ***15 minute*** 3-D dynamic acquisitions.
AV-1451: The AV-1451 protocol is acquired as a ***75 minute uptake*** followed by two **15 minute** dynamic 3-D acquisitions. **Note: Do not rinse syringe after AV-1451 injection.**
MK-6240: TheMK-6240 protocol is acquired as a ***80 minute uptake*** followed by two **15 minute** dynamic 3-D acquisitions.
Note: Do not rinse syringe after AV-1451 injection.
PI-2620: The PI-2620 protocol will be acquired using a ***45 minute uptake*** followed by a two **15 minute** 3-D dynamic acquisitions.
FDG: The FDG protocol will be acquired following a ***30 minute uptake*** followed by two **15 minute** 3-D dynamic acquisitions.

Reconstruction: FORE followed by 2D-OSEM, 6 iterations, 16 subsets. Grid: 128x128. TRIM: **ON**, if your software allows a setting for TRIM (rather than just ON or OFF), **TRIM should be set to 2.0**, Zoom: **2.0,** Smoothing Filter: **NONE** (or 0.0), All Corrections: **ON**

NOTE - *If your scanner software version has on option for "Match CT Slice location", this must be left 'OFF' (e.g. box is unchecked)*

Siemens BioGraph HiRes – 81 slice PET/CT (Model 1080) scanner:

If your scanner has list-mode capability, Please use the DIAN-Obs PET acquisition parameters as outlined on pp 9-10 of this manual.

If your scanner does not have list mode available: ***two separate emission scans*** will be acquired as closely together as possible. The first is to be started at the beginning of the tracer scan. If your scanner software version does not allow a repeat emission acquisition unless you perform a second CT scan, please contact Robert Koeppe (Koeppe@umich.edu) prior to scanning.
Scan: transmission: CT scan(s)
Scan: emission:

PiB: The PiB protocol will be acquired with a ***40 minute uptake*** followed by two ***15 minute*** 3-D dynamic acquisitions.
AV-1451: The AV-1451 protocol is acquired as a ***75 minute uptake*** followed by two **15 minute** dynamic 3-D acquisitions. **Note: Do not rinse syringe after AV-1451 injection.**
MK-6240: TheMK-6240 protocol is acquired as a ***80 minute uptake*** followed by two **15 minute** dynamic 3-D acquisitions.
PI-2620: The PI-2620 protocol will be acquired using a ***45 minute uptake*** followed by a two **15 minute** 3-D dynamic acquisitions.
FDG: The FDG protocol will be acquired following a ***30 minute uptake*** followed by two **15 minute** 3-D dynamic acquisitions.

Reconstruction: FORE followed by 2D-OSEM, 6 iterations, 16 subsets. Grid: 168x168. TRIM: **ON**, if your software allows a setting for TRIM (rather than just ON or OFF), Zoom: **2.0,** Smoothing Filter: **NONE** (or 0.0), All Location: "Off" or No" (results in PET slice thickness of ~2.00mm), All Corrections: **ON**

NOTE - *If your scanner software version has on option for "Match CT Slice location", this must be left 'OFF' (e.g. box is unchecked)*

Questions:
Contact: Bob Koeppe (Koeppe@umich.edu)

GE Discovery PET/CT scanners:

Scan: transmission: CT scan
Scan: emission: DIAN-Obs PET Acquisition Parameters

FOV:
If GE site uses a 128x128 grid (ST, STE), use 25.6 cm FOV, which yields 2mm voxels.

On newer GE systems (i.e. the Discovery 600, 690, 710) use a 25.6 cm FOV with a 192x192 matrix. This yields 1.333 mm voxels and keeps the target closer to center.

For the Discovery MI use a 30 cm FOV and a 192x192 matrix. This yields pixels of 2.5625 mm.

Reconstruction: Iterative (OSEM) reconstruction: On older systems (Advance, Discovery LS, and some older Discovery STs, FORE iterative (called 3D FORE Iterative, though the 3D is for acquisition, not reconstruction) is to be used. For newer Discovery STs and all Discovery STE, RX, 600, 690, 710, MI and Signa models, 3D Iterative (true 3D reconstruction), must be used.

4 iterations will be used for all scanner models *except the Discovery MI and Signa PET/MR* (6 iterations). The number of subsets depends on the scanner model, as the number of subsets must divide evenly into the number of crystals per ring. All smoothing should be turned off. For FORE iterative this is both the loop filter and the transaxial post-filter. For 3D-iterative (called VuePoint or VuePoint HD) this is the loop filter and both the transaxial and axial post-filters.

Advance & Discovery LS	**4 iterations**	**20 subsets**
Discovery ST	**4 iterations**	**24 subsets**
Discovery STE	**4 iterations**	**20 subsets**
Discovery RX	**4 iterations**	**21 subsets**
Discovery 600	**4 iterations**	**32 subsets**
Discovery 690	**4 iterations**	**24 subsets**
Discovery 710	**4 iterations**	**24 subsets**
Discovery MI	**6 iterations**	**16 subsets**
Signa PET/MR	**6 iterations**	**16 subsets**

Philips scanners:

Scan: transmission: CT scan for Gemini PET/CT models or Ge-68 scan for Allegro model

Scan: emission: DIAN-Obs PET Acquisition Parameters

Reconstruction: LOR-Ramla if available, or 3D-Ramla on older scanner models/software versions.
For Gemini TF models, the smoothing should be set to “Sharp”.
For Allegro and older Gemini models, the lambda parameter should be set to 0.008.
All other reconstruction parameters should be left at factory defaults.
Questions:
Contact: Bob Koeppe (Koeppe@umich.edu)

Methods:

IMPORTANT: For all sites with PET-only scanners, post-emission transmission scans should be collected for the DIAN PiB, T807, PI-2620 and FDG protocols.

NOTE: If your site is collecting dynamic PiB with 33 frames, the patient should be marked prior to the start of the scan and realigned prior to the start of the frame at 40 minutes (PiB) post-injection. This will reduce motion problems.

PiB and FDG imaging on the same day:

6 x 300 sec Frame Dynamic PiB Acquisition / Standard 6 x 300 sec Frame Dynamic FDG Acquisition.

- Upon arrival to the imaging center, compliance to the dietary requirements should be confirmed. Have the patient use the restroom and empty their bladder.
- Allow them to lie comfortably in a bed or reclining chair in a room in which the ambient noise is minimal and the degree of lighting can be controlled and minimized. Supply them with blankets/pillows as needed to maximize their comfort.
- Obtain intravenous access using either a small butterfly needle or angiocath. At this time blood glucose level should be checked. Optimally, blood glucose level should be <140 mg/dL (7.8 mmol/L). If BGL is ≥140 mg/dL, consider rescheduling the patient if possible. If this is not an option, please provide an explanation on the metadata form in the appropriate comment box following the blood glucose record.
- Draw PiB (target range: 8-18 mCi) and assay with a dose calibrator. ***Record the assayed dose (to the nearest 0.1 mCi) and assay time to the nearest minute. In the event of difficulties with radiochemical yields, the scan should not be performed if <8 mCi are available for injection. In this case the scan should be rescheduled.***
- Inject the PiB over 10-60 seconds. Rinse the syringe and flush the line with at least 10 cc of normal saline. ***Record the injection time to the nearest minute. Do NOT discontinue the IV line at this time as it will be used for the FDG scan as well, if FDG is being done on the same day.***
- Re-assay the dose syringe and record the residual activity and time of assay. Allow the subject to rest comfortably in the room for 30 minutes for the incorporation of PiB into the brain.
- At the end of the 30 minute incorporation period, have the patient use the restroom and empty their bladder. (*Note* Depending on subject capabilities, this process may need to start prior to 30min to ensure the scan begins in a timely manner.)
- Position and secure the subject in the scanner using appropriate head restraints.
- Acquire a ***dynamic***, 3D scan consisting of 6 x 300 sec frames beginning 40 minutes +/- 30 seconds after tracer injection. Obtain post emission attenuation, unless using a PET/CT.
- *Upon completion the subject can be removed from the scanner and encouraged to void. The patient will have a break of approximately 10 minutes before the FDG study can begin. This is to permit adequate decay of PiB from the brain (90 min, see below, from the time of PiB injection to the start time of the FDG PET injection.)
- Subjects may drink water (in moderation) between the PiB and FDG scans, but no food intake will be permitted (in compliance with the recommended 4 hour fast prior to the FDG scan).
- After completion of PiB scanning, subjects will be moved to a dimly lighted, quiet room and 5±0.5 mCi of FDG will be injected as a bolus. ***Record the assayed dose and assay time to the nearest minute.***
- Rinse the syringe and flush the line with at least 10 cc of normal saline. ***Record the injection time to the nearest minute.*** The IV 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 for 20 minutes for the incorporation of FDG into the brain. During the incorporation period, the patient's eyes should be open and the ears should remain un-occluded.
- At the end of the 20 minute incorporation period, have the patient use the restroom and empty their bladder. (*Note* Depending on subject capabilities, this process may need to start prior to 20min to ensure the scan begins in a timely manner.)
- Reposition the subject in the PET scanner. FDG PET scans will be acquired in dynamic, 3D mode beginning 30 min after injection of FDG for 30 min (6 x 5 min frames).
- A second transmission scan will be obtained for attenuation correction and subjects will be removed from the scanner following the completion of the second transmission scan. (*Note* If using a PET/CT scanner, the CT transmission will be done prior to the data acquisition.)
- Note: The injection of the FDG should be timed so that a minimum of 120 minutes (about 6 half-lives of C-11) will elapse from the time of injection of PiB to the start of the FDG scan. This means that a minimum of 90 minutes should elapse between the time of injection of PiB and the time of injection of FDG to provide for the nearly complete decay of C-11.

70 minute Extended Dynamic PiB Acquisition/Standard 6 x 300 sec Frame Dynamic FDG Acquisition.

- Upon arrival to the imaging center, compliance to the dietary requirements should be confirmed.
- Have the patient use the restroom and empty their bladder.
- Obtain intravenous access using either a small butterfly needle or angiocath. At this time, blood glucose level should be checked. Blood glucose level should be <140 mg/dL (7.8 mmol/L). If BGL is $\geq$ 140 mg/dL, consider rescheduling the patient if possible. If this is not an option, please provide an explanation on the metadata form in the appropriate comment box following the blood glucose record.
- Position the subject in the scanner using appropriate head restraints.
- Draw PiB (target range: 8-18 mCi) and assay with a dose calibrator. ***Record the assayed dose (to the nearest 0.1 mCi) and assay time to the nearest minute. In the event of difficulties with radiochemical yields, the scan should not be performed if <8 mCi are available for injection. In this case the scan should be rescheduled.***
- Inject the PiB over 10-60 seconds. Rinse the syringe and flush the line with at least 10 cc of normal saline. ***Record the injection time to the nearest minute. Do NOT discontinue the IV line at this time as it will be used for the FDG scan as well, if FDG is being done on the same day.***
- Re-assay the dose syringe and record the residual activity and time of assay.
- Acquire a ***dynamic***, 3D scan consisting of the following:
    - 4 x 15 sec frames
    - 8 x 30 sec frames
    - 9 x 60 sec frames
    - 2 x 180 sec frames
    - 10 x 300 sec frames
    - Obtain post emission attenuation (unless using a PET/CT)

*Please see previous scanning protocol for FDG scanning instructions.

PET Only Scanners
Acquire an attenuation correction scan using rod sources for 5-6 minutes after the acquisition of the emission scan. Segmentation and re-projection routines will be applied for attenuation correction.

PET/CT Scanners
Standard CT acquisition parameters. Verify effective mAs is between 23-50 mAs.

***Note* Siemens Biograph scanners should have the "Match CT Slice" turned off.**

Typically, the PiB scans will be followed closely by the FDG scans on the same day; however, this is for convenience to the subject and coordinators but is not a requirement (see below for schemas).

6 x 300 sec Frame Dynamic MK-6240 Acquisition

- Upon arrival to the imaging center, compliance to the dietary requirements should be confirmed.
- Have the patient use the restroom and empty their bladder.
- Obtain intravenous access using either a small butterfly needle or angiocath.
- Position the subject in the scanner using appropriate head restraints.
- Record patient pre-scan vital signs on MK-6240 metadata forms
- Draw MK-6240 (target range: 5 mCi) and assay with a dose calibrator.
- *Record the assayed dose (to the nearest 0.1 mCi) and assay time to the nearest minute.*

In the event of difficulties with radiochemical yields, the scan should not be performed if <4 mCi are available for injection. In this case the scan should be rescheduled.

If the scan cannot be rescheduled, obtain permission from the site imaging PI to continue and make a note of the low dose, reason why it may be below 4 mCi, and that the imaging PI permission was obtained on the low dose justification field that will appear when uploading the scan.

- Inject the MK-6240 over 10-60 seconds. Rinse the syringe and flush the line with at least 10 cc of normal saline. ***Record the injection time to the nearest minute.***
- Re-assay the dose syringe and record the residual activity and time of assay. Allow the subject to rest comfortably in the room for 75 minutes for the incorporation of MK-6240 into the brain.
- Toward the end of the 75-minute incorporation period, have the patient use the restroom and empty their bladder. (*Note* Depending on subject capabilities, this process may need to start prior to 75 minutes to ensure the scan begins in a timely manner.)
- Position and secure the subject in the scanner using appropriate head restraints.
- Acquire a ***dynamic***, 3D scan consisting of 6 x 300 sec frames beginning 80 minutes +/- 30 seconds after tracer injection. Obtain post emission attenuation, unless using a PET/CT.
- Record patient post-scan vital signs on MK-6240 metadata form
- Upon completion the subject can be removed from the scanner and encouraged to void.

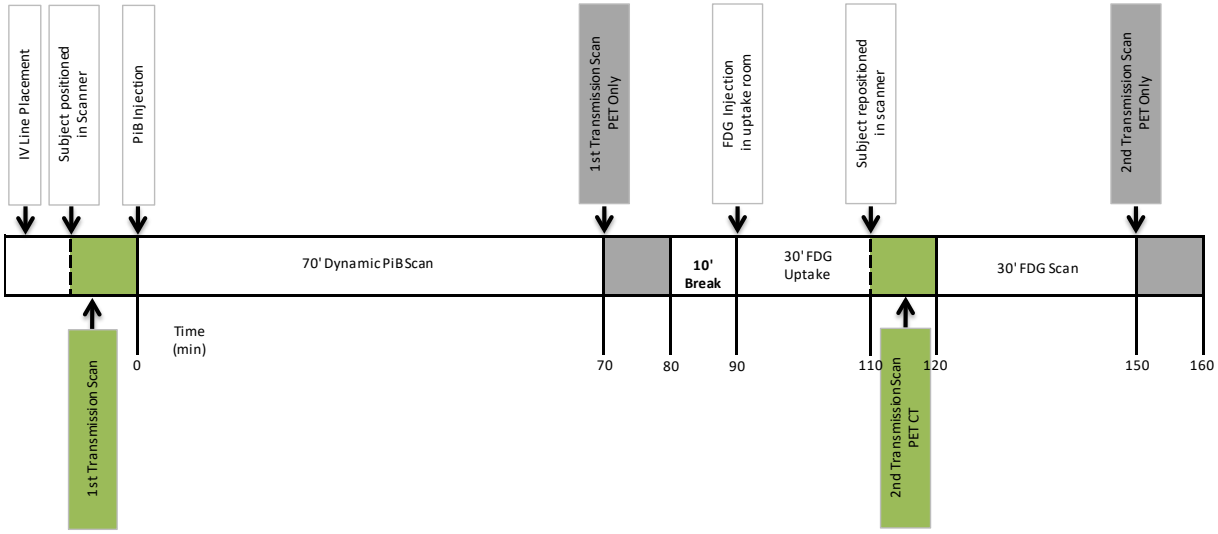
Appendix A. PET Protocol Timing Examples

***Note* the following schema show transmission scan acquisition for PET/CT (green) and PET Only (grey) scanners. CT transmissions will be obtained prior to emission data acquisitions**

Example 1: 70 min Extended Dynamic PiB and Standard 6 x 300 sec Frame Dynamic FDG

Framing Sequence

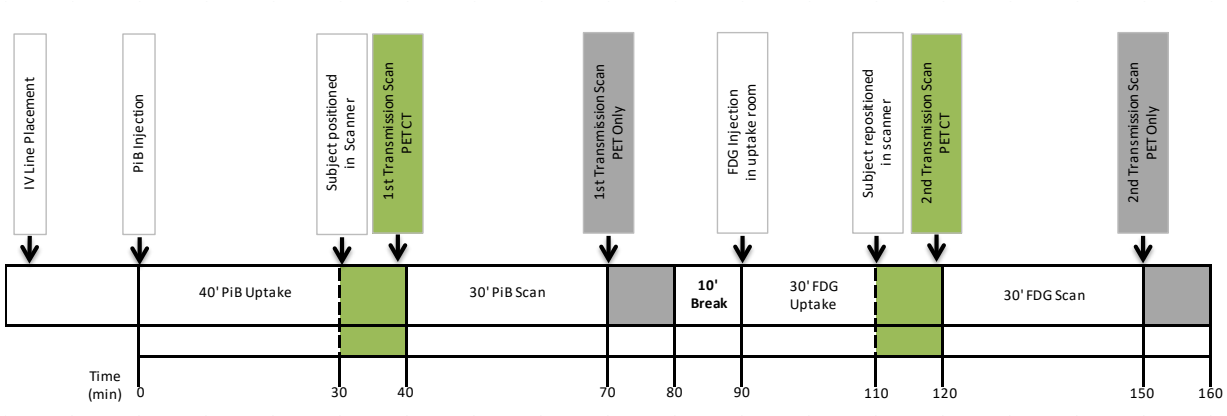
- **PiB: (4 x 15s)(8 x 30s)(9 x 60s)(2 x 180s)(10 x 300s) frames starting at time of PiB injection**
- **FDG: (6 x 300s) frames starting 30 min post FDG injection.**



Example 2: 6 x 300 sec Dynamic PiB and Standard 6 x 300 sec Frame Dynamic FDG

Framing Sequence

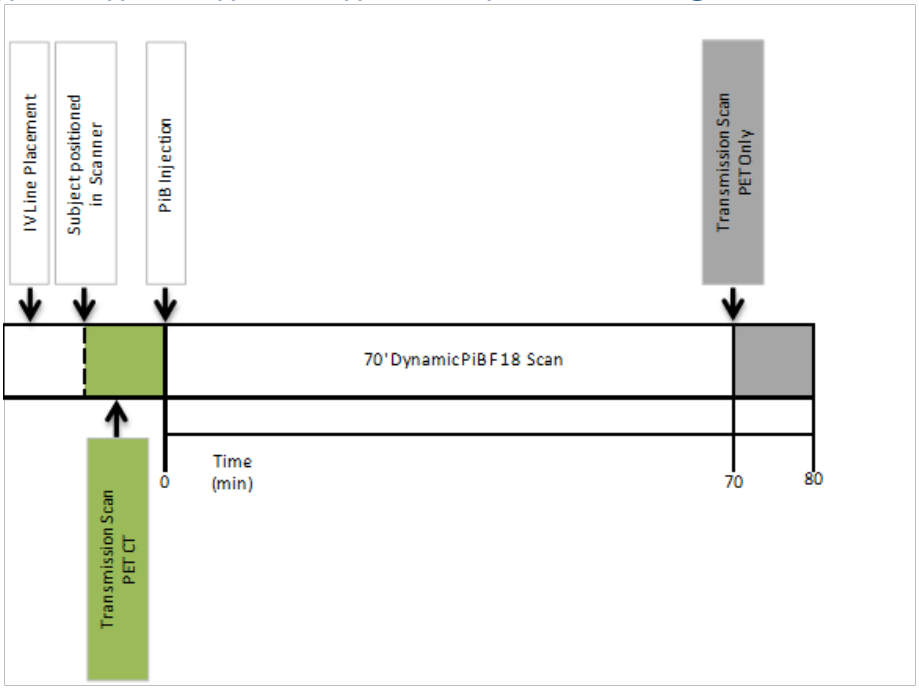
- **PiB: (6 x 300s) frames starting 40 min post PiB injection**
- **FDG: (6 x 300s) frames starting 30 min post FDG injection**



Example 3: 70 min Extended Dynamic PiB Only (Single Day)

Framing Sequence

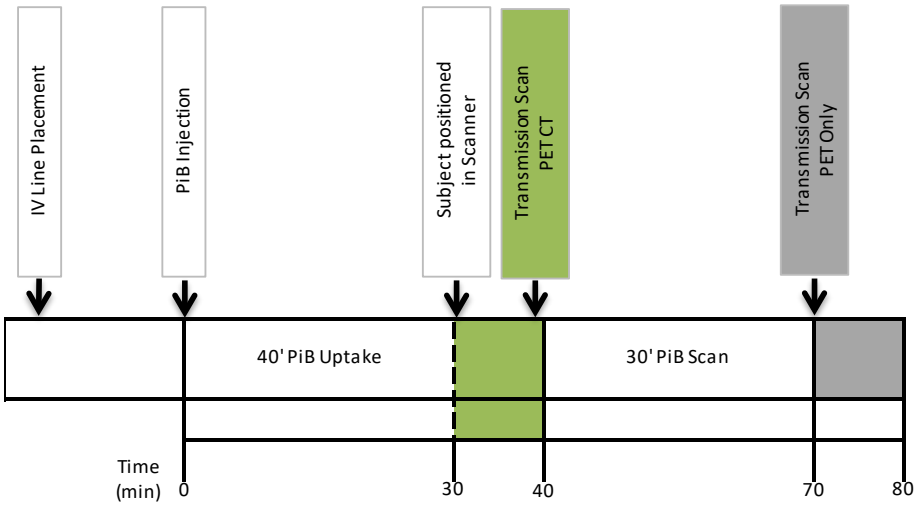
- **PiB: (4 x 15s)(8 x 30s)(9 x 60s)(2 x 180s)(10 x 300s) frames starting at time of PiB injection**



Example 4: Standard 6 x 300 sec Dynamic Acquisition PiB Only (Single Day)

Framing Sequence

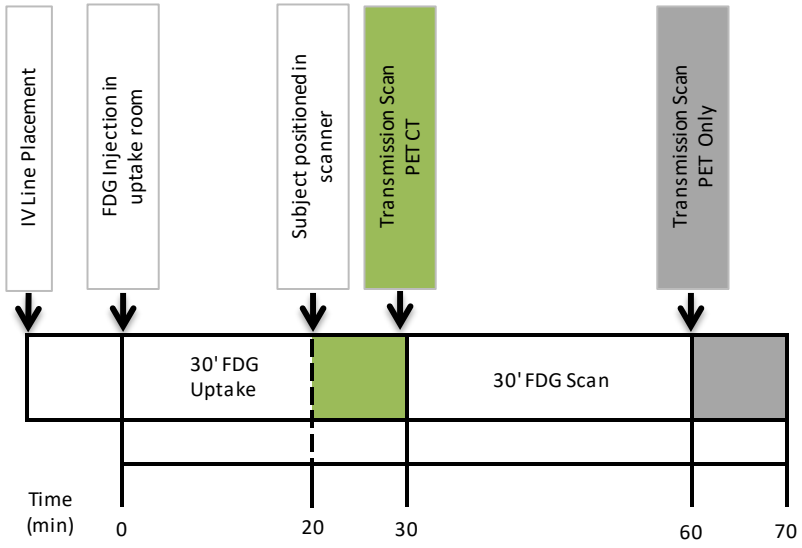
- **PiB: 6 x 300 second frames starting at 40 minutes post PiB injection**



Example 5: Standard 6 x 300 sec Frame Dynamic FDG (Single Day)

Framing Sequence

- **FDG: 6 x 300 second frames starting at 30 minutes post FDG injection**

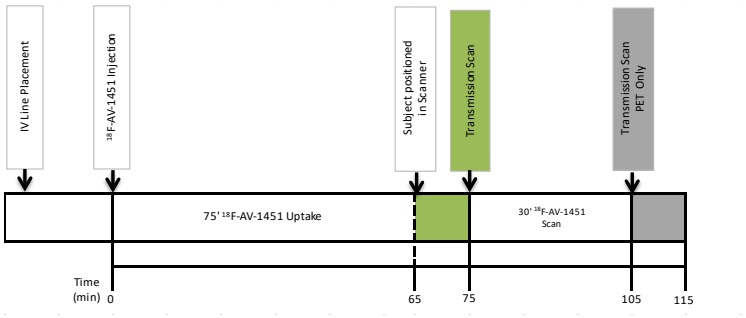


Example 6: Standard 6 x 300 sec Frame Dynamic T807 (Single Day)

(Selected Sites Only)

Framing Sequence

- **T807: 6 x 300 second frames starting at 75 minutes post T807 injection**

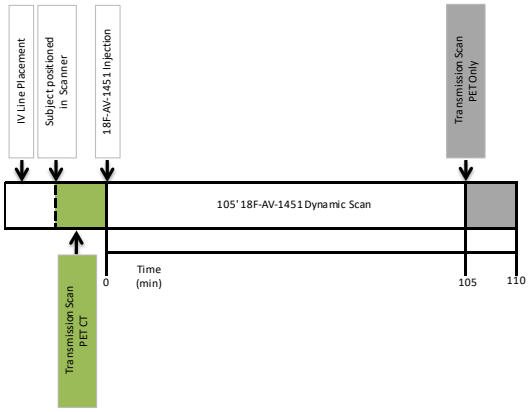


Example 7: 105 minute Continuous Dynamic T807 (Single Day)

(Selected Sites Only)

Framing Sequence

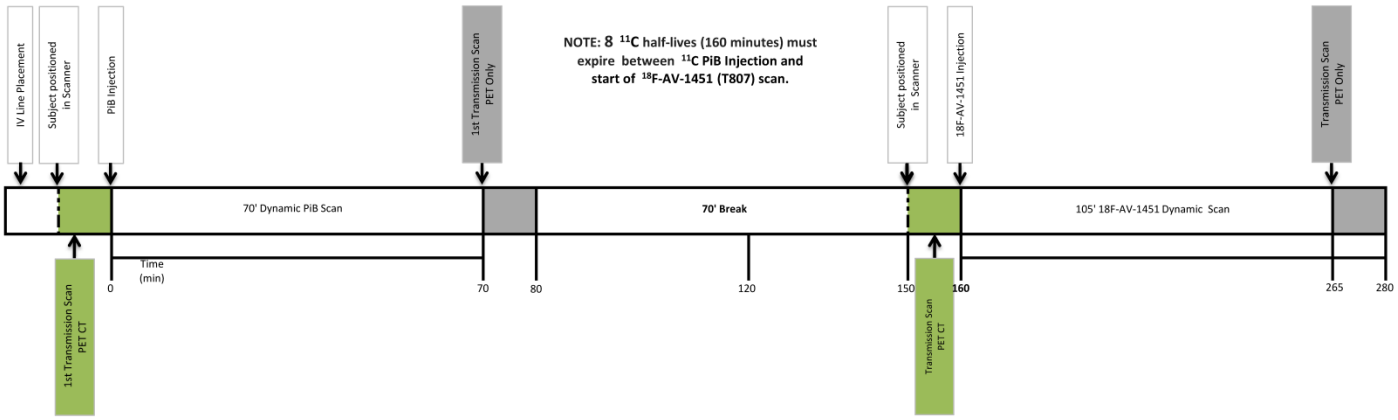
- **T807: 105 minute continuous scan starts at time of T807 injection (10 x 6s)(6 x 20s)(4 x 30s)(5 x 60s)(5 x 120s)(17 x 300s) Note: If 15 minute break taken at 1200 secs (60 minutes) then final frames (14 x 300s)**



Example 8: 70 min Extended Dynamic PiB and and 105 min Extended Dynamic T807

Framing Sequence

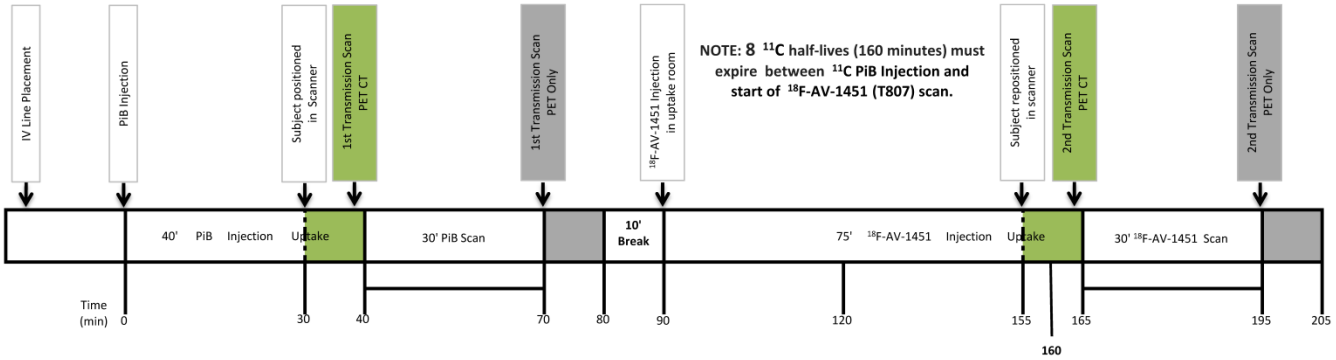
- **PiB: (4 x 15s)(8 x 30s)(9 x 60s)(2 x 180s)(10 x 300s) frames starting at time of PiB injection**
- **T807: (10 x 6s)(6 x 20s)(4 x 30s)(5 x 60s)(5 x 120s)(17 x 300s)**
  Note: If 15 minute break taken at 1200 secs (60 minutes) then final frames (14 x 300s)



Example 9: 6 x 300 sec Dynamic PiB and Standard 6 x 300 sec Frame Dynamic T807

Framing Sequence

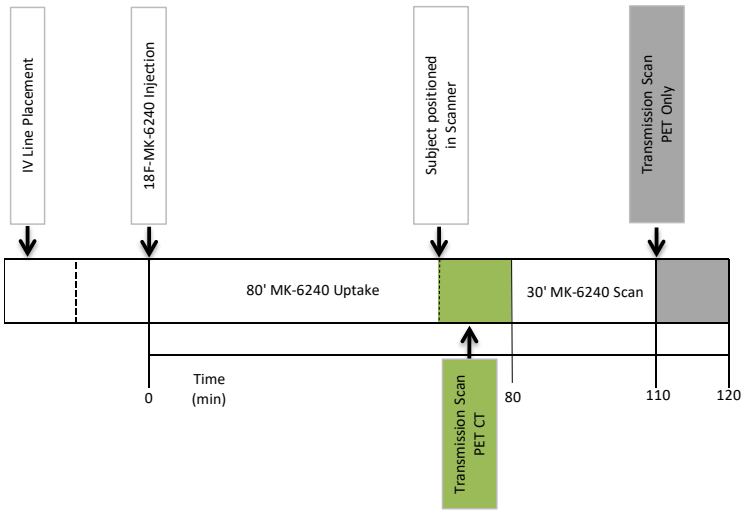
- **PiB: (6 x 300s) frames starting 40 min post PiB injection**
- **T807: (6 x 300s) frames starting 75 min post T807 injection**



Example 10: 30 min Dynamic MK-6240

Framing Sequence

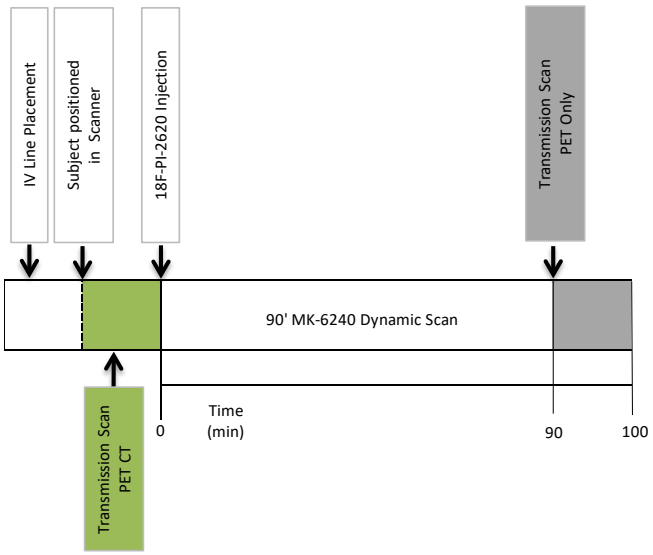
MK-6240: 80-minute uptake followed by 6 x 300s frames (30 minutes) starting at time 80 minutes post MK-2640 injection



Example 11: 90 min Extended Dynamic PI-2620

Framing Sequence

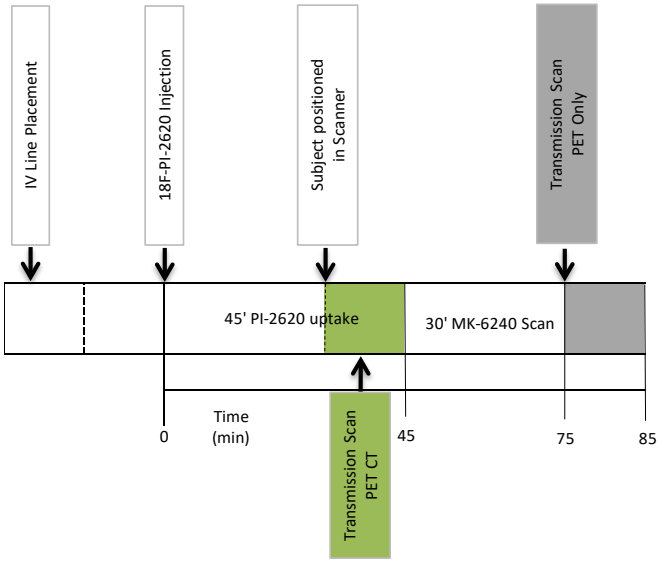
- **PI-2620: (10 x 6s) (6 x 20s) (4 x 30s) (5 x 60s) (5 x 120s) (14 x 300s) frames starting at time of PI-2620 injection**



Example 12: 30 min Dynamic PI-2620

Framing Sequence

PI-2620: 45-minute uptake followed by 6 x 300s frames (30 minutes) starting at time 45 minutes post PI-2620 injection



Quality Control :

All MRI and PET image data sets uploaded from any site will be quarantined in the DCA until the data is passed by the appropriate image QC team. All review of images should occur within two working days and the performance site will be contacted if a study does not meet criteria.

After completion of the full QC procedures, a determination will be made as to whether the scan passes or fails. In the event of scans failing QC the Imaging Core will inquire with the performance site as to the suitability of returning the patient for rescanning or if appropriate, correcting the existing scan.

Protecting Confidentiality:

The raw image files (DICOM or ECAT format) will be received by the Informatics Core over secure, encrypted channels. Prior to upload, the header section of the files will be automatically edited to remove identifying fields (e.g. participant name, date of birth). All image files distributed to the quality control sites and investigators will be labeled with the anonymous subject and study accession numbers generated by DIAN-Obs clinical operations.

Appendix B: Data Upload

1. DCA Site Overview

The DCA website enables users to review, retrieve, and upload image and non-image study data. Data within the DCA are organized within separate projects. In order to interact with the data for a particular project, you must be granted explicit access to that project following project specific guidelines set forth by the Radiologics LLC.

2. DCA Training & Upload Manual Request

If your site requires a copy of the DCA Training and Upload Instruction Manual please contact the DCA help desk.

dca-helpdesk@radiologics.com

3. Research Participant Images from Alternate Acquisition Site

If a scan is performed at an alternate acquisition site for another Performance Center, a CD/DVD containing the full imaging session and a complete, signed metadata form must be sent via overnight carrier to the subject's Performance Center. Once received, the Performance Center will upload the session and a scanned copy of the metadata form to the DCA. Physical media must be archived at the Performance Center.

All uploads from an alternate Acquisition Site must be uploaded using the Performance Site's ID and notation. The metadata form must note the Performance Site and Acquisition Site in the appropriate fields.

4. Uploading Quality Control Images

The process for uploading quality control images is the same as that for research participants.
Please refer to the *DCA Training manual* (sent separately by Radiologics)for session creation, upload of Quality Control Images (phantom), and online field entry requirements. ***No metadata form is required*** for PET phantoms. Note that you will need to enter the exact date and scan start time for the session to proceed with upload.

If qualifying a Siemens BioGraph mMR please contact **dian-pet@dian-info.org**

Appendix C: DIAN-Obs Imaging Site Readiness Checklist

The following steps are required to complete all imaging readiness for the DIAN Observational study. In order for the PET and MR scans to be uploaded to the DCA for qualification as outlined on page 2 of this checklist, DCA access must first be granted.

DIAN Central Archive (DCA) - Certification Checklist

Receive Site Initiation Packet from DIAN-Obs Informatics Core via email:

- ❑ User Access Form
- ❑ Certification Process Overview Document

Site/Coordinator processes Site Initiation Packet:

- ❑ Review Certification Process Overview Document
- ❑ Site/Coordinator completes User Access Forms → obtain PI and Designee signatures on form
- ❑ Site/Coordinator scans and emails both completed forms to Informatics

DCA User Training: DIAN-Obs Informatics Core / Radiologics, LLC will send the following documents to each user noted on the User Access Form and the below noted action is required to be completed.

- ❑ Training Manual → each user must review the manual
- ❑ Training Video → each user must view the video
- ❑ Training Record Form → each user must complete the Training Record Form and have it scanned back to the Informatics Core contact [the site/coordinator should ensure that each user returns this to the informatics core, or facilitate this process by collecting them from each user and returning them on behalf of all users]

DCA Certification: The DIAN-Obs Informatics Core / Radiologics, LLC will email the Certificate of Completion to each user after receipt of their completed Training Record Form. The email will contain the DCA website instructing the user to log on and register for an account.

DCA Account Registration:

- ❑ Each trained user must login to the DCA website (dca.wustl.edu) and click on the *Register* link to create an account.
- ❑ An email will be sent to each registered user asking them to verify their email address.
- ❑ Once email is verified, the DCA administration will receive notice to activate the user account.
- ❑ Once activated, the user will receive an email that the account has been activated.

DCA Certification Complete!

- ❑ Certificate received and filed.

Magnetic Resonance (MR) Imaging – Qualification Checklist

The following steps need to be completed by each MR imaging site. Upon completion and receipt of the applicable scans, Mayo ADIR will issue a qualification letter.

- ❑ Complete and Return the DIAN MR Survey
- ❑ Install the DIAN MR Protocol (EDX) sent by Mayo ADIR after receipt of your survey
- ❑ Conduct the Volunteer Scan Session → Upload to the DCA
- ❑ Receipt of MR Qualification Letter from DIAN / Mayo-ADIR

PET – Qualification Checklist

The following steps need to be completed by each PET imaging site. Upon completion and receipt of the applicable scans, University of Michigan will issue a qualification letter.

- ❑ Complete and Return the DIAN PET Survey
- ❑ Complete and Return the DIAN RAM Questionnaire with a copy of the RAM license
- ❑ Conduct two Hoffman Phantom Qualification Scans using the same scanner but on separate dates → upload both scans to the DCA. ***NOTE:*** *Repurposing scans from other studies is acceptable provided sessions are reconstructed using protocol outlined in the DIAN-Obs PET Technical Procedures Manual*
- ❑ Receipt of PET Qualification Letter from DIAN-Obs / University of Michigan

Imaging Tracers – Qualification Checklist

PIB: Upon receipt of PET Survey, Dr. Neale Scott Mason, University of Pittsburgh Medical Center (UPMC) will contact the PET center to request facility and CMC documentation. UPMC and the DIAN imaging Core will arrange for technology transfer if the site is not currently producing PiB for human studies.

- ❑ Submit PiB CMC documentation to Dr. Mason (masonns@upmc.edu)
- ❑ Receipt of PiB Certification Report from Dr. Mason
- ❑ Preparation and submission of site PiB IND or reference to WU DIAN PiB IND. A CRA letter may be requested from Dr. Mason / UPMC

FDG: FDG Survey to be reviewed at Washington University and certification issued.

- ❑ Complete and Return the DIAN FDG Survey
- ❑ Receipt of FDG certification

^{18}F-AV-1451: Avid Radiopharmaceuticals *may require* separate scanner qualification for use with ^{18}F-AV-1451.

- ❑ Previous scanner qualification by Avid
- ❑ Screen shots of ^{18} F-AV-1451 acquisition and reconstruction protocols
- ❑ Receipt of ^{18}F-AV-1451 Qualification Letter from Avid

MK-6240: PET Survey required. Cerveau will contact the PET center to ensure it is prepared to receive the tau radioligand

- ❑ Update radioactive materials license to include the MK-6240 tracer
- ❑ Complete Onboarding protocol for MK-6240
- ❑ Ensure PET center is within coverage area of a production cyclotron (4-hours max travel)

^{18}F-PI-2620: Pet Survey required. LMI will contact the PET center to ensure it is prepared to receive the tau radioligand

- ❑ Update radioactive materials license to include the PI-2620 tracer
- ❑ Complete Onboarding protocol for PI-2620
- ❑ Ensure PET center is within coverage area of a production cyclotron (4-hours max travel) or
- ❑ Meets LMI CMC requirements for PI-2620 production

Imaging Certification Complete!

Appendix D: Reconstruction Checklist, Dose Ordering Information & Metadata Forms

Be sure to complete each metadata form ***as the study is being acquired.*** The PET metadata form must be provided to the imaging staff by the study coordinator prior to the scan. A scanned PDF of completed form must be uploaded to the DCA (Appendix B Section G).

A *printed* hardcopy radiotracer log is to be maintained with an entry for ***every DIAN-Obs PET session*** and initialed by the PET technologist. This will record batch # and tracer activity and may be requested as a secondary review process as part of a DIAN-Obs audit.

IMPORTANT: The Acquisition Site on the metadata form will usually be the identical to the Performance Center. If a subject is scanned at alternate site other than the subject's Performance Center, the *Acquisition Site Number* and *Acquisition Site Name* must be noted in the appropriate fields.

All uploads to the DCA from an alternate Acquisition Site must be uploaded using the Performance Center's ID and notation

IMPORTANT: A PDF version of the PET Metadata Form must be uploaded to the DCA with the imaging session. See Appendix B Section G for Instructions.