QIBA Profile. ^{18}F-labeled PET tracers targeting Amyloid as an Imaging Biomarker

Version PUBLIC COMMENT

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Open Issues:

The following open issues have been raised. They are provided here to capture the associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. Comments on these issues are highly encouraged during the Public Comment stage.

Claim Context If and how to address concern that large (>8% change in SUVR across time) may be accounted for by biologic change unrelated to amyloid deposition difference alone.
Conformance Methodology The methodology to perform conformance testing of the image analysis workstation is included; this relies upon using a Digital Reference Object (DRO), which is still a work in progress, funded as a NIBIB groundwork project.
Region Segmentation Requirements If and how to define requirements around anatomic region segmentation (whether anatomic specific to a subject (e.g. MRI-PET fused) or atlas based)) across time which may or may not be radiotracer dependent.
Conformance Testing Need to describe a study that actors need to perform to test that 1. Their wCV is < 0.029, 2. That the wCV is constant over the range of SUVR and 3. That linearity with a slope of one is a reasonable assumption.
References Literature references are incomplete. These will be completed during the Public Comment phase.

1. Executive Summary

This QIBA Profile documents specifications and requirements to provide comparability and consistency for the use of PET imaging using 18F labeled tracers which target amyloid across scanners in neurology. The document primarily addresses PET/CT imaging; however, a dedicated PET that has transmission capabilities can also be used. PET/MR scanners are excluded in this version because of their novelty and unknown quantification differences as compared to PET/CT and dedicated PET scanners. The guidance in this Profile can be applied for both clinical trial use as well as individual patient management. This document organizes acquisition, reconstruction and post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge.

The document, developed through the efforts of the amyloid Profile writing group in the QIBA Nuclear Medicine Technical Subcommittee, has shared content with the QIBA FDG-PET Profile, as well as additional material focused on the devices used to acquire and analyze amyloid tracer PET data.

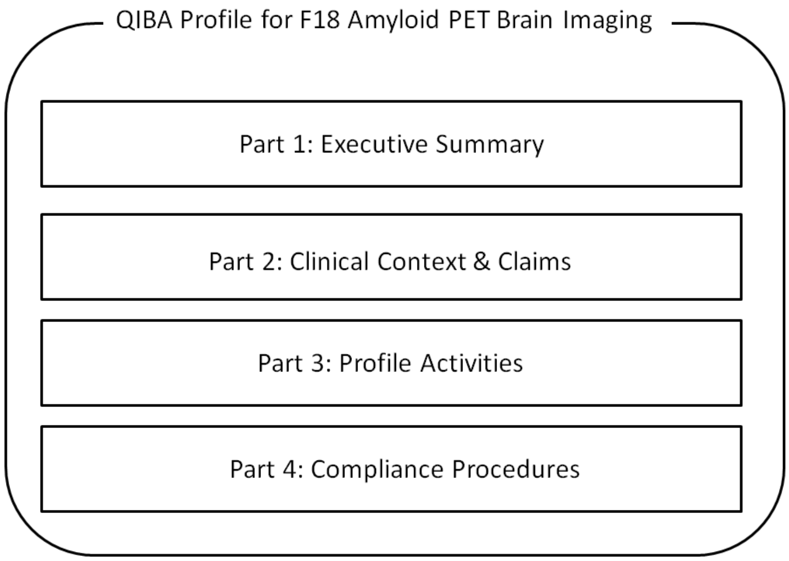


Figure 1: Illustration of the Profile components

The Profile Part 3 is derived from multiple sources, including material contained in the work performed by the Alzheimer's Disease Neuroimaging Initiative (ADNI). A high level of image measurement precision may be most important for a cross-sectional Claim wherein the amyloid tracer is used primarily to select amyloid positive subjects. For the current Profile, which is a longitudinal Claim, the primary purpose is to assess for change in amyloid load following an intervention; precision may be more important than bias as long as bias remains constant over time.

Summary for Clinical Trial Use

The QIBA Amyloid-PET Profile defines the technical and behavioral performance levels and quality control specifications for brain amyloid tracer PET scans used in single- and multi-center clinical trials of neurologic disease, primarily dementia. The specific claims for accuracy are detailed below in the Claims.

The aim of the QIBA Profile specifications is to minimize intra- and inter-subject, intra- and inter-platform, and inter-institutional variability of quantitative scan data due to factors other than the intervention under investigation. PET studies using an amyloid tracer, performed according to the technical specifications of this QIBA Profile provides qualitative and/or quantitative data for multi-time point comparative assessments (e.g., response assessment, investigation of predictive and/or prognostic biomarkers of treatment efficacy). While the Profile details also apply to studies assessing subjects at a single time point, a cross-sectional Claim is not currently included in this Profile.

A motivation for the development of this Profile is that while a typical PET scanner measurement system (including all supporting devices) may be stable over days or weeks; this stability cannot be expected over the time that it takes to complete a clinical trial. In addition, there are well known differences between scanners and/or the operation of the same type of scanner at different imaging sites.

The intended audiences of this document include:

- Technical staff of software and device manufacturers who create products for this purpose.
- Biopharmaceutical companies, neurologists, and clinical trial scientists designing trials with imaging endpoints.
- Clinical research professionals.
- Radiologists, nuclear medicine physicians, technologists, physicists and administrators at healthcare institutions considering specifications for procuring new PET/CT (or PET/MR in subsequent document versions) equipment.
- Radiologists, nuclear medicine physicians, technologists, and physicists designing PET/CT (and PET/MR) acquisition protocols.
- Radiologists, nuclear medicine physicians, and other physicians or physicists making quantitative measurements from PET images.
- Regulators, nuclear medicine physicians, neurologists, and others making decisions based on quantitative image measurements.

Note that specifications stated as 'requirements' in this document are only requirements to achieve the claim, not 'requirements for standard of care.' Specifically, meeting the goals of this Profile is secondary to properly caring for the patient.

2. Clinical Context and Claims

Accumulation of amyloid-B (AB) fibrils in the form of amyloid plaques is a neuropathological requirement for the pathologic diagnosis of dementia due to Alzheimer’s disease (AD). Among the various biomarkers in development to assess AB, 18F PET amyloid tracers (see Table in Section 3.1.3.1.2 of current approved radiotracers for qualitative amyloid burden assessment which) offer the potential of directly detecting and quantifying cortical AB deposition. The rationale for their use in neurology is based on the typically increased presence of cortical AB deposition in individuals with mild cognitive impairment (MCI) due to AD and AD compared to normal control subjects without amyloid deposition.

Utilities and Endpoints for Clinical Utility

B-amyloid (AB) imaging with PET permits in vivo assessment of AB deposition in the brain.

This QIBA Profile specifically addresses the requirements for measurement of 18F- amyloid tracer uptake with PET as an imaging biomarker for assessing the within subject change in brain amyloid burden over time (longitudinal Claim) to inform the assessment of disease status or possibly to evaluate therapeutic drug response. Quantitative assessment of amyloid burden at a single time point (cross sectional or bias Claim) is not part of the current Profile.

Biomarkers useful in clinical research for patient stratification or evaluation of therapeutic response would be useful subsequently in clinical practice for the analogous purposes of initial choice of therapy and then individualization of therapeutic regimen based on the extent and degree of response as quantified by amyloid-PET.

The technical specifications described in the Profile are appropriate for measuring longitudinal changes within subjects. Portions of the Amyloid PET Profile details are drawn from the FDG-PET Profile and are generally applicable to quantitative PET imaging for other tracers and in other applications.

A negative amyloid PET scan indicates sparse to no neuritic plaques and a positive amyloid scan indicates moderate to frequent amyloid neuritic plaques.

Claim:

If Profile criteria are met, then:

Claim 1: Brain amyloid burden as reflected by the SUVR is measurable from 18F amyloid tracer PET with a within subject coefficient of variation of 2.9%

Claim 2: A measured change in SUVR of Δ % indicates that a true change has occurred if Δ > 8 %, with 95% confidence.

Claim 3: If Y1 and Y2 are the SUVR measurements at two time points, then the 95% confidence interval for the true change is $(Y2-Y1) \pm 1.96 \times \sqrt{([Y1 \times 0.029]^2+[Y2 \times 0.029]^2)}$.

This Profile's Claims have been informed by an extensive review of the literature (See Appendix B), including a meta-analysis that was performed as part of the groundwork effort; however, it is currently a consensus claim that has not yet been substantiated by studies that strictly conform to the specifications in this document. The Committee recognizes that the threshold change metric (8%) currently cited in the Claim may not be practical or relevant for the assessment of biologic change or a modification of biologic change with a therapeutic intervention, since accumulation rates reported in the literature are on average from 1% to a few percent per year. However, the cited threshold must be supported by relevant test-retest literature. The reference test-retest studies that were used to determine the threshold were limited to those meeting a test-retest time window of 60 days or less. However, these studies did not necessarily incorporate the approaches to limit variability that are recommended in this Profile. While more recently published and unpublished studies have suggested tighter tolerances when factors such as reference region are optimized, those studies did not meet the test-retest duration criterion of 60 days or less. Despite these limitations, it is the Committee's opinion that by sharing the outlined performance requirements contained herein, the community of professionals using amyloid imaging in both clinical trials and clinical practice will be able to obtain more robust data which can then refine the Claim thresholds.

The following important considerations are noted:

1. This Claim applies only to subject scans that are considered evaluable with PET. In practice this means that scans are of sufficient diagnostic quality and performed with appropriate analysis requirements such that the target and reference tissue ROIs are evaluable. More details on which subject's scans are evaluable are described in Section 3.6.5.3.

2. Details of the claim were derived from a review of the literature and are summarized in Appendix B. In these reports, it was assumed that the repeatability of SUVR could be described.

3. This Claim is applicable for single-center studies using the same scanner model (and release). For multi-center studies, if 18F-amyloid tracer PET imaging is performed using the same scanner and protocol for each subject at each time point (as described in the Profile), then it is anticipated that this Claim will be met.

4. For this longitudinal Claim the percent change in SUVR is defined as [(SUVR at Time Point 2 minus SUVR at Time Point 1) / SUVR at Time Point 1] x 100.

5. The statistical metric for Claim 1 is the Repeatability Coefficient (RC) and the statistical metric for Claim 2 is the within-subject coefficient of variation.

6. For both Claims, it is presumed that a) the wCV is constant over the range of SUVR values and b) any bias in the measurements is constant over the range of SUVR values (linearity).

7. In this Profile, SUVR will be measured using pixel counts or SUVmean of the target regions of interest normalized to that of a reference region. As SUVR simply represents the target-to-reference ratio, reconstructed images do not need to be converted to SUV images prior to SUVR calculation (See Figure 3 legend). SUV is a simplified metric representing the radiotracer uptake at a prescribed uptake time interval post injection. SUV is a composite signal consisting of contributions from radioactivity present in tissue arising from tracer signal in blood (typically 3-8% of tissue consists of blood volume), the tracer free, non-specifically and/or non-selectively bound in tissue and the tracer specifically bound to a target of interest, in this case amyloid (Gunn RN et al. JCBFM. 2001 Jun;21(6):635-52, Innis et al, JCBFM. 2007 Sep;27(9):1533-9, Schmidt KC[1], Turkheimer FE, Q J Nucl Med. 2002 Mar;46(1):70-85**.**) . By normalising SUV to that of a reference region a simplified metric for the distribution volume ratio (DVR) is derived attempting to cancel or compensate for the contributions from the free and non-specifically bound tracer in tissue. However, the absolute signals and relative contributions arising from the various compartments are uptake time dependent as a result of differences in perfusion and non-specific and specific binding across the brain. In particular, it should be noted that perfusion does not only determine the wash-in (delivery) of the tracer, but also the wash-out of the tracer. Moreover, the wash-out is affected by the relative contributions of non-specific and specific binding as well, i.e., more 'binding slows down' wash-out. The latter also explaining the upward bias seen in SUVR compared with DVR (van Berckel et al, J Nucl Med. 2013 Sep;54(9):1570-6). A detailed discussion on the various sources of bias when using the simplified reference tissue model (and SUVR) can be found in (Salinas et al. JCBFM Feb;35(2):304-11, 2015). From the fundamental kinetic properties of radiotracers it can be understood that both SUV and SUVR (as surrogate for DVR) are perfusion dependent and that changes in perfusion across the brain as well as longitudinally will result in changes in SUVR. Consequently, changes in SUVR may not represent only a change in specific signal (amyloid) but could, at least in part, be the result of changes or variability in perfusion (van Berckel et al, J Nucl Med. 2013 Sep;54(9):1570-6) and/or tissue clearance (Carson RE, Channing MA, Blasberg RG, Dunn BB, Cohen RM, Rice KC, Herscovitch P. Comparison of bolus and infusion methods for receptor quantitation: application to [18F]cyclofoxy and positron emission tomography. J Cereb Blood Flow Metab. 1993 Jan;13(1):24-42). Whether or not a change in SUVR is affected by changes in amyloid and/or perfusion ideally should be first demonstrated in a small cohort before SUVR is used in the larger clinical trial. At the very least these validation studies should be performed to assess the minimally required decrease in SUVR that is needed to rule out false positive findings because of (disease and/or drug related) perfusion effects.

In addition, this claim should be re-assessed for technology changes, such as PSF (point spread function) based reconstruction or TOF (time of flight) imaging that were not utilized in published test-retest studies. A standard utilized by a sufficient number of studies does not exist to date. The expectation is that from future studies and/or field testing, data will be collected and changes made to this Claim or the Profile specifications accordingly.

3. Profile Activities

The following figure provides a graphical depiction that describes the marker at a technical level.

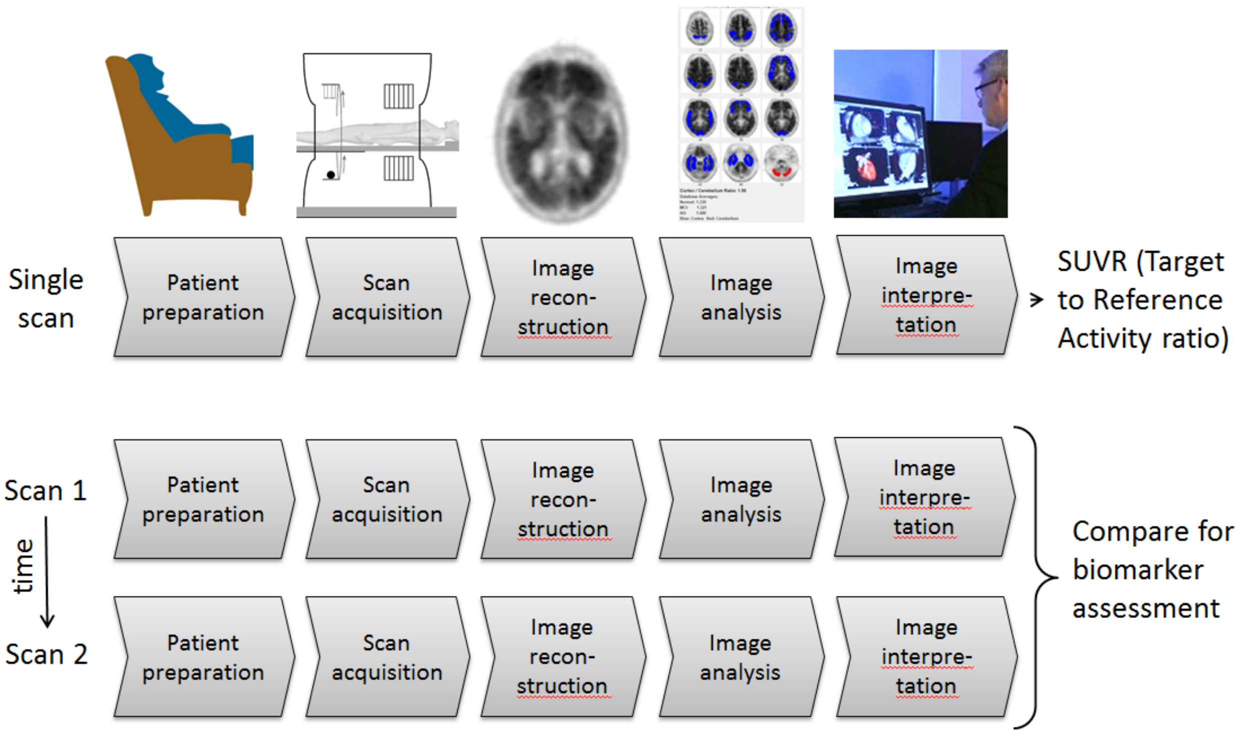


Figure 3: The method for computing and interpreting brain amyloid burden using PET may be viewed as a series of steps using either one scan (corresponding to a fit for use of a future 'Cross-sectional' Claim) or two or more scan sequences or time points (corresponding to a fit for use of the current Profile's 'Longitudinal' Claim). For a given scan, the SUVR represents the ratio of tissue concentration for a designated brain region (or composite regions) compared to the activity from a reference region (which has typically been cerebellum (whole or gray) or pons but may involve other regions– see Section 4.4). The ratio of concentration from these distinct regions (target/reference) is then calculated, which is termed the SUVR.

Furthermore, as discussed in the Image Analysis Section of this Profile, the *Centiloid Scale* may, after further investigation, provide a mechanism whereby a study can be performed with different amyloid PET tracers mapped to a standard which is then comparable (e.g., by using a linear scaling process and looking at mean values [See Section 3.4.3.3.3]) to some (to be defined) degree. At this time, pending validation of the centiloid methodology, this Profile requires the use of a single radiotracer in a multi-center trial presuming pooling of data across centers is performed.

Patients may be selected or referred for amyloid-PET imaging though a variety of mechanisms.

The imaging steps corresponding to Figure 1 are:

1) Patients or subjects are prepared for scanning. The amyloid tracer is administered. Patient waits for bio-distribution and uptake of amyloid tracer. See Section 3.1.3.1.2 for ligand-specified timing.
2) Emission and transmission data are acquired (typically the PET scan and CT scan if a PET-CT scanner).
3) Data correction terms are estimated and the attenuation and scatter corrected images are reconstructed.
4) Images are reviewed for qualitative interpretation.
5) Quantitative (and/or semi-quantitative) measurements are performed.

Note that steps 4 and 5 may occur in either order or at the same time, depending upon the context of the review (clinical research versus clinical practice) with reference to the specifications described in each tracer's package insert. Currently, the quantitative use of amyloid-PET tracers is not approved by any regulatory authorities in clinical practice. More details on the requirements are given below.

Images may be obtained at a single time point or multiple time points over months or years, for example at a minimum of two time points before and after therapeutic intervention for a response assessment.

The following sections describe the major components illustrated in Figure 3:

Section	Title	Performed by
3.1	Subject Handling	Personnel, (including Technologists and Schedulers) at an Image Acquisition Facility
3.2	Image Data Acquisition	Technologist, at an Image Acquisition Facility using an Acquisition Device
3.3	Image Data Reconstruction	Technologist, at an Image Acquisition Facility using Reconstruction Software
3.4	Image Analysis	Imaging Physician or Image Analyst using one or more Analysis Software tools
3.5	Image Interpretation	Imaging Physician before or after information obtained by Image Analysis using a pre-defined Response Assessment Criteria

Image data acquisition, reconstruction and post-processing are considered to address the collection and structuring of new data from the subject. Image analysis is primarily considered to be a computational step that transforms the data into information, extracting important values. Interpretation is primarily considered to be judgment that transforms the information into knowledge.

3.1. Subject Handling

This Profile will refer primarily to 'subjects', keeping in mind that the recommendations apply to patients in general, and that subjects are often patients too.

3.1.1 Subject Selection and Timing

The utility of correlative anatomic brain imaging, CT or MRI, can be viewed in two different contexts. From a clinical perspective, the anatomic imaging study is used to assess for evidence of bleed, infection, infarction, or other focal lesions (e.g., in the evaluation of subjects with dementia, the identification of multiple lacunar infarcts or lacunar infarcts in a critical memory structure may be important). From the perspective of establishing performance requirements for quantitative amyloid PET imaging, the purpose of anatomic imaging (separate from the utility of providing an attenuation correction map) is to provide assessment of cortical atrophy and consequently a falsely decreased SUVR. The image analyst should also be aware of the possibility of falsely increased SUVR due to blood-brain barrier (BBB) breakdown, such as in the case of intracranial bleed. The effect of differential BBB integrity inter-time point is currently not quantified in the scientific literature. While the performance of anatomic imaging is not a performance requirement of the Profile, the value of performing such imaging and the incorporation of its analysis with the amyloid PET findings may provide additional value in the interpretation for an individual subject. This should be considered in the design and implementation of the study protocol.

Aside from the exclusion (absolute or relative contraindications) of subjects who are unable to remain still enough to obtain adequate imaging (See Section 3.1.2.3 for information on subject sedation), subject selection for amyloid PET imaging is an issue beyond the scope of this Profile. Refer to Appropriate Use Criteria for Amyloid PET: A Report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association and manufacturer guidance for more information regarding patient selection.

3.1.1.1 Timing of Imaging Test Relative to Intervention Activity

The study protocol should specifically define an acceptable time interval that should separate the performance of the amyloid tracer PET scan from both (1) the index intervention (e.g., treatment with an amyloid reducing therapeutic agent) and (2) other interventions (e.g., prior treatment). This initial scan (or time point) is referred to as the “baseline” scan (or time point). The time interval between the baseline scan and the initiation of treatment should be specified as well as the time intervals between subsequent amyloid PET studies and cycles of treatment. Additionally, the study protocol should specifically define an acceptable timing variance for acquisition of the amyloid PET scan around each time point at which imaging is specified (i.e., the acceptable window of time during which the imaging may be obtained “on schedule”).

3.1.1.2. Timing Relative to Confounding Activities

There are no identified activities, tests or interventions that might increase the chance for false positive and/or false negative amyloid tracer PET studies which need to be avoided prior to scanning.

3.1.1.3. Timing Relative to Ancillary Testing

Various neuropsychiatric tests may be performed on or around the day of amyloid tracer imaging and should be coordinated at the time of scheduling.

3.1.2 Subject Preparation

Management of the subject can be considered in terms of three distinct time intervals (1) prior to the imaging session (prior to arrival and upon arrival), (2) during the imaging session and (3) post imaging session completion. The pre-imaging session issues are contained in this section while the intra-imaging issues are contained in section 3.2.1 on image data acquisition.

3.1.2.1. Prior to Arrival

There are no dietary or hydration requirements or exclusions.

The conformance issues around these parameters are dependent upon adequate communication and oversight of the Scheduler or Technologist at the Image Acquisition Facility with the subject. Communication with the subject and confirmation of conformance should be documented.

3.1.2.2. Upon Arrival

Upon arrival, confirmation of subject compliance with pre-procedure instructions should be documented on the appropriate case report forms.

3.1.2.3 Preparation for Exam

Subject preparation after arrival and prior to imaging should be standardized among all sites and subjects throughout the conduct of the clinical trial.

- Measurement and documentation of the subject's weight (and height), though encouraged, is not a requirement of this Profile since the measurand, SUVR, is by definition a ratio of SUVs.
- The waiting and preparation rooms should be relaxing and warm (> 75° F or 22° C) during the entire uptake period (and for as long as reasonably practicable prior to injection, at least 15 minutes is suggested as acceptable). Blankets should be provided if necessary.
- The subject should remain recumbent or may be comfortably seated;
- After amyloid tracer injection, the subject may use the toilet. The subject should void immediately (within 5 – 10 minutes) prior to the PET image acquisition phase of the examination.
- Sedation is not routinely required. It is not certain whether sedation will interfere with amyloid tracer uptake; some preclinical testing indicates a possible interaction, but not all tracers have been tested for possible interaction effects. The decision regarding whether or not to use sedation is beyond the scope of this Profile and requires clinical evaluation of the particular subject for contraindications, as well as knowledge of whether the particular tracer is subject to interaction with the sedating agent. Since these interactions have not been fully defined, subject preparation (with or without sedation) should be consistent across time points for a given subject.
- The amount of fluid intake and use of all medications (e.g., diuretic, sedative) must be documented on the appropriate case report form.
- The subject should remove any bulky items from their pockets such as billfolds, keys, etc. In addition, they should remove eyeglasses, earrings and hair clips/combs (and anything that could cause discomfort while the head is resting in the head holder) if present. They should also remove hearing aids if possible although it is important that they can follow instruction (and hear them if necessary) to remain still while in the scanner.

3.1.3. Imaging-related Substance Preparation and Administration

3.1.3.1. Radiotracer Preparation and Administration

3.1.3.1.1 Radiotracer Description and Purpose

The specific amyloid radiotracer being administered should be of high quality and purity. For example, the amyloid seeking radiopharmaceutical must be produced under Current Good Manufacturing Practice as specified by the FDA, EU, European Pharmacopeia or another appropriate national regulatory agency. U.S. regulations such as 21CFR212 or USP<823> Radiopharmaceuticals for Positron Emission Tomography must be followed in the U.S. or for trials submitted to US Regulatory.

While beyond the scope of this document, for any new amyloid tracer it cannot be assumed that SUVR reflects amyloid load without validation, i.e., first full kinetic analysis needs to be performed to check that SUVR has a linear relationship with BP_{ND}.

3.1.3.1.2 Radiotracer Activity Calculation and/or Schedule

The amyloid seeking radiotracer activity administered will depend upon the specific tracer utilized (See Table below). Typically, the dose ranges between about 185 – 370MBq (5 – 10 mCi); for regulatory approved tracers, this should be according to the package insert. The administered activity typically depends upon the local imaging protocol. The local protocol may require fixed activity, or the activity may vary as a function of various parameters including but not limited to subject size or age or scanning mode. The exact activity and the time at which activity is calibrated should be recorded. Residual activity remaining in the tubing, syringe or automated administration system or any activity spilled during injection should be recorded. The objective is to record the net amount of radiotracer injected into the subject to provide accurate factors for the calculation of the net SUV.

Parameter	Florbetapir (Amyvid) [1]]	Flutemetamol (Vizamyl) [2]	Florbetaben (Neuraceq) [3]	NAV4694
Tracer Admin Activity	370 MBq Max 50 mcg mass dose	185MBq Max 20 mcg mass dose	300 MBq Max 30 mcg mass dose	300 MBq

Parameter	**Entity/Actor**	**Specification**
Administered amyloid Radiotracer Activity	Imaging Technologist	The Technologist shall 1. Assay the pre-injection radiotracer activity (i.e. radioactivity) and time of measurement, 2. Record the time that radiotracer was injected into the subject, 3. Assay the residual activity in the syringe (and readily available tubing and components) after injection and record the time of measurement. 4. Inject the quantity of radiotracer as prescribed in the protocol. These values shall be entered into the scanner during the PET/CT acquisition. For scanners that do not provide for entry of residual activity information, the net injected radioactivity should be manually calculated by decay correcting all measurements to the time of injection and then subtracting the residual radioactivity from the pre-injection radioactivity. The net injected radioactivity is then entered into the scanner during the PET acquisition.

Parameter	Entity/Actor	Specification
		All data described herein on activity administration shall be documented.
		All data should be entered into the common data format mechanism (Appendix E).

3.1.3.1.3 Radiotracer Administration Route

Amyloid seeking radiotracer should be administered intravenously through an indwelling catheter (21 gauge or larger) into a large vein (e.g., antecubital vein). This is usually administered as a manual injection; a power injector may be used especially for studies in which SUVR measures of amyloid load are compared with dynamic measures (BP_{ND}). Intravenous ports should not be used, unless no other venous access is available. If a port is used, an additional flush volume should be used. As reproducible and correct administration of radiotracer is required for quantification purposes, extravasation or paravenous administration should be avoided. If an infiltration or extraneous leakage is suspected, the event should be recorded. The anatomical location of the injection site should be documented on the appropriate case report form or in the Common Data Format Mechanism (Appendix E).

Please note that CT contrast agents are not recommended nor supported in the profile.

Parameter	Entity/Actor	Specification
Amyloid radiotracer Administration	Technologist or Physician	Technologist or Physician shall administer the amyloid radiotracer intravenously through an indwelling catheter (24 gauge or larger), preferably into a large vein (e.g., antecubital vein). Intravenous ports should not be used, unless no other venous access is available. A three-way valve system should be attached to the intravenous cannula so as to allow at least a 10 cc normal (0.9% NaCl) saline flush following radiotracer injection.
Suspected infiltration or extraneous leakage	Technologist and/or Physician or Physicist	Technologist shall 1. Record the event and expected amount of amyloid tracer: Minor (estimated less than 5%), Moderate (estimated more than 5% and less than 20%), Severe (estimated more than 20%). Estimation will be done based on images and/or known injected volumes. 2. Image the infiltration site.
		Record the event and expected amount of amyloid tracer into the common data format mechanism (Appendix E).

3.2. Image Data Acquisition

This section summarizes the imaging protocols and procedures that shall be performed for an amyloid-PET exam by using either a PET/CT or a dedicated PET scanner with the requirement that a Germanium source can be used to perform attenuation correction. Note that PET scanners that do not measure in some way the attenuation of the brain and use a calculated algorithm for estimating the attenuation and scatter corrections are excluded from this profile. In addition, due to their novelty, PET/MR scanners are not covered in this version of the profile. More research and data need to be done with these scanners to understand any differences they may have in quantifying PET amyloid data as compared to PET/CT and dedicated PET scanners. Going forward in this document, PET scanner can mean either a PET/CT or a dedicated PET scanner.

For consistency, clinical trial subjects should be imaged on the same device over the entire course of a study. It is imperative, that the trial sponsor be notified of scanner substitution if it occurs.

For clinical trials with quantitative imaging requirements, a subject should have all scans performed on only one scanner unless quantitative equivalence with a replacement scanner can be clearly demonstrated. However, it should be noted that there are currently no accepted criteria for demonstrating quantitative equivalence between scanners. It is anticipated that future version of this Profile will provide such criteria.

When Amyloid PET imaging is performed across time points for a given subject (longitudinal claim), follow up scans should be performed with identical acquisition parameters as the first (baseline), inclusive of all the parameters required for both the CT and PET acquisitions as described further in this Section.

For amyloid tracer PET/CT perform imaging in the following sequence:

- CT Scout (i.e., topogram or scanogram etc.), followed by the following two acquisitions, in either order (ensuring that the same sequence is performed for a given subject across time points):
- CT (non-contrast) for anatomic localization and attenuation correction and
- PET Emission scan acquisition

For amyloid tracer scan performed on a dedicated PET system (no CT), the first two bulleted steps above are not performed. Instead, perform the Germanium-based attenuation correction scan first and then proceed with the PET Emission scan acquisition.

The issues described in this Section should be addressed in the clinical trial protocol, ideally with consistency across all sites and all subjects (both inter-subject, and intra- and inter-facility) with the target of consistency across all time points (longitudinal utility) for each given subject. The actual details of imaging for each subject at each time point should always be recorded.

3.2.1 Imaging Procedure

The imaging exam consists of two components, the PET emission scan and the transmission scan (performed either with CT or with a Germanium source). From these data sets, the non-attenuation-corrected PET images may be reconstructed for quality control purposes and attenuation-corrected PET images are reconstructed for qualitative interpretation and quantitative analysis. Instrument specifications relevant to the Acquisition Device are included in Section 4.0, Conformance Procedures.

3.2.1.1 Timing of Image Data Acquisition

Amyloid tracer uptake is a dynamic process that may increase at different rates and peak at various times dependent upon multiple variables, different for each radiotracer. Therefore, it is extremely important that (1) in general, the time interval between amyloid tracer administration and the start of emission scan acquisition is consistent and (2) when repeating a scan on the same subject, it is essential to use the same interval between injection and acquisition in scans performed across different time points.

Parameter	Florbetapir (Amyvid) [1]	Flutemetamol (Vizamyl) [2]	Florbetaben (Neuraceq) [3]	NAV4694
Tracer Uptake Time (mpi = mins post injxn)	30 – 50 mpi	90 - mpi	45 - 130 mpi	50 – 70 mpi
Duration of Imaging Acquisition	10 min	20 min	15 – 20 min	20 min

The “target” tracer uptake time is dependent upon the radiotracer utilized. Reference the above table for acceptable tracer uptake times (in minutes post injection [mpi]) for each of the currently available tracers. The exact time of injection must be recorded; the time of injection initiation should be used as the time to be recorded as the radiotracer injection time. The injection and flush should be completed within one minute with the rate of injection appropriate to the quality of the vein accessed for amyloid tracer administration so as to avoid compromising the integrity of the vein injected.

When performing a follow-up scan on the same subject, especially in the context of therapy response assessment, it is essential to use the same time interval. To minimize variability in longitudinal scanning, for a given subject, the tracer uptake time should be exactly the same at each time point. There is to date no scientific literature quantifying the effect on SUVR with varying tracer uptake times in a no change scenario. The consensus recommendation, to balance practical and ideal, for this Profile is a target window of ± 5 minutes.

If, for scientific reasons, an alternate time (between activity administration and scan acquisition) is specified in a specific protocol, then the rationale for this deviation should be stated; inter-time point consistency must still be followed.

Parameter	**Entity/Actor**	**Specification**
Tracer Injection Time	Technologist	The time of amyloid tracer injection shall be entered into PET scanner console during the acquisition.
Tracer Uptake Time:	Technologist	The Technologist shall ensure that the tracer uptake time for the baseline scan is within the acceptable range for the specific radiotracer (see Tracer Uptake Table in Section 3.2.1.1). When repeating a scan on the same subject, especially in the context of therapy response assessment, the Technologist shall apply the same time interval used at the earlier time point ± 5 minutes.

The following sections describe the imaging procedure.

3.2.1.2 Subject Positioning

Proper and consistent subject head positioning is critically important for amyloid PET imaging. It is important to take the time necessary to ensure not only that the subject is properly positioned but 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 scan used for attenuation correction is the single most common cause of failed studies.

NOTE: The successful implementation of strategies to minimize head motion (and maximize signal to noise) is critical to overall conformance to the Profile requirements. This can be addressed both at the time of image acquisition (through the use of head immobilization techniques described in the paragraphs immediately below) and at the time of image acquisition set-up and reconstruction, described in Section 3.3.2.2.1.

Position the subjects on the PET or PET-CT scanner table so that their head/necks are relaxed. To minimize head motion, the subject's head should be immobilized using the institution's head holder/fixation equipment (e.g., thermoplastic mask, tape, etc.). It may be necessary to add additional pads beneath the neck to provide sufficient support. Vacuum bean bags can also be used in this process. The head should be approximately positioned parallel to the imaginary line between the external canthus of the eye and the external auditory meatus. Foam pads can be placed alongside the head for additional support. Velcro straps and/or tape should be used to secure the head position.

It should be assured that the head of the subject is positioned in the scanner with the total brain within the field of view (FOV). Special attention must be paid to include the entire cerebellum in the image as this region serves as a reference region for subsequent quantification.

For dedicated amyloid tracer PET brain scans, the arms should be positioned down along the body. If the subject is physically unable to maintain arms alongside the body for the entire examination, then the arms can be positioned on their chest or abdomen.

Use support devices under the back and/or legs to help decrease the strain on these regions. This will assist in the stabilization of motion in the lower body.

The Technologist shall document factors that adversely influence subject positioning or limit the ability to comply with instructions (e.g., remaining motionless).

Parameter	**Entity/Actor**	**Specification**
Subject Positioning	Technologist	The Technologist shall position the subject according to the specific protocol specifications consistently for all scans.

Positioning Non-compliance	Technologist	The Technologist shall document issues regarding subject non-compliance with positioning.
		The Technologist shall document issues regarding subject non-compliance with breathing and positioning using the common data format mechanism (Appendix E).

Parameter	**Entity/Actor**	**Specification**
Motion non-compliance	Technologist	The Technologist shall document issues regarding subject non-compliance with not remaining still.
		The Technologist shall document issues regarding subject non-compliance (not remaining still) motion using the common data

Parameter	Entity/Actor	Specification
		format mechanism (Appendix E).

3.2.1.3 Scanning Coverage and Direction

Anatomic coverage should include from the skull base to the skull vertex, ensuring complete inclusion of the cerebellum. The anatomic coverage should be included in a single bed position.

Parameter	Entity/Actor	Specification
Anatomic Coverage	Technologist	The Technologist shall perform the scan such that the anatomic coverage (including the entire brain from craniocervical junction to vertex) is acquired in a single bed position according to the protocol specifications and the same for all time points.

3.2.1.4 Scanner Acquisition Mode Parameters

We define acquisition mode parameters as those that are specified by the Technologist at the start of the actual PET scan. These include the acquisition time for the single bed position and the acquisition mode (3D mode only). These parameters do not include aspects of the acquisition that occur earlier (e.g., injected amount of 18F-amyloid tracer or uptake duration) or later (e.g., reconstruction parameters) in the overall scan process.

PET Acquisition

If possible, the PET data should be acquired in listmode format (for fullest flexibility for correcting for head movement) or divided into multiple acquisitions with a maximum of 5 minutes each. Individualized, site-specific acquisition parameters should be determined upon calibration with the appropriate phantom (see below).

Parameter	Entity/Actor	Specification
PET acquisition mode	Study Sponsor	The key 3-D PET acquisition mode parameters (e.g., time per bed position, acquisition mode, etc.) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key acquisition mode parameters shall be specified according to pre-determined harmonization parameters.
PET acquisition mode	Technologist	The key PET acquisition mode parameters (e.g., time per bed position, acquisition mode, etc.) shall be set as specified by study protocol and used consistently for all patient scans.
		PET should be acquired in listmode format (best) or dynamic

Parameter	Entity/Actor	Specification
		time frames of no more than 5 minutes each.

CT Acquisition

For the CT acquisition component of the PET/CT scan, this Profile only addresses the aspects related to the quantitative accuracy of the PET image. In other words, aspects of CT diagnostic accuracy are not addressed in this Profile. In principle, any CT technique (parameters include kVp, mAs, pitch, and collimation) will suffice for accurate corrections for attenuation and scatter. However, it has been shown that for estimating PET tracer uptake in bone, lower kVp CT acquisitions can be more biased. Thus higher kVp (greater than or equal to 80 kVp) CT acquisitions are recommended in general (Abella et al). In addition, if there is the potential for artifacts in the CT image due to the choice of acquisition parameters (e.g., truncation of the CT field of view), then these parameters should be selected appropriately to minimize propagation of artifacts into the PET image through CT-based attenuation and scatter correction.

The actual kVp and exposure (CTDI, DLP) for each subject at each time point should be recorded. CT dose exposure should be appropriately chosen wherever possible, particularly in smaller patients. The radiation principle ALARA (As Low As Reasonably Achievable) for minimizing radiation dose should be considered during imaging protocol development. Refer to educational initiatives, such as Image Wisely (www.imagewisely.org) which provides general information on radiation safety in adult medical imaging, though not specific to amyloid imaging. Note that the ALARA principle is for radiation mitigation and does not address the diagnostic utility of an imaging test.

Parameter	Entity/Actor	Specification
CT acquisition mode	Study Sponsor	The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model and with the lowest radiation doses consistent for the role of the CT scan: diagnostic CT scan, anatomical localization, or corrections for attenuation and scatter.
		If diagnostic or anatomical localization CT images are not needed, then the CT acquisition mode shall utilize the protocol that delivers the lowest possible amount of radiation dose to the subject (e.g., an ultra-low low dose protocol) that retains the quantitative accuracy of corrections for attenuation and scatter.
CT acquisition mode	Technologist	The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be set as specified by study protocol and used consistently for all subject scans.
CT acquisition mode	Technologist	If CT kVp is not specified in the study protocol, a minimum kVp of 100 shall be used and used consistently for all subject scans.

Parameter	Entity/Actor	Specification
CT Technique: Protocol Design	Technologist / Physician / Medical Physicist	A team comprising a Technologist / Physician / Medical Physicist shall ensure that CT protocols are designed such that dose exposure is the lowest radiation dose necessary to achieve the diagnostic objective. The protocol shall be recorded and documented.
CT Technique: Dose Exposure	Technologist	The Technologist shall ensure that CT dose exposure is the lowest radiation dose necessary to achieve the diagnostic objective.

Regarding CT radiation exposure, the lowest radiation dose necessary to achieve the diagnostic objective should be used. For a given protocol, the purpose of performing the CT scan (i.e., only needed for attenuation correction and/or anatomic localization versus one intended for diagnostic purposes) should be determined. The CT technique (tube current, rotation speed, pitch, collimation, kVp, and slice thickness) used should result in as low as reasonably achievable exposure needed to achieve the necessary PET image quality. The technique used for an imaging session should be repeated for that subject for all subsequent time points assuming it was properly performed on the first study.

3.3. Imaging Data Reconstruction and Post-Processing

3.3.1 Imaging Data Reconstruction

Reconstructed image data is the PET image exactly as produced by the reconstruction process on the PET scanner, i.e., a PET image volume with no processing other than that occurring during image reconstruction. This is always a stack of DICOM slices/files constituting a PET image volume that can be analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS system, etc. See Section 4.0 for specifications.

The PET reconstruction parameters include the choice of reconstruction algorithm, number of iterations and subsets (for iterative algorithms), the type and amount of smoothing, the field of view and voxel size. The quantitative accuracy of the PET image should be independent of the choice of CT reconstruction parameters, although this has not been uniformly validated. In addition if there is the potential for artifacts in the CT image due to the choice of processing parameters (e.g., compensation for truncation of the CT field of view), then these parameters should be selected appropriately to minimize propagation of artifacts into the PET image through CT-based attenuation and scatter correction.

Parameter	Entity/Actor	Specification
PET image reconstruction	Study Sponsor	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key PET image reconstruction parameters shall be specified according to pre-determined harmonization parameters.

PET image reconstruction	Technologist	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be identical for a given subject across time points.
PET image reconstruction	Technologist	If available, any reconstruction algorithm that uses point spread function (PSF) modeling should NOT be used.
PET image reconstruction	Technologist	If available, the time of flight (TOF) option can be used; the use or non-use of TOF must be consistent for a given subject across time points.
PET Matrix/Voxel size	Technologist	The Technologist shall perform the image reconstruction such that the matrix, slice thickness, and reconstruction zoom shall yield a voxel size of ≤ 2.5 mm in the x and y dimensions and ≤ 3 mm in the z dimension. The final size shall not be achieved by re-binning, etc., of the reconstructed images.
Correction factors	Technologist	All quantitative corrections shall be applied during the image reconstruction process. These include attenuation, scatter, random, dead-time, and efficiency normalizations. However, no partial volume correction should be performed.
Calibration factors	Scanner	All necessary calibration factors needed to output PET images in units of Bq/ml shall be automatically applied during the image reconstruction process.

As part of the image reconstruction and analysis, correction factors for known deviations from the acquisition protocol can potentially be applied. Corrections for known data entry errors and errors in scanner calibration factors should be corrected prior to the generation of the reconstructed images, or immediately afterwards.

3.3.2 Image Data Post-processing

Processed image data are images that have been transformed in some manner in order to prepare them for additional operations enabling measurement of amyloid burden. Some post-processing operations are typically performed by the PET technologist immediately following the scan. Additional steps may be performed by a core imaging lab, or by an analysis software package accessed by the radiologist or nuclear medicine physician.

Initial post-processing operations typically performed by the PET technologist at the imaging site include binning image time frames into a pre-specified discrete frame duration and total number of frames, and putting the images into a spatial orientation specified by the post-processing protocol.

In post-processing images, only those steps specified per protocol should be performed, as each transform can slightly modify the image signal, and the intent is to preserve the numerical accuracy of the true PET image values. Studies including full dynamic imaging and kinetic modeling rather than evaluation of a late timeframe static scan may require additional processing as specified in the individual protocol.

3.3.2.1 **Ensure image orientation**

Whether the image is being prepared for a quantitative "read" by a physician using clinical diagnostic software, or for transmission to a facility for centralized image quality control, processing, and analysis, it is important to ensure that the image is spatially oriented per protocol. This step may occur before or after the creation of a static image below, depending upon the actors and image transfer sequence involved in the protocol.

Parameter	Entity/Actor	Specification
Image orientation	PET technologist	The raw image will be spatially oriented per study protocol.

3.3.2.2 Create Static Image

Depending upon the study protocol, one or more steps may be involved in the creation of the late timeframe static image that is then further processed and used for measurement of the SUVR. In the simplest case, the image may be acquired as a single frame (e.g., 20 minutes long), thus forming a static image without the need to combine timeframes. In this case, Section 3.3.2.2.2 below is not applicable. Due to the inability to correct for subject motion, this single frame approach may increase the risk of variability outside of the tolerances targeted in this Profile. Alternatively, and commonly in clinical trials, the output may be a set of discrete time frame images (e.g., four five-minute frames) that are then combined into a single static image in subsequent steps. The alternative approach of full dynamic data acquisition typically involves many (>15) frames of variable length, starting with rapid frames acquired immediately at tracer injection.

3.3.2.2.1 Intra-scan inter-timeframe assessment and alignment

For a scan comprised of multiple timeframes, it is important to ensure that the frames are spatially aligned so that the same brain tissue is located in the same coordinates for measurement across the frames. It is preferable that this alignment be performed prior to attenuation correction (that is, as part of the steps in the previous Section 3.3.2.2) in order to prevent embedded error due to misalignment between emission and transmission scan. However, at present, because of limitations in the tools provided with typical scanner workstations, inter-timeframe alignment is typically not performed during image reconstruction and attenuation correction. Rather, visual checks are typically applied and excessive motion may or may not be flagged. If automated, precise tools become available in scanner workstations in the future, the inter-frame alignment and static image formation described in this section may become part of the image reconstruction process. Even when inter-timeframe alignment is performed prior to attenuation correction or at the imaging site, it is important that the discrete binned frames prior to inter-frame alignment, the transmission scan, and the alignment parameters applied, be made available for quality control in later processing and analysis steps.

Inter-frame alignment is typically performed using automated software that employs mathematical fitting algorithms to match the image from each timeframe to a reference. The reference frame may be that acquired closest to the time of transmission scan (e.g., the first frame in late frame acquisition if the transmission scan precedes the emission scan) or as otherwise stated per protocol. The amounts of translation or linear adjustment, in each of the x, y, and z directions, and the amount of rotational adjustment in each of three orthogonal directions are measured by the software. Depending upon the software platform, these parameters are available for review by the image analyst, or may be pre-programmed to make pass/fail or other decisions. Large values (greater than 4 degree rotation or 4 mm translation) indicate that subject motion is likely embedded within one or more frames introducing noise (signal variability) that cannot be removed from those particular frames. In addition, unless attenuation correction was performed on a frame by frame basis during image reconstruction, large values indicate that emission-transmission scan misalignment error is also embedded in one or more frames.

The study protocol should define the allowable translation and rotation permitted between the reference frames and other frames. Frames exceeding these limits may be removed, with the following caveats: (a) removal of too many frames (e.g. more than half of the total acquisition window) may result in inadequate total counts and a noisy scan; and (b) frame removal should be consistent across longitudinal scans for the same subject, or slight error can be introduced. Note that particularly in certain subject populations it is not uncommon to observe translational or rotational motion exceeding 2 mm or 2 degrees, and exceeding 5 mm or 5 degrees in some scans. Typical clinical studies of MCI and AD patients have had mean (standard deviation) values of 1.7 (1.1) mm for maximum translation and 1.5 (1.1) degrees for maximum rotation. Motion tends to worsen with longer duration scans. The decision to extend allowable motion thresholds becomes a balance between retaining subject frames and tolerating increased signal variability.

Currently, most scanner workstations do not provide readily used automated tools for inter-frame motion measurement and correction, and automated alignment to the transmission (or CT) scan prior to attenuation correction. Once such tools are available, the activity of frame alignment would best be performed prior to attenuation correction, to prevent embedded attenuation correction error that cannot be removed through subsequent inter-frame alignment. On occasion, even with current tools, this can be performed at the site. Even when realignment at the imaging site becomes feasible, the inter-frame alignment parameters of the original scan acquisition should be available to the Image Analyst, as under certain conditions enough within-frame motion may have occurred to merit removal of the frame regardless of inter-frame correction.

Parameter	**Entity/Actor**	**Specification**
Inter timeframe consistency	Image analyst or, pending protocol, PET technologist	When a multi-frame PET scan is provided, the translational and rotational adjustment required to align the frames will be assessed prior to combining frames into a single scan.
Action based on inter-timeframe consistency check	Image analyst or, pending protocol, PET technologist	If inter-frame alignment has been performed prior to attenuation correction, frames will be removed if inter-frame translation exceeds a recommended threshold of 4 mm or inter-frame rotation exceeds 4 degrees (or less if indicated by study protocol) or if inter-frame alignment has not been performed prior to attenuation correction, frames will be removed if inter-frame translation exceeds a recommended threshold of 4 mm or inter-frame rotation exceeds a recommended threshold of 4 degrees from position of the CT scan used for attenuation correction (or less if indicated by

Parameter	Entity/Actor	Specification
		study protocol).

3.3.2.2.2 Combine discrete timeframes

Once all or a subpopulation of the appropriately aligned timeframes have been identified, a composite image is generated for further processing and analysis. For late timeframe scans, this is accomplished through averaging or summation of the timeframes into a single image volume. In full dynamic scanning, a “parametric” image can be created through a more complex procedure that involves measuring signal in amyloid “rich” (having high tracer binding) and amyloid “poor” (low tracer binding) regions, or using blood measurements if available, and solving simultaneous equations to determine voxel values. The parametric image can then be measured using the same Volume of Interest or other methods described below, with the difference that the measure becomes a Distribution Volume Ratio (DVR) rather than SUVR.

Static Image generation	Image analyst or image processing workstation	Only timeframes identified as appropriately aligned will be included in this image generation.

3.3.3 Imaging Data Storage and Transfer

Discussions of archiving PET data often mention 'raw data'. This is an ambiguous term as it can refer to: ***scanner raw data*** (i.e., sinograms or list-mode) or image raw data. To avoid confusion, the term raw data should not be used without making it clear which form is under discussion.

Image raw data is the image data exactly as produced by the reconstruction process on the PET or PET/CT scanner. i.e., a stack of DICOM slices/files constituting a PET image volume with no processing other than that occurring during image reconstruction. This is typically a stack of DICOM slices/files constituting a PET image volume that can be analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS system, etc. If inter-frame alignment is performed prior to attenuation correction, then “raw data” may include both the emission and transmission frames prior to any inter-frame or inter-scan alignment, the realigned frames that were used for attenuation correction, and the attenuation corrected frames.

Post-processed image data are images that have been transformed after reconstruction in some manner. This is typically a stack of DICOM slices/files constituting a PET image volume that can still be analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS system, etc.
For archiving at the local site or imaging core lab (if relevant), the most important data are the original images, i.e. the image raw data. In the unlikely event that the scanner raw data (which should be archived by the local site) is required for later reprocessing; this should be made clear in the protocol.

Parameter	Entity/Actor	Specification
Data archiving: raw	Technologist	The originally reconstructed PET images (image raw data), with attenuation correction, and CT images shall always be

Parameter	Entity/Actor	Specification
images		archived at the local site. If scanner raw data need to be archived for future reprocessing, this should be defined prospectively in the Protocol.
Data archiving: post-processed images	Image analyst	If a static image has been generated by aligning frames and summing or averaging discrete timeframes, or through other parametric image generation, the image will be archived at the site where the static image generation occurred.

3.4. Image Analysis

The Image Analyst, through interaction with the Workstation Analysis tools, shall be able to perform specified measurements on the images. Image Analysis has qualitative and quantitative tasks. Both tasks require high quality image submission and consistency of image interpretation. Quantitative imaging requires additional system characteristics described further in Section 3.2, Image Data Acquisition, and Section 3.6, Quality Control, of this Profile.

3.4.1 Input Data

The output of image Reconstruction and Post-processing (inclusive of Static Image Generation) resulting in a single image volume, corrected for attenuation, scatter, randoms and radiotracer decay, is considered the input for static scan Image Analysis. In the case of full dynamic imaging for kinetic analysis, the Post-processing output may be a set of timeframes. The original input data as received, without modification, should be maintained as a separate file (or set of files), to be stored along with the processed data that is ultimately used to perform measurement (See Section 3.2).

3.4.2 Image Quality Control and Preparation

Before Image Analysis is performed, stringent image quality control is essential to ensure that images are suitable for processing and analysis. The elements of raw image quality control that should be performed during performance of post-reconstruction processing are defined in Section 3.3, Image Post-Processing. Elements of post-processed image quality control that should be performed by the Image Analyst or the Processing Workstation software prior to further processing and analysis of the image data are listed in Section 3.6, Quality Control.

3.4.2.1 Correction for Partial Volume Effects

Partial Volume Effects Correction (PVEc) is NOT recommended as a “by default” step in this Profile due to the fact that the process itself can introduce a great deal of variability, countering the tolerance goals of the Profile. However, we discuss this step here, as it may be included in certain study protocols particularly if methodology is systematically employed that does not increase variability. As background on this topic, due to the limits of PET scanner resolution, the signal measured at the borders of white and gray tissue, or tissue and cerebrospinal fluid (CSF) can contain contributions from both types of tissue within the boundaries of the same voxel. In particular, some amyloid PET tracers have high levels of nonspecific white matter uptake, producing high signal intensity that “spills into” neighboring gray tissue measures. In addition, neurodegenerative patients may exhibit substantial, progressive atrophy, increasing spill-in from CSF that can dilute increases or accentuate decreases originating from the atrophic tissue elements. Several different mathematical algorithms and approaches have been developed to correct or compensate for PVE and tissue atrophy. However, these approaches are not necessarily sensible in the setting of amyloid imaging and quantification. Simply applying correction for the loss of cerebral gray matter results in upscaling of image signal intensity, and is most appropriate when the tissue origin of the signal is lost, resulting in the atrophy (ex loss of synaptic neuropil in FDG cerebral glucose metabolism imaging). In the case of amyloid deposits in neurodegenerative dementia, however, the deposits are not contained with normal cerebral gray matter elements; amyloid plaques are extracellular accumulations and are unlikely to degenerate as gray matter atrophies due to losses of synapses and neurons ensues. Thus, applying gray matter atrophy-correction PVEc may inappropriately “upscale” the amyloid signal from atrophic cortical regions. Usual PVEc approaches result in a new image, typically containing only gray matter, and has been shown to increase the apparent amyloid in AD patients by as much as 30% to 56%. The most sensible approach to PVEc in amyloid images is to apply correction for spillover from subcortical white matter into the gray matter regions, which is likely to become increasingly problematic as the cortical gray matter becomes atrophic. Appropriate use of PVEc can potentially help to increase sensitivity to longitudinal change, and to reduce error associated with changes in atrophy or white matter uptake. However, PVEc methods can also introduce variability, and results are highly sensitive to subjective selections of the parameters used in calculating the correction. Effects upon measurement of longitudinal change have varied from no effect to an increase in measured change. The tradeoff between benefit vs. these considerations must be considered and the decision as to whether or not to use may be study dependent. The point in the process at which PVE correction is applied may vary, for example either applied to spatially normalized images or to native images, prior to or after the creation of a SUVR image.

3.4.2.2 Image Smoothing

Depending upon whether more than one scanner and reconstruction software combination is being used to acquire patient data, and the objective of the image analysis, it may be necessary to smooth the image. Smoothing applies a mathematical filter to the image signal at each voxel to help compensate for differences in spatial resolution that exist between different scanners. Even if the same scanner is used for each visit by a particular subject, being able to compare the SUVR value to a threshold derived using images from multiple scanners, or to other study subjects whose data is collected on other scanners, requires adjustment for scanner differences. If not reconciled, these differences can cause a few percent difference in SUVR.

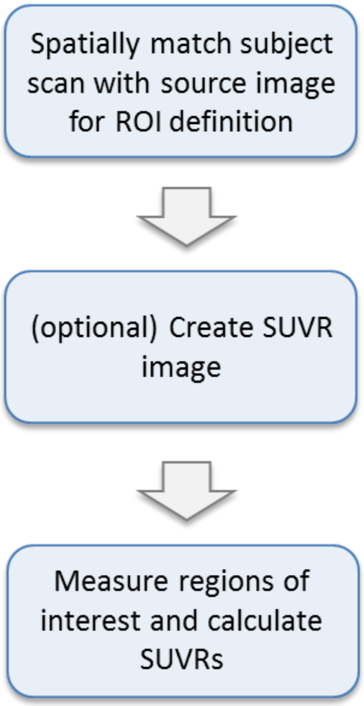
By “spreading” signal out, smoothing also helps to increase the spatial overlap of amyloid accumulation across different subjects, increasing the ability to identify group effects in voxel-based comparisons. However, smoothing also dilutes signal, particularly in small structures, and can also increase the mixing of white, gray, and CSF signal.

Parameter	Entity/Actor	Specification
Image smoothing	Image analyst	When combining scans from different scanners and/or reconstruction software that produce different image resolutions, filtering will be applied per protocol to produce comparable

		signal for the same amount of radioactivity.

3.4.3 Methods to Be Used

The methodology and sequence of tasks used to perform amyloid tracer analysis have historically varied across studies depending upon the radiotracer, image analysis workstation, software workflow and parameters determined to be of interest in the study design. Processing and analysis steps have ranged from a manual workflow to a semiautomatic workflow (which requires some user interaction with the workstation) to an automatic workflow (with little or no user interaction), with various alternatives possible at each step. An outline of the major steps typically included in the workflow is provided below. These steps are associated with a Standardized Uptake Value Ratio (SUVR) calculation approach using an equilibrium stage "late timeframe" image. Details, considerations impacting analysis reliability, and guidelines are then provided. Points where order of operations can vary without impacting end result, such as the option to generate an SUVR image prior to target region measurement, are noted. Notes are also included regarding the alternative use of the full dynamic scan and kinetic modeling to produce measures of amyloid burden.



Spatially match subject scan with source image on which regions of interest (ROIs) have been defined. This may be the subject's MRI scan, segmented into anatomical regions, or it may be a "template" MRI or PET scan on which regions have been pre-defined. If a template is used, a spatial transformation or "warping" is required to match the template and subject scan so that the defined regions can be mapped onto the subject scan.

As an optional step, create an intensity-normalized version of the scan ("Standardized Uptake Value Ratio", or "SUVR" image) by dividing all voxels in the scan by the average measured intensity in a selected reference region (such as cerebellum). This can be useful for visual assessment and comparisons between scans.

Apply boundaries ("masks") for target regions of interest and measure average intensity. If the image has already been intensity normalized to the selected reference region, these are equal to the SUVR. If the image has not been intensity normalized, or to use a different reference region, measure reference region intensity and calculate SUVR as target region intensity divided by reference region intensity. Other voxel-based analyses may also be performed.

Figure 4. Typical steps in image processing and measurement for SUVR calculation

Despite variability in workflows that may be applied, several fundamental factors can impact the accuracy and reproducibility of measurement. These are discussed below and guidance provided to achieve accuracy and reproducibility.

3.4.3.1 Spatially Match Subject and Template

The fitting of Volumes of Interest (VOIs) to a scan for amyloid studies has typically been performed by automated software, reducing the subjectivity, inter-reader differences, and labor intensity of manual delineation. In order to measure pre-defined VOIs for SUVR calculation (or DVR in the case of full dynamic scanning), it is necessary to map these spatial boundaries to the subject's specific brain morphology or vice versa. The following approaches can be applied: (a) Spatial mapping of individual brain scans to a template brain having pre-defined VOI boundaries; (b) Spatial mapping of the template brain and pre-defined VOI boundaries based upon a probabilistic atlas of gray matter segments or otherwise delineated regions to the individual brain scans; and (c) Use of segmentation algorithms that "find" each anatomical structure of interest within the subject's native morphology using the subject's MRI (e.g., Freesurfer). Mapping individual subject scans to a brain template is also required to allow scans to be compared to one another using voxel-based analysis. Segmentation results are dependent upon the MRI sequence used; even the same sequence may produce different results on different MRI scanners.

Spatial Mapping	Image Analyst / Workstation	Perform spatial mapping consistently as defined in the Protocol

3.4.3.1.1 "Fuse" MRI and PET images

The majority of amyloid test-retest studies and most clinical trials with quantitative amyloid imaging have used the subject's MRI scan as a high resolution vehicle for the spatial mapping approaches described above. With clinical application as a consideration, processing pipelines using specific amyloid PET radiotracers have been developed to use PET-to-PET spatial transformation. An optimized PET-to-PET transformation approach has been developed for flutemetamol, and similar approaches have been developed for other tracers. In cases where an MRI is used, the subject's MRI and PET are "fused" or co-registered to one another using a linear transformation performed by automated software. While either MRI or PET can serve as the target to which the other is co-registered, registering the MRI to the PET prevents interpolation of the PET image. However, preserving the resolution of the MRI image, typically higher than that of the original PET, is useful for later operations including segmentation of the MRI and transformation to template space. This can be accomplished by co-registering the PET to MRI, or by up-sampling the PET prior to co-registration of the MRI to the PET or otherwise preserving output resolution.

Since mapping operations performed on the MRI will be applied to its co-registered PET scan, it is critical to ensure that the PET and MRI have been properly aligned to one another. Visual inspection should be conducted with careful attention to proper left-right orientation and alignment in all three planes (transaxial, sagittal, and coronal) ; quantitative goodness of fit measures can also be applied. Successful fusion may be indirectly checked through verification of correct VOI placement and/or correct spatial normalization. However, if misalignment occurs, one must backtrack to determine where in the process this happened, and verification of each step is recommended. Automated methods to assure goodness of fit may also be employed.

Parameter	**Entity/Actor**	**Specification**
PET and MRI image fusion	Image analyst	When coregistering a subject's PET and MRI images, accurate alignment of the images in all planes (transaxial, coronal, sagittal) will be

		verified.

3.4.3.1.2 Longitudinal PET co-registration

For longitudinal amyloid measurement, co-registering subsequent PET scans to the baseline PET scan is recommended, as separate MRI to PET co-registrations or separate spatial warping operations (described below) may produce slightly different alignments. This can cause differences in VOI measurement, and even a few percent can be significant for longitudinal evaluation. Goodness of fit of inter-PET scan alignment should be visually verified; quantitative metrics such as correlation can also be applied.

Successful longitudinal co-registration may again be indirectly checked through verification of correct VOI placement and/or correct spatial normalization. In addition, if a process involving separate spatial normalization of longitudinal scans is applied and achieves comparable fit, the result would be acceptable. However, if misalignment occurs, one must backtrack to determine where in the process this happened, and therefore explicit verification of proper longitudinal coregistration is recommended.

Parameter	Entity/Actor	Specification
Co-registration of longitudinal scans	Image analyst	When coregistering a subject's longitudinal PET images, accurate alignment of the images in all directions (transaxial, coronal, sagittal) will be verified.

3.4.3.1.3 Spatial Mapping of Subject Image and Template Image

Depending upon the approach taken to map regions of interest or reference regions to the PET scan, spatial transformation (or "warping") between the image and a template image may be necessary. If the subject's native space MRI is segmented and used to define region of interest boundaries, and no voxel-based group analyses are performed, then spatial warping is not required. However, if regions pre-defined in template space are to be applied to the scan, then the transformation is a critical step.

The mapping between subject image and template image is accomplished through automated spatial normalization or warping software algorithms. When an MRI is used, the transformation is determined though a "warp" between subject MRI and template, and the same mathematical transform is applied to the coregistered PET scan (if transforming to template space) and/or to the ROIs (if transforming to the native subject scan). The accuracy of the spatial transformation depends upon the algorithm. Certain software and software versions have shown superior alignment of cerebellum, deep structures such as putamen and medial temporal regions, and ventricles as compared to older algorithms (Klein et al, 2009).

When an MRI is not available, the subject PET scan can be transformed directly to the template PET. Since the signal within gray matter and the intensity contrast between gray and white matter in a negative amyloid scan are substantially different than those in an amyloid positive scan, images at the extremes of positive and negative may not spatially normalize well. To address this, various approaches have been developed that test the fit to a series of templates (Lundqvist et al, 2013), selecting the best fit. Other confounds in PET-based spatial normalization can occur when the amyloid PET image has high intensity signal in portions of dura or skull, or missing (truncated) tissue at the top or bottom of the brain. Various additional steps have been employed to address these issues.

Regardless of the approach used for spatial normalization, an accurate match between subject and template is critical to amyloid measurement. Goodness of fit should be evaluated using visual inspection, and quantitative goodness of fit algorithms can also be applied. As a note, ad hoc manual (e.g. touch screen or mouse based) modification of warping results should not be used as changing the fit for one set of slices through "eyeballing" is very likely to introduce error into other slices.

Parameter	Entity/Actor	Specification
Spatial mapping with template image	Image analyst	When spatially mapping a subject image and a template image to one another accurate alignment of the images in all directions (transaxial, coronal, sagittal) will be verified visually.

3.4.3.2 VOI Placement: Target / Reference

3.4.3.2.1 Determine Target Regions for Measurement

The selection and delineation of target regions for amyloid measurement vary depending upon study objectives and should be specified in the protocol. For clinical application, some manufacturers have specified predefined VOIs associated with a threshold SUVR that they have correlated to autopsy data. Some clinical trials have used a cortical average consisting of 4 – 6 regions, with individual regional amyloid measures providing further information. When "emerging" subjects with amyloid levels nearer to threshold are studied in clinical trials, analysis of specific sub-regions may become important.

Given a specified anatomical region (e.g., frontal, or cingulate), there are several ways to define the tissue that is included in the region, and several considerations that are not mutually exclusive, listed below. Automation of region definition is important given the high level of subjectivity that can be associated with manual definition.

- *Region Boundaries:* Some approaches use the entire anatomical region, whereas others define a sub-region empirically determined to accumulate greatest amyloid burden.
- *Method to match the region to subject's anatomy:* Some methods apply a standard atlas of region definitions (pre-defined anatomical boundaries based upon reference brains), and rely upon the transformation between the subject's morphology and the atlas template to match the atlas regions to the subject. These may be referred to as "probabilistic" regions. Other approaches estimate anatomical boundaries based upon the individual subject's MRI, incorporating atlas reference information in a more complex way (e.g., Freesurfer).
- *Region confinement to gray tissue:* When atlas based regions are applied, these may or may not be thresholded (restricted) using the gray tissue segment from the subject's MRI. This masking can help to assure alignment between template regions and the subject's actual morphology, and can be done using either native space images or warped images.
- *Region erosion from surrounding tissue or CSF:* VOI boundaries may be eroded (e.g., perimeter reduced by one to two voxels) away from the neighboring CSF and white tissues, in order to reduce atrophy effects and spillover from non-gray tissue types. This is most often applied to probabilistic regions that

tend to be larger and incorporate tissue adjacent to gray matter.

- *"Native space" vs. "Template space":* VOIs may be defined only in template space, for measuring the subject's warped scan, or may be transformed to the subject's native scan. Use of the native scan can reduce interpolation and signal changes arising from stretching or compressing subject anatomy.

Comparisons of different approaches to regional definition, including whether native vs. template scans are used, have yielded high correlation coefficients (Landau et al, 2013). However, it is important to note that measurement of different portions of tissue will give different results. It is therefore important that the same tissue definition be applied across scans and across subjects within a study.

Parameter	Entity/Actor	Specification
Target Region Definition	Image Analyst	The same target region definitions (which may be transformed to each individual subject's morphology) will be applied consistently to subjects and across a study.

3.4.3.2.2 Determine Reference Region

The definition of the reference region is one of the most critical aspects of image analysis. Reference regions are used for image comparison because raw image counts for the same subject will change from scan to scan due to injected dose, scanner calibration, or other factors unrelated to amyloid. If every region in the brain changes in the same proportion due to these factors, then such changes will cancel by taking the ratio of target region to reference region. The reference region is typically a region that does not accumulate or lose amyloid, enabling changes in target regions due to amyloid to be detected.

This Profile does not dictate a particular reference region, since tracer manufacturers and leading research institutions have differed and continue to evolve, on this topic. However, there is a growing body of evidence that certain reference regions exhibit less longitudinal variability and it has been shown that the optimal reference region can be different for each radiotracer (Villemagne, AAIC 2015). In addition, certain practices should be followed to minimize variability arising from the scanner and to ensure the validity of the reference measurement. These considerations are discussed below.

The cerebellar cortex (gray matter) has been a reference region of choice in numerous studies of amyloid since it typically does not accumulate fibrillar amyloid and because its gray tissue kinetics are assumed be reasonably matched to those of gray tissue target regions. Because of its low signal and lack of binding, the cerebellar cortex provides the most sensitive reference for measuring cross sectional differences. However, due to its low signal level, small swings in value will create large swings in calculated SUVR. Further, the physical location of the cerebellum toward the edge of the scanner transaxial field of view makes it susceptible to edge noise, scatter, and tissue exclusion (particularly in scanners with a shorter axial field of view). In head rotation and in emission-transmission scan misalignment, the posterior edge of the cerebellar cortex can be particularly impacted. In addition, slight shifts in position can cause a blending of white and gray tissue that will impact the reference measurement. Further, the cerebellum is located in transaxial slices that are not in proximity to several typical target VOIs, and signal in those slices may not change in the same way due to technical factors. In longitudinal studies, for one radiotracer, the cerebellar cortex has been demonstrated to show stability over time (Villemagne, AAIC 2015) while for others variability with regard to measured change has been shown, decreasing statistical power. Even in cross-sectional measurements, technical noise embedded in the cerebellum (or any reference region) may cause a subject whose amyloid burden is at the threshold of positivity to “tip” in one direction or another. At a minimum, the inferior margin of the cerebellar reference boundaries should not extend to the edge of the FOV, where the greatest technical variability occurs. Alternate reference region comparisons are also recommended to ensure that noise has not driven the SUVR result.

Use of whole cerebellum has been specified as a reference of choice with some ligands, and can reduce variability arising from shifts that include more white matter (Joshi, JNM 2015), since it is already included. However, the same issues with spatial location, edge noise, and lower average signal still apply. As an alternative reference, the pons has been applied in multiple studies, and found to have a slightly lower variability. Its advantages include higher signal due to white matter inclusion, and more central location in the brain at a slightly further distance from the edge of the scanner transaxial field of view. Some studies using florbetapir, flutemetamol and 11C-PIB have found that the pons exhibited lower longitudinal variability than a cerebellar reference region (include reference). However, the narrow cylindrical size and shape of the pons make it vulnerable to subject motion, and it, too, can be affected by technical variability. Subcortical white matter provides another alternate reference region, with the advantages of higher signal, larger measurement volume, transaxial alignment with target regions of interest. Studies have demonstrated benefit in lower variability using subcortical white matter, and thus greater statistical power in measuring longitudinal change, relative to other reference regions (reference needed). One consideration in the use of a white matter reference is that the kinetic properties of white matter differ from those of the gray tissue target regions, with unclear impact upon measurement validity. However, findings seem to support the ability to detect increases in amyloid positive populations as expected and seen with gray tissue reference regions, yet with lower variability. Combinations of whole cerebellum, pons, and subcortical white matter, or cerebellar white matter and pons, or “amyloid poor” gray regions other than cerebellum have also been applied with reductions in longitudinal variability (for florbetapir) resulting in increased statistical power (add a reference to justify the composite reference region). It should be noted, however, that the signal from reference regions using subcortical white matter may be affected by vascular pathology, common in the elderly.

The use of a combined reference, subcortical white matter, or other “amyloid poor” regions proximal to target regions may be advised (radiotracer dependent), particularly for longitudinal studies and for measurement of amyloid in subjects near the threshold of positivity. A cross check across reference regions can also be used to screen for reference region reliability.

Parameter	Entity/Actor	Specification
Reference Region Definition	Image Analyst	The reference region definition will conform to protocol by including the specified tissue. Quality control measures will be applied to ensure that longitudinal change is not attributable to technical noise or artifact in a particular reference region.

3.4.3.2.3 Apply Regions to Subject Scans for Measurement

Target VOIs may be applied for measurement either to the non-intensity normalized image, or to an SUVR image that was first generated by dividing each voxel by the average value in the reference region. When placing VOIs, it is critical to ensure accurate fit, and that only appropriate tissue is included. Potential sources of error include the following:

Differences in tissue composition: Positioning of a cortical VOI toward the edge of gray matter in one scan vs. toward white matter in a second longitudinal scan will introduce measurement error due to the tissue composition and partial volume effects. In cross-sectional measurement, these differences can also be significant for subjects at threshold of positivity.

Tissue truncation: If the scan does not have a complete cerebellum or other region, and the VOI samples the empty space, a large error can result depending upon proportion of missing tissue for the VOI.

Differences in tissue sampled: Measuring different portions of tissue (e.g., the full region in one scan vs. only a part of the region due to tissue truncation in the second scan) across longitudinal scans can introduce errors of a few to several percent.

Parameter	Entity/Actor	Specification
Region placement	Image Analyst	The placement of all regions of interest and reference region(s) will be verified to be on the correct tissue
Region placement	Image Analyst	All regions will be checked to ensure that boundaries do not include empty space (scan truncation). Regions will be adjusted using a consistent approach, such as automated exclusion of voxels, with a sub-threshold value, to exclude voxels where tissue is missing.
Region placement	Image Analyst	The same portion of tissue will be measured between longitudinal scans for the same subject.

3.4.3.2.4 Generate SUVR Image

Once a reference region has been applied to the scan, and either before target region measurement, or afterward, a SUVR image (or DVR in the case of a fully dynamic scan) can optionally be generated by dividing each voxel value by the reference region mean.

This is useful for visual comparison and evaluation of images, regardless of which regions are to be measured quantitatively. Once an SUVR image has been generated, target VOIs can also be applied and measured without further division by a reference region value.

3.4.3.3 Create SUVR

3.4.3.3.1 Measure Regional Values

The mean value within each VOI is calculated as the numerator for the SUVR. A cortical average may be calculated as the average of multiple VOIs, or weighted by the number of voxels in each VOI.

3.4.3.3.2 Calculate SUVR

The SUVR is calculated by dividing the VOI value by the reference region value (which will be 1.0 if measured on a SUVR image). If a parametric image was generated using full dynamic scanning, or if a kinetic model is being applied to a multi-timeframe dynamic image, a DVR value is generated instead.

3.4.3.3.3 Relating SUVR values to other studies

Different protocols involve different tracers, target regions, and reference regions, and all of these contribute to how the SUVR can be interpreted with regard to amyloid burden. A value of 1.2, for example, can be amyloid positive using one tracer and/or set of regions for analysis, but amyloid negative using a different tracer and/or regions. In order to reconcile findings across data acquisition, processing, and analysis protocols, the concept of the Centiloid was developed (Rowe et al, 2013). The Centiloid is not intended to dictate the method for acquiring and processing data, but rather to provide a way to equate results obtained with a broad variety of protocol parameters. The basis for the Centiloid is a "gold standard" set of results derived from young healthy controls and elderly AD patients. These results have been generated using the radiotracer 11C-PiB and a defined set of target region, reference region, and image processing and analysis steps. A linear progression of values from 0 (no amyloid) to 100 (mean for amyloid positive sporadic AD patients) has been established using these values. To establish the equivalent "Centiloid value" for a tracer and/or acquisition and analysis protocol that differ from the gold standard, two sets of relationships are empirically derived. Using the control image set provided by the Centiloid project, it is first confirmed that by using the prescribed regions and analysis approaches, the values can be generated with a correlation exceeding x%. Secondly, using the new tracer and/or acquisition and analysis parameters, values are generated using both the "gold standard" method and 11C-PiB, and the alternate tracer and/or methods. The regression between the two sets of results yields a transform equation that can be applied to results to convert them to "Centiloid units" for comparison to other studies. If a tracer and set of approaches are being applied that for which conversion to Centiloid units has already been established, this reference transform can be applied to new studies using the same parameters.

3.4.4 Required Characteristics of Resulting Data

The specific trial protocol shall prospectively define the SUVR (regions to be measured, which regions are to be included in a cortical average if applicable, and how the average is to be calculated) that is required for the imaging endpoint. SUVR measures and the analysis tools used to obtain them, including software version shall be specified for each protocol and shall be used consistently across all subjects and across all sequential measurements.

It should be clear which values belong to which brain region. Reports must clearly associate the region, including any hemispheric reference, with the measured value via column headers or other information display. Correct association of value and region should be assured via documentation that may include audit log via software that has been validated to correctly produce this information, DICOM coordinates captured along with the SUV, provision of the sampling "masks" or boundaries used to make the measurements for each subject, or secondary screen captures of the ROI for identification. The volume of each region measured, in voxels that can be translated into cc, or in cc, should also be included, along with the minimum, maximum, and standard deviation within the region mentioned.

The reference tissue (e.g., cerebellum (whole or gray), pons, subcortical white matter, combination, other) must be reported along with the target region SUV data. Identification should be specific, indicating whether gray, white, or both tissue types were included, and which slices were included or excluded.

The analysis software should generate a report that is clear, traceable, and interpretable.

3.5. Image Interpretation and Reporting

No QIBA Profile specification can be provided for image interpretation at this time. Image Interpretation is considered to be beyond the scope of this document.

In other words, how quantitative response is measured should be specified *a priori* by the trial itself. This also applies to target lesion selection.

Parameter	Entity/Actor	Specification
Image Reporting	Imaging Facility	Imaging reports shall be populated from DICOM header information using structured reporting.

3.6. Quality Control

The following section deals with multiple aspects of quality control in amyloid-PET studies. This includes selecting and qualifying a PET/CT imaging facility, imaging personnel and PET/CT scanners and ancillary equipment. In addition, the use of phantom imaging (prior to study initiation and ongoing) is discussed as well as identifying subjects whose data may need to be censored due to a lack of data integrity. Finally, post-image-acquisition quality assessment is detailed.

3.6.1 Imaging Facility

It is essential to implement quality processes that ensure reliable performance of the scanner and consistent image acquisition methodology. These processes must be in place prior to subject imaging and be followed for the duration of the trial. A facility "imaging capability assessment" is a prerequisite to facility selection for participation in any clinical trial involving the use of amyloid-PET/CT as an imaging biomarker. This imaging capability assessment will include:

- Identification of appropriate imaging equipment intended for use in the trial
- Documented performance of required quality control procedures of the scanner and ancillary equipment (e.g., radionuclide calibrator)
- Radiotracer quality control procedures
- Experience of key personnel (technologists, radiologists, physicists and/or other imaging experts)
- Procedures to ensure imaging protocol conformance during the trial

3.6.1.1 Site Accreditation/Qualification Maintenance

Whilst imaging facility accreditation is generally considered to be adequate for routine clinical practice purposes (e.g., ACR, IAC, and TJC), facility qualification (e.g., EARL, SNMMI-CTN, ACRIN, and imaging core labs) -may be required for clinical research/clinical trial participation. In order to be considered to be conformant with this Profile, an imaging scanner/facility must provide documentation of current qualified status. Appropriate forms, checklists or other process documents should be maintained and presented upon request to verify that ongoing quality control procedures are being performed in a timely manner as dictated by specific clinical study requirements. If exceptions to any of the performance standards stated below occur and cannot be remediated on site, the site should promptly communicate the issue to the appropriate internal overseer for advice as to how the irregularity should be managed. In addition to documenting the level of performance required for this Profile (and the level of performance achieved), the frequency of facility accreditation/qualification also needs to be described.

It is important to note that that imaging facility Accreditation and/or Qualification, as defined in this Profile, are considered necessary, but are not sufficient for being conformant with this Profile. In order to be conformant with the Profile, and thus to support the claims of the Profile, all normative requirements must be met.

Parameter	**Entity/Actor**	**Specification**
Accreditation / Qualification	Imaging Site & Image Acquisition Device	Shall maintain and document Accredited status for clinical practice (ACR, IAC, TJC, etc.) or Qualified status for clinical trials (e.g. ACRIN, SNMMI-CTN, EARL, iCROs, etc.).

3.6.2 Imaging Facility Personnel

For each of the personnel categories described below, there should be training, credentialing, continuing education and peer review standards defined. Guidelines for training/credentialing for each resource category are summarized below (UPICT Protocol Section 2.1). Note that only physicians reading the PET/CT amyloid scans need specific training and certification for PET amyloid interpretation.

Parameter	**Entity/Actor**	**Specification**
Personnel Roster	Imaging Facility Coordinator	Each site shall, at the time of trial activation and prior to subject accrual, have the support of certified technologists, physicists, and physicians (as defined below), experienced in the use of amyloid-PET/CT in the conduct of clinical trials.
Technologist	Imaging Facility Coordinator	Technologist certification shall be equivalent to the recommendations published by the representatives from the Society of Nuclear Medicine Technologists Section (SNMTS) and the American Society of Radiologic Technologists (ASRT) and should also meet all local, regional, and national regulatory requirements for the administration of ionizing radiation to patients.
Medical Physicist	Imaging Facility Coordinator	Medical physicists shall be certified in Medical Nuclear Physics or Radiological Physics by the American Board of Radiology (ABR); in Nuclear Medicine Physics by the American Board of Science in Nuclear Medicine (ABSNM); in Nuclear Medicine Physics by the Canadian College of Physicists in Medicine; or equivalent certification in other countries; or have performed at least two annual facility surveys over the last 24 months.
Physician	Imaging Facility Coordinator	Physicians overseeing PET/CT scans shall be qualified by the ABR (Diagnostic and/or Nuclear Radiology) or American Board of Nuclear Medicine (ABNM) or equivalent within the United States or an equivalent entity appropriate for the geographic location in which the imaging study(ies) will be performed and/or interpreted. Physicians interpreting the scans should have appropriate, specific initial training in interpretation of amyloid brain PET studies (specific to the PET amyloid tracer being used) and maintain continuing proficiency as outlined by

Parameter	Entity/Actor	Specification
		national imaging professional societies, appropriate for the geographic location in which imaging studies are performed.

3.6.3 Amyloid- PET Acquisition Scanner

Amyloid-PET studies as described in this Profile require either a PET/CT scanner or a dedicated PET scanner with the ability to acquire a transmission image. PET/MR scanners may be added in future versions of this Profile. The scanners should be identified based on manufacturer, name and model. Hardware specifications should be documented. Scanner software name and version should be documented at the time of trial initiation and at the time of any and all updates or upgrades.

The scanner must undergo routine quality assurance and quality control processes (including preventive maintenance schedules) appropriate for clinical applications, as defined by professional and/or regulatory agencies. In order to assure adequate quantitative accuracy and precision of imaging results, additional quality assurance measures are required, as discussed below.

For consistency, clinical trial subjects should be imaged on the same device over the entire course of a study. A replacement scanner of the same make and model may be used if it is properly qualified. It is imperative, however, that the trial sponsor be notified of scanner substitution if it occurs.

For clinical trials with quantitative imaging requirements, a subject should have all scans performed on only one scanner unless quantitative equivalence with a replacement scanner can be clearly demonstrated. However, it should be noted that there are currently no accepted criteria for demonstrating quantitative equivalence between scanners. It is anticipated that future version of this Profile will provide such criteria."

Parameter	Entity/Actor	Specification
Physical Inspection	Technologist	Shall, on a daily basis, check gantry covers in tunnel and subject handling system.
QA/QC Checks	Technologist	At a minimum, QA/QC procedures shall be performed each day according to vendor recommendations. Daily QC procedures shall be performed prior to any subject scan.

3.6.3.1 Ancillary Equipment

3.6.3.1.1 Radionuclide Calibrator

The following guidelines are collected from ANSI standard N42.13, 2004 and IAEA Technical Report Series TRS-454. All requirements assume measurements on unit doses of amyloid tracer and that calibration sources are in the 'syringe' geometry (i.e., no bulk doses).

The Constancy test ensures reproducibility of an activity measurement over a long period of time by measuring a long-lived source of known activity.

The Accuracy test ensures that the activity values determined by the radionuclide calibrator are correct and traceable to national or international standards within reported uncertainties.

The Linearity test confirms that, for an individual radionuclide, the same calibration setting can be applied to obtain the correct activity readout over the range of use for that radionuclide calibrator.

Parameter	Entity/Actor	Specification
Constancy	Technologist	Shall be evaluated daily (or after any radionuclide calibrator event) using a NIST-traceable (or equivalent) simulated 18F, Cs-137, or Co-57 radionuclide calibrator standard and confirmed that net measured activity differs by no greater than ±2.5 % from the expected value.
Accuracy	Technologist	Shall be evaluated monthly (or after any radionuclide calibrator event) with a NIST-traceable (or equivalent) simulated F-18 radionuclide calibrator standard. Shall confirm that net measured activities differ no greater than ±2.5% from expected value.
		The scanner calibration shall be tested using a NIST-traceable (or equivalent) simulated 18F source object, e.g. a uniform cylinder, large enough to avoid partial volume effects or other resolution losses.
Linearity	Technologist or Radiation safety officer or Qualified Medical Physicist	Shall be evaluated annually (or after any radionuclide calibrator event) using either 18F or Tc-99m and should be within ±2.5 % of the true value over an operating range of 37-1110 MBq (1 to 30 mCi) and the true value is determined by a linear fit (to the log data) over the same operating range.
PET Radiation Dose	Dose Calibrator	Shall record the radiation dose from the administered activity and accompanying information in a DICOM Radiopharmaceutical Administration Radiation Dose Structured Report.

3.6.3.1.2 Scales and stadiometers

Scales and stadiometers should be inspected and calibrated at installation and annually.

Parameter	Entity/Actor	Specification
Scales	Approved personnel	Shall be evaluated annually or after any repair by qualified personnel. Shall be confirmed that error is less than +/- 2.5% from expected values using NIST-traceable or equivalent standards.

3.6.3.1.4 Clocks and timing devices

The PET and CT scanner computers and all clocks in an imaging facility used to record activity/injection measurements should be synchronized to standard time reference within +/-1 minute. These include any clocks or timekeeping systems that are connected with a subject’s amyloid-PET study, in particular those associated with the radionuclide calibrator, the injection room, the scanner, and the acquisition computer(s). The synchronization of all clocks (to date, time of day and to time zone) should be monitored periodically as part of ongoing QA program. In particular, clocks should be inspected immediately after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur). Correct synchronization could be achieved using the Consistent Time Integration Profile as defined in the IHE IT Infrastructure Technical Framework. The Consistent Time Profile requires the use of the Network Time Protocol (NTP) (www.NTP.org).

Parameter	Entity/Actor	Specification
Scanner and site clocks	Approved personnel	PET and CT scanner computers and all clocks in an Imaging facility used to record activity/injection measurements shall be synchronized to standard time reference within +/-1 minute. Synchronization of all clocks used in the conduct of the amyloid-PET study shall be checked weekly and after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur)
Scanner and site clocks	Specific Device	Provide time synchronization as per the IHE Consistent Time Integration Profile.
Dose calibrator clock	Dose Calibrator	Electronic record of output from a dose calibrator shall be synchronized with other time keeping devices.

3.6.4 Phantom Imaging

3.6.4.1 Uniformity and Calibration

Verification of scanner normalization with a uniform phantom is a minimum requirement for all scanners used in clinical trials including those that only have qualitative endpoints. A Hoffman or equivalent phantom may be used in place of a uniform phantom to verify scanner normalization via in-plane and axial comparisons to an analytical gold standard for that phantom over the complete field of view to be used by the amyloid measurand. For trials with quantitative PET measurements, this assessment should also include a comparison against a radionuclide calibrator to ensure quantitative accuracy; that is, a comparison of the absolute activity measured versus the measured amount injected should be performed. This comparison is particularly important after software or hardware upgrades. If the trial requires absolute quantification in baseline images or absolute changes in longitudinal studies, it should be considered to include an image quality and/or contrast recovery QC assessment as part of the routine QC procedures and/or scanner validation process. Clinical trials using only relative changes in longitudinal studies may not require contrast recovery assessments provided there is appropriate consideration for the minimum size of target lesions based on the partial volume effect.

An essential requirement for extracting quantitative data from images is that there be known calibration accuracy and precision and/or cross calibration of the PET system against the (locally) used radionuclide calibrator (within 10%). The QC procedures should utilize the same acquisition/reconstruction protocol, software and settings that are used for the subject scans.

Parameter	Entity/Actor	Specification
Phantom tests: Frequency of uniformity measurements	Imaging Site	Shall perform at baseline, quarterly and after scanner upgrades, maintenance or repairs, and new setups.
Uniformity QC	Technologist	At least quarterly and following software upgrades, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom. 1. Visual check that no streak artifacts or axial plane non-uniformities are present. 2. The standard deviation of a large central 2D ROI shall be compared with similar previous scans to check for measurable differences. 3. The mean values of a large central 2D ROI for all image slices shall be compared with similar previous scans to check for measurable differences.
Phantom tests: transaxial uniformity measurement	Imaging Site	Shall measure the transaxial (within plane) uniformity as specified in NEMA NU2 1994; uniformity should be $\leq$ 10 % for each qualified axial slice (see below).
		Shall measure the transaxial (within plane) uniformity as specified in NEMA NU2 1994; uniformity should be $\leq$ 5 % for each qualified axial slice (see below).
Phantom tests: axial uniformity measurement	Imaging Site	Shall measure the axial uniformity by placing a circular ROI that is at least 1 cm in diameter less than the active diameter of the cylinder phantom, centered on each of the axial planes. Calculate the COV (std dev/mean * 100) of each ROI. Axial planes whose COV is $\leq$ 10 % qualify for use (e.g. some of the end planes may not qualify).
		Shall measure the axial uniformity using the same procedure as above, except axial planes whose COV is $\leq$ 5 % qualify for use.
		Harmonized image reconstruction protocols are available. (i.e., known recovery coefficients versus size for a given test object such as the modified NEMA NU-2 Image Quality phantom.

3.6.4.2 Resolution

The assessment of adequate resolution should include both a qualitative evaluation (using clinical or anthropomorphic phantom images) and quantitative assessment (using phantom-defined criteria).

Parameter	Entity/Actor	Specification
Resolution	Nuclear Medicine Physician	Shall perform, on at least an annual basis, and document a qualitative resolution QC test by using the manufacturer's settings and demonstrating resolution of normal gross anatomic features within clinical images of the brain.
Resolution	Medical Physicist	Shall perform (during an initial site qualification process, and then at least every one year) and document performance of a quantitative assessment (using a phantom with differing size defined targets such as the Hoffman, ACR or NEMA IQ phantoms) for spatial resolution.
		Follow the modified procedure developed by Lodge et al. [JNM 2009; 50:1307-1314] to use a slightly tilted uniform phantom to get axial and in-plane spatial resolution.

3.6.4.3 Noise

Parameter	Entity/Actor	Specification
Phantom tests: Frequency of noise measurements	Imaging Site	Shall perform at baseline, quarterly and after scanner upgrades, maintenance or repairs, and new setups.
Phantom test: noise measurements	Medical Physicist	A uniform cylinder phantom or equivalent shall be filled with an 18-F concentration in the uniform area (approximately 0.1 to 0.2 μC/ml), and scanned using the intended acquisition protocol. Using a rectangular or spherical region as close as possible to, but no smaller than, 3 cm to a side, the COV of the voxel values within the region should be below 15%, for the slices within the central 80% of the axial FOV.

3.6.4.3 Amyloid-PET Specific Phantom Measurements

The above more general phantom evaluations of a PET scanner are needed to qualify it for clinical practice or a clinical trial. However, more purpose-specific phantoms are also needed to simulate the human brain, amyloid uptake patterns, and the amyloid SUVR measurand. Purpose-specific phantom options that might be considered on a per-protocol basis include, but are not limited to:

1. Each site uses a single phantom for the duration of the trial but not necessarily the same model of phantom used at other sites.

2. All sites use phantoms of the same model for the duration of the trial.
3. All sites use phantoms built to precise specifications for the duration of the trial.
4. All sites share a single phantom for the duration of the trial.

The phantom scans and performance evaluation should be performed prior to the start of a trial and repeated during the course of the trial as specified by the individual protocol. Any changes to scanner equipment, either hardware or software, should be immediately reported to the trial sponsor and/or imaging CRO and may result in the need for re-qualification prior to imaging additional trial subjects. In particular, it is strongly recommended that subjects in a longitudinal study be scanned on the same PET system with the same software version whenever possible.

Generally, the purpose-specific phantom scans must provide a metric to characterize these imaging properties:

- Spatial resolution – PET scanner hardware, reconstruction methods and reconstruction parameter selections can result in dramatically different spatial resolutions in the reconstructed images. Because partial volume effects (especially between gray and white matter regions) can bias many amyloid PET measurands, it is essential to calibrate the spatial resolution of each scanner using the acquisition and reconstruction protocol planned for patient imaging. A post-reconstruction smoothing operation can then be applied for calculation of a measurand at a uniform spatial resolution between scanners.
- Uniformity – In-plane and axial uniformity of the purpose-specific phantom should be within 10% throughout the scanner field of view to be used in the calculation of the amyloid PET measurand.
- Absence of reconstruction artifacts – Reconstructed purpose-specific phantom data should be visually free of reconstruction artifacts, such as streaks due to failing detectors or axial plane non-uniformities due to errors in normalization.
- Qualitative and quantitative accuracy – Measurands using ratios, such as the SUVR must demonstrate accuracy with 10% of an analytical or otherwise known gold standard.

An anthropomorphic phantom, such as the 3D Hoffman phantom or equivalent, ideally with a spatial distribution similar to the cortical gray/white matter is required to characterize the five imaging properties listed above. A uniform phantom or a point source phantom by themselves is not adequate to sufficiently characterize the amyloid imaging properties of a PET scanner. The phantom should be adequate to model and characterize effects of attenuation correction and scatter correction. Contrast ratios of amyloid tracer uptake vary between normal and abnormal subjects, and also between different amyloid tracers. However, it is recommended that the phantom be filled such that the activity concentration in the highest uptake regions be similar to the expected white matter uptake in subjects with amyloid deposition. For the Hoffman phantom, it is recommended that the activity at the start of the scan be 0.5-0.6 mCi (18.5-22.2 MBq) to obtain approximately a 15 kBq/ml activity in the gray matter regions of the phantom. See Appendix H for best practices guidance for this phantom.

The Hoffman phantom should be centered in the FOV of the PET scanner and data acquired for 20 minutes. Moreover, image reconstruction methods and settings should equal those specified in the study. The post-processing and data analysis should be as similar as possible to those used with patient data.

A baseline assessment of the scanner imaging properties is required before any subjects are scanned in the trial, and after any major hardware of software modifications that could affect these properties. Following a baseline qualification assessment using the Hoffman phantom, routine manufacturer-recommended QA procedures (e.g. daily QC checks, quarterly normalization, etc.) using simpler phantoms may be adequate to demonstrate acceptable scanner performance over the course of a clinical trial. A baseline qualification assessment is required at least annually in an extended study.

The normative list below is based on the Hoffman anthropomorphic, NEMA Image Quality, ACR, and uniform cylinder phantoms as appropriate.

Parameter	Entity/Actor	Specification
Phantom tests: Frequency of measurements based on Hoffman phantom data	Imaging Site	Needed as an initial baseline characterization and thereafter annually as well as after major scanner upgrades, maintenance or repairs.
Phantom test: resolution measurement	Imaging Site	Acquire data using the Hoffman phantom and compute the FWHM "Hoffman equivalent" [Joshi/Koeppe NeuroImage 46 (2009) 154-159] FWHM resolution, in transverse and axial directions. The resolution should be <= 8.0 mm FWHM.
Phantom test: gray/white matter ratio measurement	Imaging Site	Register the Hoffman phantom PET image to the digital representation of the phantom, and compute the gray/white matter ratio. This ratio should be > 0.55. See Appendix I for more details.
Phantom test: SUVR accuracy	Imaging Site	Using the Hoffman phantom PET image perform the same post-processing and image analysis to confirm the SUVR accuracy. See Appendix I for more details.

3.6.4.4 Phantom imaging data analysis

For amyloid-PET image analysis, there are many combinations of hardware and software that are used. The software alone comprises multiple layers including the operating system, several base modules for input and display, and the components that draw/calculate ROIs and calculate the SUVR. See Section 4.4 and Appendix F.

3.6.5 Quality Control of Amyloid-PET studies

3.6.5.1 Data Integrity

The integrity of DICOM image headers should be reviewed and confirmed for DICOM standard compliance, regulatory compliance (including privacy protection, such as may be required by such rules as the HIPAA Privacy Rule if applicable), protocol compliance, sufficiency for the intended analysis (e.g., to compute SUV) and consistency with source data such as CRFs.

3.6.5.2 Determination of Image Quality

CT and 68-Ge transmission images should be reviewed by the Image Analyst for assessment of image quality and for potential artifacts such as beam hardening, metal objects, and motion. PET images should be compared to the transmission images for proper image registration and potential attenuation correction artifacts. Both uncorrected and attenuation corrected images may need to be assessed to identify any artifacts caused by contrast agents, metal implants and/or subject motion. For example, movement or mis-registration can lead to poor quality quantitative data and invalid numbers. Some images may be too poor in quality to quantify. Statistical quality of images is important to report, but not a full substitute for quality.

3.6.5.3 Determination of subjects unsuitable for Amyloid-PET analysis

3.6.6 Quality Control of Interpretation

To promote quantifiable performance standards for the quality control of interpretation there is a need for intra-reader variability studies. In a two-Reader paradigm, then inter-reader variability is needed as well. It is currently unclear what statistics to evaluate and how these performance metrics should be used in the analysis.

4. Conformance Procedures

Relation of this Profile to Expectations for QIBA Profile Conformance

Definitions (from Appendix C):

<u>Qualified</u>: The imaging site is formally approved by an appropriate body (i.e., ACRIN, CQIE, SNM-CTN, EANM-EARL, an imaging laboratory or CRO) for a specific clinical research study.

<u>Accredited</u>: Approval by an independent body or group for broad clinical usage (requires ongoing QA/QC) e.g., ACR, IAC, TJC.

<u>Conformant</u>: The imaging site and equipment meet all the requirements described herein, which are necessary to meet the QIBA Profile claim.

The requirements included here are intended to establish a baseline level of capabilities. Providing higher levels of performance or advanced capabilities is both allowed and encouraged. Furthermore, the QIBA Profile is not intended to limit equipment suppliers in any way with respect to how they meet these requirements. Institutions meeting the stated criteria are considered to be QIBA Conformant.

4.1. Performance Assessment: Image Acquisition Site

Typically, clinical sites are selected due to their competence in neurology and access to a sufficiently large subject population under consideration. For imaging sites, it is important to have availability of:

- Appropriate imaging equipment and quality control processes,
- Appropriate ancillary equipment and access to radiotracer and contrast material,
- Experienced Technologists (CT and PET trained) for the subject handling and imaging procedure,
- Appropriately trained Radiologists/Nuclear Medicine Physicians for image analysis and diagnostic interpretation,

- Appropriately trained image analysts, with oversight by a Radiologist or Nuclear Medicine Physician,
- Medical Physics support to ensure appropriate scanner and equipment calibration,
- Processes that assure imaging QIBA Profile-conformant image generation in appropriate time window

A QA/QC program for PET scanners and ancillary devices must be in place to achieve the goals of the clinical trial. The minimum requirements are specified above. This program shall include (a) elements to verify that imaging facilities are performing imaging studies correctly and (b) elements to verify that facility's PET scanners are performing within specified calibration values. These may involve additional PET and CT phantom testing that address issues relating to both radiation dose and image quality (which may include issues relating to water calibration, uniformity, noise, spatial resolution – in the axial plane-, reconstructed slice thickness z-axis resolution, contrast scale, and others) and constancy. There is agreement that some performance testing (e.g. constancy phantom) adds value; however, acceptable performance levels, frequency of performance, triggers for action and mitigation strategies need further definition before these can be required. This phantom testing may be done in addition to the QA program defined by the device manufacturer as it evaluates performance that is specific to the goals of the clinical trial.

Parameter	**Entity/Actor**	**Specification**
PET Scanner	Acquisition Facility	This Profile shall only address full ring PET scanners that have the capability of acquiring a transmission image for attenuation correction and have a minimum axial FOV of 15 cm for a single bed position.
CT Scanner Calibration	Technologist	Shall perform daily water equivalent phantom analysis; ensure that output is acceptable and manually enter on form /electronic database.
PET Scanner Calibration	Technologist	Shall perform daily/weekly/monthly scanner QA and vendor recommended maintenance procedures (e.g., replace weak transmission sources for dedicated PET scanner); ensure that output values are acceptable and manually enter on form/electronic database
PET Scanner Calibration Constancy Check	Technologist	Shall perform constancy phantom (e.g., Ge-68 cylinder) scan (preferably NIST traceable or equivalent to gather information regarding uniformity as well) at least weekly and after each calibration.
Radionuclide calibrator		Calibrated to 18F using NIST traceable source or equivalent either by site or calibrator manufacturer.

4.2. Performance Assessment: PET Acquisition Device

Distinct from the performance specifications and frequency of testing described in Section 4.1, which apply to quality control of the Acquisition Device at the imaging facility, this Section defines performance specifications of the Acquisition Device to be met upon leaving the manufacturing facility. In order to be in conformance with this Profile, the Acquisition Device should be held to the same standard whether a mobile utility or a fixed installation; a mobile scanner may require additional calibration to achieve this performance.

The PET scanner should use DICOM attributes to follow version numbers of software for: 1 Acquisition, 2 Reconstruction, 3 Post-processing, 4 Display/ROI analysis, 5 Dynamic Analysis. Performance requirements regarding software version identification, documentation and tracking across time are described in Section 4.5.

The PET scan acquisition start time should be used for the decay reference time and the integral model should be used for decay correction. The scanner should perform all decay corrections (i.e. not the operator). Image data are to be given in units Bq/ml. "Derived" images (distinct from "Original") should be flagged following the DICOM standard and should retain the scan acquisition date and time fields.

All needed information for fully corrected administered activity (e.g., residual activity, injection time, calibration time) is required. Note that use of the term <u>administered activity</u> below refers to fully corrected net radioactivity.

Baseline level conformance requires that the DICOM image set from the subject's PET scan and necessary metadata (that is not currently captured by all PET scanner acquisition processes) is captured in trial documentation, e.g., case report forms. The metadata is required to perform the quantitative analysis and perform quality control on SUV covariates. This includes for example, post-injection residual activity and subject height. This data should be captured in the 'Common Data Format Mechanism' as described in Appendix E.

The DICOM format used by the PET scanner should meet the Conformance Statement written by manufacturer of the PET system. PET data shall be encoded in the DICOM PET or Enhanced PET Image Storage SOP Class, and in activity-concentration units (Bq/ml) with additional parameters in public DICOM fields to calculate SUVs (e.g., height, weight, scale factors). CT data should be encoded in CT or Enhanced CT Image Storage SOP Class. DICOM data shall be transferred using the DICOM Part 8 network protocol or as offline DICOM Part 10 files for media storage including CDs and DVDs. They shall be transferred without any form of lossy compression.

The meta-information is the information that is separate, or in addition to, the image values (in units of Bq/ml) that is deemed necessary for quantitatively accurate representation of PET SUVs. The meta-information may also include other information beyond that need for calculation of SUVs, i.e. the type and or sequencing of therapy, the blood glucose levels, the scanner SUV stability history, etc. The actual mechanism of capturing the information is not specified in this Profile. The intent here is to list what information should be captured rather than the mechanism itself. The mechanism can range from paper notes, to scanned forms or electronic data records, to direct entry from the measurement equipment into pre-specified DICOM fields (i.e., from the PET scanner or auxiliary measurement devices such as the radionuclide calibrator). Ideally all of the specified meta-data will be captured by direct electronic entry to DICOM fields, after suitable modification of the DICOM format for PET imaging.

In some facility workflows, the Acquisition Device may also provide workstation/analysis tool functionality. For example, the display of an SUV statistic (considered in Section 4.4.1) or display of Tracer Uptake Time (considered in Section 4.4), may also apply to the Acquisition Device, if used in this manner.

The concept endorsed here is that the needed meta-data is identified. Through revisions of this Profile, the

DICOM standard, and technology the meta-data is inserted into the analysis stream (Figure 3) in a more direct manner and technology and accepted standards evolve.

Parameter	Entity/Actor	Specification
CT calibration tracking	Acquisition Device	Daily water equivalent phantom values shall be tracked in the DICOM header.
PET calibration factor	Acquisition Device	The current SUV calibration factor shall be included in the DICOM header.
PET QA status	Acquisition Device	Date/time and status of system-wide QA checks should be captured separately.
Radionuclide calibrator calibration	Acquisition Device	Calibration factor for an F-18 NIST -traceable (or equivalent) source with identifying information shall be tracked in the DICOM header with Date/Time.
PET Scanner calibration	Acquisition Device	Shall be able to be calibrated according to the following specifications: • Using an ACR type uniform cylinder containing F-18 in water (ideally the same used for dose calibrator cross-calibration) • Using a long scan time of 60 min or more (to minimize noise), and an ACR-type ROI analysis The average measured SUV shall be in the range of 0.98 to 1.02. (Note this is not the performance expected during clinical imaging operation as discussed in preamble to this Section). Slice-to-slice variability shall be no more than ± 5%. (not including end slices, as per ACRPET Core Lab).
		In-plane uniformity for above phantom shall be less than 5 %.
Weight	Acquisition Device	Shall be able to record patient weight in lbs or kg as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Weight field (0010,1030) in the DICOM image header, as per DICOM standard.
		Patient weight shall be specifiable with 4 significant digits. Patient weight shall be transferrable directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Height	Acquisition Device	Shall be able to record patient height in feet/inches or cm/m as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard.

Parameter	Entity/Actor	Specification
		Patient height shall be specifiable with 3 significant digits. Patient height shall be transferrable directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Administered Radionuclide	Acquisition Device	Shall be able to accept the radionuclide type (i.e., F-18) from the DICOM Modality Worklist either from the NM/PET Protocol Context, if present, or by deriving it from the Requested Procedure Code via a locally configurable tables of values. Shall be able to enter the radionuclide type (i.e., F-18) by operator entry into the scanner interface. Shall be recorded in Radionuclide Code Sequence (0054,0300) in the DICOM image header (e.g., (C-111A1, SRT, "^{18}Fluorine")).
		Shall be able to accept the radionuclide type (i.e., F-18) directly from the measurement device (dose calibrator) or management system, using the Sup 159 Radiopharmaceutical Administration Radiation Dose Report bypassing all operator entry, but still permitting operator correction.
Administered Radiotracer	Acquisition Device	Shall be able to record the specific radiotracer as supplied by operator entry into the scanner interface. Shall be recorded in Radionuclide Code Sequence field (0054,0300) in the DICOM image header, e.g., (C-B1031, SRT, "Fluorodeoxyglucose F^{18}").
Administered Radiotracer radioactivity	Acquisition Device	Shall be able to enter the administered radioactivity, in both MBq and mCi, as supplied by operator entry into the scanner interface. Shall be recorded in Radionuclide Total Dose field (0018,1074) in the DICOM image header in Bq.
		Shall be able to record with separate entry fields on scanner interface: (1) the pre-injection 18F-Amyloid tracer radioactivity (2) time of measurement of pre-injection 18F-Amyloid tracer radioactivity (3) the residual activity after injection (4) time of measurement the residual radioactivity after injection Shall automatically calculate the administered radioactivity and store in the Radionuclide Total Dose field (0018,1074) in the DICOM image header. Alternatively, shall be able to receive this information as per DICOM Supplement 159.

Parameter	Entity/Actor	Specification
		Patient Administered Radiotracer radioactivity information shall be transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Administered Radiotracer Time	Acquisition Device	Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072).
		Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078). I.e. not Radiopharmaceutical Start Time field (0018,1072). Shall be able to record the time of the stop of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Stop Date Time field (0018,1079).
Decay Correction Methodology	Acquisition Device	Encoded voxel values with Rescale Slope field (0028,1053) applied shall be decay corrected by the scanner software (not the operator) to a single reference time (regardless of bed position), which is the start time of the first acquisition, which shall be encoded in the Series Time field (0008,0031) for original images. Corrected Image field (0028,0051) shall include the value "DECY" and Decay Correction field (0054,1102) shall be "START", which means that the images are decay corrected to the earliest Acquisition Time (0008, 0032).
Scanning Workflow	Acquisition Device	Shall be able to support Profile Protocol (Section 3) PET and CT order(s) of acquisition. Shall be able to pre-define and save (by imaging site) a Profile acquisition Protocol for patient acquisition.
		Shall be able to interpret previously-reconstructed patient images to regenerate acquisition protocol. Shall be configurable to store (or receive) acquisition parameters as pre-defined protocols (in a proprietary or standard format), to allow re-use of such stored protocols to meet multi-center specifications and to achieve repeatable performance across time points for the same subject.
CT Acquisition Parameters	Acquisition Device	Shall record all key acquisition parameters in the CT image header, using standard DICOM fields. Includes but not limited to: Actual Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation Time, Exposure and Slice Width in the DICOM image header.

Parameter	Entity/Actor	Specification
CT based attenuation correction	Acquisition Device	Shall record information in PET DICOM image header which CT images were used for corrections (attenuation, scatter, etc.).
PET-CT Alignment	Acquisition Device	Shall be able to align PET and CT images within ±2 mm in any direction.
		Shall be able to align PET and CT images within ±2 mm in any direction under maximum load over the co-scan length.
CT Absorbed Radiation Dose	Acquisition Device	Shall record the absorbed dose (CTDI, DLP) in a DICOM Radiation Dose Structured Report.
Activity Concentration in the Reconstructed Images	Acquisition Device	Shall be able to store and record (rescaled) image data in units of Bq/ml and use a value of BQML for Units field (0054,1001).
Tracer Uptake Time	Acquisition Device	Shall be derivable from the difference between the Radiopharmaceutical Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072) and the Series Time field (0008,0031) or earliest Acquisition Time field (0008,0032) in the series (i.e., the start of acquisition at the first bed position), which should be reported as series time field (0008,0031).
PET Voxel size	Acquisition Device	See Section 4.3 (PET Voxel size) under the Reconstruction Software specification requirements.
CT Voxel size	Acquisition Device	Shall be no greater than the reconstructed PET voxel size. Voxels shall be square, although are not required to be isotropic in the Z (head-foot) axis. Not required to be the same as the reconstructed PET voxel size.
Subject Positioning	Acquisition Device	Shall be able to record the subject position in the Patient Orientation Code Sequence field (0054,0410) (whether prone or supine) and Patient Gantry Relationship Code field Sequence (0054,0414) (whether head or feet first).
Scanning Direction	Acquisition Device	Shall be able to record the scanning direction (craniocaudal vs. caudocranial) into an appropriate DICOM field.
Documentation of Exam Specification	Acquisition Device	Shall be able to record and define the x-y axis FOV acquired in Field of View Dimensions (0018,1149) and reconstructed in Reconstruction Diameter (0018,1100).
		Shall be able to define the extent of anatomic coverage based on distance from defined landmark site (e.g., vertex, EAM). (both the landmark location (anatomically) and the distance scanned from

Parameter	Entity/Actor	Specification
		landmark) would require DICOM tags). Shall be able to be reportable for future scanning sessions. The Acquisition Device shall record the z-axis FOV which represents the actual distance of scan anatomic coverage (cm).
Differential Acquisition Time	Acquisition Device	Shall be able to acquire and record non uniform scan times dependent upon areas of clinical concern. Recording can be done through the use of Actual Frame Duration (0018,1242) and Frame Reference Time (0054, 1300).
DICOM Compliance	Acquisition Device	All image data and scan parameters shall be transferable using appropriate DICOM fields according to the DICOM conformance statement for the PET scanner.
DICOM Data transfer and storage format	PET Scanner or Display Workstation	PET images shall be encoded in the DICOM PET or Enhanced PET Image Storage SOP Class, using activity-concentration units (Bq/ml) with additional parameters stored in public DICOM fields to enable calculation of SUVs. PET images shall be transferred and stored without any form of lossy compression.

Parameter	Entity/Actor	Specification
DICOM Editing	Acquisition Device	Shall be able to edit all fields relevant for SUV calculation before image distribution from scanner. Shall provide appropriate warnings if overriding of the current values is initiated.

4.3. Performance Assessment: Reconstruction Software

Reconstruction Software shall propagate the information collected at the prior Subject Handling and Imaging Acquisition stages and extend it with those items noted in the Reconstruction section.

Parameter	Entity/Actor	Specification
Metadata	Reconstruction Software	Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Reconstruction section.

Data can be reconstructed including all corrections needed for quantification as well as without scatter and attenuation correction. Analytical or iterative reconstruction methods should be applied. If the system is capable of providing resolution recovery and/or time of flight, then the decision to ‘turn on’ or ‘turn off’ this /these capabilities should be made prospectively, as dictated by the specific protocol, and should be consistent for a given subject across multiple time points.

Standardization of reconstruction settings is necessary to obtain comparable resolution and SUV recoveries across the same subject and inter-subject across sites.

Parameter	Entity/Actor	Specification
Data Corrections	Reconstruction Software	PET emission data must be able to be corrected for geometrical response and detector efficiency, system dead time, random coincidences, scatter and attenuation.
Reconstruction Methodology	Reconstruction Software	Shall be able to provide iterative and/or analytical (e.g., filtered back projection) reconstruction algorithms.
		Shall be able to indicate, for both TOF and Resolution recovery, if either is being used for purposes of image reconstruction.
Reconstruction Methodology / Output	Reconstruction Software	Shall be able to perform reconstructions with and without attenuation correction.
Data Reconstruction 2D/3D Compatibility	Reconstruction Software	Shall be able to perform reconstruction of data acquired in 3D mode using 3D image reconstruction algorithms. If 3D mode data can be re-binned into 2D mode, shall be able to perform reconstruction of data acquired in 3D mode using 2D image reconstruction algorithms.
Quantitative calibration	Reconstruction software	Shall apply appropriate quantitative calibration factors such that all images have units of activity concentration, e.g., kBq/mL.
Voxel size	Reconstruction software	Shall allow the user to define the image voxel size by adjusting the matrix dimensions and/or diameter of the reconstruction field-of-view.
		Shall be able to reconstruct PET voxels with a size 2.5 mm or less in the transaxial directions and 2.5 mm or less in the axial dimension (as recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices). Pixels shall be square, although voxels are not required to be isotropic in the z (head-foot) axis.
		Shall be able to reconstruct PET voxels with a size of 2 mm or less in all three dimensions (as recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices). Voxels shall be isotropic.
Reconstruction	Reconstruction	Shall allow the user to control image noise and spatial resolution by adjusting reconstruction parameters, e.g., number of iterations, post-

Parameter	Entity/Actor	Specification
parameters	software	reconstruction filters.
		Shall be able to record reconstruction parameters used in image DICOM header using the Enhanced PET IOD, developed by DICOM working group.
Reconstruction protocols	Reconstruction software	Shall allow a set of reconstruction parameters to be saved and automatically applied (without manual intervention) to future studies as needed.

4.4. Performance Assessment: Image Analysis Workstation

Currently, there is no commercially available tool with which image analysis workstation conformance can be assessed. Versions of a Hoffmann brain DRO have been used by some labs to perform some of the necessary tasks, but not all requirements, as defined in this Profile can be assessed with this/these DROs.

A digital reference object (DRO) series of synthetic PET volumes derived from a single patient's MRI scan (also provided) shall be used to evaluate conformance of the image analysis workstation (IAW). Users should use the DRO series (as per the DRO user's guide in Appendix F) to verify correct implementation of VOI placement for both target and reference regions, SUVR calculations, PET alignment to standardized atlases (when applicable), system linearity and system reproducibility.

Parameter	Entity/Actor	Specification
Performance Evaluation	Image Analyst & Analysis Workstation	Shall use the DRO series to verify adequate performance as described in Appendix F and save the results with any study compliant with this Profile.
Repeatability	Image Analysis Workstation	Shall be validated to achieve repeatability with a within-subject CV of less than or equal to 2.6%. See Appendix F.
	Image Analyst	Shall, if operator interaction is required by the Image Analysis Workstation tool to perform measurement, be validated to achieve repeatability with a within-subject CV of less than or equal to 2.6%. See Appendix F.
Linearity	Image Analysis Workstation	Shall be validated to achieve: • slope ($\widehat{A}_1$) between 0.95 and 1.05 • R-squared (R^2) >0.90 See Appendix F.

The post-processing software, which may be integral to the scanner workstation or provide by a third-party vendor, shall have the ability to perform the operations specified in Section 3.3.2, Image Data Post-processing.

Parameter	Entity/Actor	Specification

Parameter	Entity/Actor	Specification
Metadata	Image Post-processing workstation	Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Image Analysis Workstation section.
		Shall be able to display all information that affects SUVRs either directly in calculation (e.g., region of interest intensity) or indirectly (image acquisition parameters).
Image acquisition parameters: Display	Image Post-processing workstation	Shall be capable to display or include link to display the number of minutes between injection and initiation of imaging (as per derivation guidelines described in Section 4.2), and the duration of each timeframe in cases where the image consists of multiple timeframes.

The Image Post-processing workstation will allow for the following operations that may or may not have been performed as part of image reconstruction.

Parameter	Entity/Actor	Specification
Decay correction	Image Post-processing workstation	Shall allow for image decay correction if not performed during reconstruction. Shall use either the Acquisition Time field (0008,0032) or Radiopharmaceutical Start Time (0018,1072), if necessary. If a series (derived or not) is based on Acquisition Time decay correction, the earliest Acquisition Time (0008,0032) shall be used as the reference time for decay correction.
Image orientation	Image Post-processing workstation	Shall allow user to orient image per protocol in x, y, and z directions.
Intra-scan, inter-frame alignment	Image Post-processing workstation	Shall be able to automatically spatially align the different timeframes that may have been acquired
Intra-scan, inter-frame alignment	Image Post-processing workstation	Shall allow selection of an anchor frame to which other frames are aligned
Intra-scan, inter-frame alignment	Image Post-processing workstation	Shall measure and display the translational and rotational parameters necessary to align each frame to the reference frame.
Static image creation	Image Post-processing workstation	Shall allow exclusion of one or more frames from the static image that is created through frame averaging or summation
Static image creation	Image Post-processing workstation	Shall be able to sum and/or average the selected timeframes to create a static image for analysis
Smoothing	Image Post-processing	Shall be able to apply a 3D smoothing filter if indicated as

Parameter	Entity/Actor	Specification
	workstation	part of study protocol
Data storage and transfer	Image Post-processing workstation	Shall be able to store images after each major step of image manipulation (e.g., after frame summation)

The features required of the analysis workstation are dependent in part upon the methods chosen for definition and application of the target and reference regions of interest to the PET scan. Certain additional features such as kinetic modeling for full dynamic scans, partial volume correction, and MRI segmentation to create regions of interest may also be relevant per study protocol, but their description is beyond the scope of this document.

Parameter	Entity/Actor	Specification
Image Quality control: Visual inspection	Image Analysis workstation	Shall be able to display each image in a manner such that all image slices in the transaxial, sagittal, and coronal views may be examined visually.
Spatial mapping: Image fusion (co-registration)	Image Analysis workstation	Shall be able to automatically and accurately spatially align the PET image with the subject's MRI scan in cases where this approach is implemented.
Spatial mapping: Co-registration between visits	Image Analysis workstation	Shall be able to automatically and accurately spatially align multiple PET visits to one another when this approach is implemented.
Spatial Mapping: warp to template	Image Analysis workstation	Shall be able to automatically and accurately spatially map the subject's scan and template to each other when this approach is implemented.
Target and reference region definition	Image Analysis workstation	Shall provide either the means for defining target and reference region of interest boundaries to be applied to the subject scan, or for importing pre-defined region of interest boundaries (or masks) that may have been generated using other software (such as generated through segmentation of subject's MRI or pre-defined based upon an image template and atlas).
SUVR image creation	Image Analysis workstation	Shall be able to create an SUVR image by dividing each voxel by the average value within a selected reference region, if this option is implemented.
Region placement	Image Analysis workstation	Shall be able to apply (place for measurement) pre-specified regions of interest onto the PET scan in an anatomically accurate manner.

Parameter	Entity/Actor	Specification
Region placement quality control	Image Analysis workstation	Shall allow means for quality assurance that regions for measurement have been accurately placed on the PET scan (either by final region placement inspection and/or inspection and/or automatic quality measurements performed at each image manipulation step)
Region of interest measurement	Image Analysis workstation	Shall be able to calculate the mean value within each region of interest, and store for SUVR calculations (if not based on an SUVR image) and/or reporting.
SUVR calculation	Image Analysis workstation	Shall be able to calculate SUVR values by dividing the mean value in a target region by the mean value in the reference region (if not based on an SUVR image).
SUVR output	Image Analysis workstation	Shall be able to store and output SUVR values for display and for transfer to a study report, to a precision as required by the study protocol.

4.5. Performance Assessment: Software version tracking

Ideally, the PET scanner should be able to build a list on the console of the dates of all software versions (software changes that might impact quantitative accuracy would typically be inclusive of hardware change). Furthermore, the scanner software version should be identified and tracked across time, with updates and changes in scanner software noted during the trial. At a minimum, Software Versions should be manually recorded during the qualification along with the phantom imaging performance data and the record should be updated for every software-upgrade over the duration of the trial. This includes the flagging of the impact on quantification for now; in the future, record all software version numbers in DICOM header.

Parameter	Entity/Actor	Specification
Software Version tracking	Acquisition Device	Shall record the software version(s) used for acquisition and reconstruction in appropriate DICOM field(s).
Software version back-testing compatibility	Workstation	Shall provide mechanism to provide analysis of the image data using updated as well as prior (platform-specific) versions of analysis software.

References

Test-Retest Papers & Methodology

1. Clinical Validation of 18F-AZD4694, an Amyloid-b–Specific PET Radioligand, Zsolt Csele´nyi, Maria Eriksdotter Jo¨nhagen, Anton Forsberg, Christer Halldin, Per Julin, Magnus Schou, Peter Johnstro¨m, Katarina Varna¨s, Samuel Svensson, and Lars Farde, J Nucl Med 2012; 53:415–424, DOI: 10.2967/jnumed.111.094029.

2. Performance Characteristics of Amyloid PET with Florbetapir F 18 in Patients with Alzheimer's Disease

and Cognitively Normal Subjects, Abhinay D. Joshi, Michael J. Pontecorvo, Chrisopher M. Clark, Alan P. Carpenter, Danna L. Jennings, Carl H. Sadowsky, Lee P. Adler, Karel D. Kovnat, John P. Seibyl, Anupa Arora, Krishnendu Saha, Jason D. Burns, Mark J. Lowrey, MarkA.Mintun, Daniel M. Skovronsky, and the Florbetapir F 18 Study Investigators, J Nucl Med 2012; 53:378–384, DOI: 10.2967/jnumed.111.090340.

3. 18F-Flutemetamol Amyloid Imaging in Alzheimer Disease and Mild Cognitive Impairment A Phase 2 Trial, Rik Vandenberghe, MD, PhD, Koen Van Laere, MD, PhD, Adrian Ivanoiu, MD, PhD, Eric Salmon, MD, PhD, Christine Bastin, PhD, Eric Triau, MD, Steen Hasselbalch, MD, DMSc, Ian Law, MD, PhD, Allan Andersen, MD, Alex Korner, MD, PhD, Lennart Minthon, MD, Gae¨ tan Garraux, MD, PhD, Natalie Nelissen, PhD, Guy Bormans, PhD, Chris Buckley, MD, Rikard Owenius, Lennart Thurfje, Gill Farrar, PhD, and David J. Brooks, MD, DSc, FRCP, ANN NEUROL 2010;68:319–329, DOI: 10.1002/ana.22068. Eur J Nucl Med Mol Imaging (2009) 36:1629–1638, DOI 10.1007/s00259-009-1129-6.

4. Test-retest variability of quantitative [11C] PIB studies in Alzheimer’s disease. Nelleke Tolboom, Maqsood Yaqub, Ronald Boellaard, Gert Luurtsema, Albert D. Windhorst, Philip Scheltens, Adriaan A. Lammertsma, Bart N. M. van Berckel.

5. Longitudinal Assessment of Aß and Cognition in Aging and Alzheimer Disease, Victor L. Villemagne, Kerryn E. Pike, Gaël Chételat, Kathryn A. Ellis, Rachel S. Mulligan, Pierrick Bourgeat, Uwe Ackermann, Gareth Jones, Cassandra Szoeke, Olivier Salvado, Ralph Martins, Graeme O’Keefe, Chester A. Mathis, William E. Klunk, David Ames, Colin L. Masters, and Christopher C. Rowe. Ann Neurol. 2011 January ; 69(1): 181–192. doi:10.1002/ana.22248.

6. Amyloid Imaging with 18F-Florbetaben in Alzheimer Disease and Other Dementias, Victor L. Villemagne, Kevin Ong, Rachel S. Mulligan, Gerhard Holl, Svetlana Pejoska, Gareth Jones, Graeme O’Keefe, Uwe Ackerman, Henri Tochon-Danguy, J. Gordon Chan, Cornelia B. Reininger, Lueder Fels, Barbara Putz, Beate Rohde, Colin L. Masters, and Christopher C. Rowe. J Nucl Med 2011; 52:1210–1217, DOI: 10.2967/jnumed.111.089730

7. Test-retest variability of high and low SA [18F] BAY 94-9172 in Alzheimer's disease and normal ageing. C. C. Rowe, S. Pejoska, R. Mulligan, G. Chan, L. Fels, H. Kusi,2 C. Reininger,2 B. Rohde,2 B. Putz, V. L. Villemagne. Poster presented at the Society of Nuclear Medicine Meeting, Salt Lake City, UT, 2009.

Centiloid Papers

1. THE CENTILOID SCALE: STANDARDIZATION OF AMYLOID IMAGING MEASURES, Christopher Rowe, William Klunk, Robert Koeppe, William Jagust, Michael Pontecorvo, Michael Devous, Marybeth Howlett, Daniel Skovronsky, Keith Johnson, Julie Price, Chet Mathis, Mark Mintun, Alzheimer's & Dementia: The Journal of the Alzheimer's Association Volume 9, Issue 4, Supplement , Page P8, July 2013, doi:10.1016/j.jalz.2013.04.026.

Non-imaging DX Tests

1. Plasma phospholipids identify antecedent memory impairment in older adults, Mark Mapstone, Amrita K Cheema, Massimo S Fiandaca, Xiaogang Zhong, Timothy R Mhyre, Linda H MacArthur, William J Hall, Susan G Fisher, Derick R Peterson, James M Haley, Michael D Nazar, Steven A Rich, Dan J Berlau, Carrie B Peltz, Ming T Tan, Claudia H Kawas & Howard J Federoff, Nature Medicine advance online publication, March 2014, doi:10.1038/nm.3466.

List of Medicines in Development for Alzheimer's Disease

1. Medicines in Development Alzheimer’s Disease presented by America’s Biopharmaceutical Research

Companies (PhRMA), 2013 Report, http://www.phrma.org/sites/default/files/Alzheimer's%202013.pdf.

ADNI References (http://www.adni-info.org/scientists/ADNIStudyProcedures.aspx)

1. ADNI II Procedures Manual- http://www.adni-info.org/Scientists/Pdfs/adniproceduresmanual12.pdf

2. ADNI Protocol - http://www.adni-info.org/Scientists/Pdfs/ADNI2_Protocol_FINAL_20100917.pdf

3. Review Articles - The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans Michael W. Weiner, Paul S. Aisen, Clifford R. Jack, Jr., William J. Jagust, John Q. Trojanowski, Leslie Shaw, Andrew J. Saykin, John C. Morris, Nigel Cairns,Laurel A. Beckett, Arthur Toga, Robert Green, Sarah Walter, Holly Soares, Peter Snyder,Eric Siemers, William Potter, Patricia E. Cole, Mark Schmidt; and the Alzheimer's Disease Neuroimaging Initiative Alzheimer's & Dementia 6 (2010) 202–211

Amyloid PET: Clinical

1. Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Keith A. Johnson, Satoshi Minoshima, Nicolaas I. Bohnen, Kevin J. Donohoe, Norman L. Foster, Peter Herscovitch, Jason H. Karlawish, Christopher C. Rowe, Maria C. Carrillo, Dean M. Hartley, Saima Hedrick, Virginia Pappas, William H. Thies

2. Update on Appropriate Use Criteria for Amyloid PET Imaging: Dementia Experts, Mild Cognitive Impairment, and Education. Keith A. Johnson, Satoshi Minoshima, Nicolaas I. Bohnen, Kevin J. Donohoe, Norman L. Foster, Peter Herscovitch, Jason H. Karlawish, Christopher C. Rowe, Saima Hedrick, Virginia Pappas, Maria C. Carrillo, and Dean M. Hartley, J Nucl Med 2013; 54:1011–1013, DOI: 10.2967/jnumed.113.127068.

3. Pending journal permission: Schmidt ME et al, Manuscript regarding Approaches to Reduce Variability in Amyloid Imaging – this manuscript will contain a list of references, all of which could be applicable

4. Book chapter: Schmidt ME, Matthews D, Andrews R, Mosconi L. Positron Emission Tomography in Alzheimer Disease: Diagnosis and Use ad Biomarker Endpoints. Chapter 5, p. 131-194. Translational Neuroimaging – Tools for CNS Drug Discovery, Development, and Treatment, McArthur RA editor, 2013, Academic Press. This, too, contains a comprehensive list of references.

5. Analysis method paper: Lundqvist R, Lilja J, Thomas BA, Lötjönen J, Villemagne VL, Rowe CC, Thurfjell L. Implementation and validation of an adaptive template registration method for 18F-flutemetamol imaging data. J Nucl Med. 2013 Aug;54(8):1472-8. There are several additional papers that pertain to PiB also, by the Klunk/Price group at Pittsburgh.

6. Scanner quality control: Makris NE, Huisman MC, Kinahan PE, Lammertsma AA, Boellaard R. Evaluation of strategies towards harmonization of FDG PET/CT studies in multicentre trials: comparison of scanner validation phantoms and data analysis procedures. Eur J Nucl Med Mol Imaging. 2013 Oct;40(10):1507-15.

Amyloid PET: Quantitative Dynamic Imaging and Methodology

1. Hiroshi Ito, Hitoshi Shimada, Hitoshi Shinotoh, Harumasa Takano, Takeshi Sasaki, Tsuyoshi Nogami, Masayuki Suzuki, Tomohisa Nagashima, Keisuke Takahata, Chie Seki, Fumitoshi Kodaka, Yoko Eguchi, Hironobu Fujiwara, Yasuyuki Kimura, Shigeki Hirano, Yoko Ikoma, Makoto Higuchi, Kazunori Kawamura, Toshimitsu Fukumura, Éva Lindström Böö, Lars Farde and Tetsuya Suhara. Quantitative Analysis of Amyloid Deposition in Alzheimer Disease Using PET and the Radiotracer 11C-AZD2184, Published online: April 14, 2014.J Nucl Med., Doi: 10.2967/jnumed.113.133793

2. Longitudinal Amyloid Imaging Using 11C-PiB: Methodologic Considerations. Bart N.M. van Berckel, Rik

Ossenkoppele, Nelleke Tolboom, Maqsood Yaqub, Jessica C. Foster-Dingley, Albert D. Windhorst, Philip Scheltens, Adriaan A. Lammertsma, and Ronald Boellaard. J Nucl Med 2013; 54:1570–1576, DOI: 10.2967/jnumed.112.113654.

3. Amyloid-B Imaging with Pittsburgh Compound B and Florbetapir: Comparing Radiotracers and Quantification Methods Susan M. Landau1–3, Christopher Breault3, Abhinay D. Joshi3, Michael Pontecorvo3, Chester A. Mathis4, William J. Jagust1,2,5, and Mark A. Mintun3, for the Alzheimer's Disease Neuroimaging Initiative

4. PET Quantification of 18F-Florbetaben Binding to b-Amyloid Deposits in Human Brains. Georg A. Becker, Masanori Ichise, Henryk Barthel, Julia Luthardt, Marianne Patt, Anita Seese, Marcus Schultze-Mosgau, Beate Rohde, Hermann-Josef Gertz, Cornelia Reininger, and Osama Sabri. J Nucl Med 2013; 54:723–731, DOI: 10.2967/jnumed.112.107185.

5. Automated Quantification of 18F-Flutemetamol PET Activity for Categorizing Scans as Negative or Positive for Brain Amyloid: Concordance with Visual Image Reads. Lennart Thurfjell, Johan Lilja, Roger Lundqvist, Chris Buckley, Adrian Smith, Rik Vandenberghe and Paul Sherwin. J Nucl Med 2014; 55:1623-1628.

6. Accuracy of CT-based attenuation correction in PET/CT bone imaging. M. Abella, A. M. Alessio, D. A. Mankoff, L. R. Macdonald, J. J. Vaquero, M. Desco, and P. E. Kinahan. Phys. Med. Biol May 2012; 57:9,. 2477–2490.

Package Inserts

1. Amyvid [package insert]. 2012. Available at: http://pi.lilly.com/us/amyvid-uspi.pdf. Accessed June 11, 2013.
2. Vizamyl [package insert]. 2013. Available at: http://www3.gehealthcare.com/en/Products/Categories/~/media/Downloads/us/Product/Product-Categories/Nuclear-Imaging-Agents_Non-Gatekeeper/Vizamyl/GEHealthcare-Vizamyl-Prescribing-Information.pdf. Accessed May 5, 2014.
3. Neuraceq [package insert]. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf. Accessed May 5, 2014.

Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Nuclear Medicine Coordinating Committee. The Amyloid PET Biomarker Committee, a subcommittee of the Nuclear Medicine Coordinating Committee, is composed of physicians, scientists, engineers and statisticians representing the imaging device manufacturers, image analysis software developers, image analysis facilities and laboratories, biopharmaceutical companies, academic institutions, government research organizations, professional societies, and regulatory agencies, among others. A more detailed description of the QIBA Amyloid-PET Biomarker Committee and its work can be found at the following web link: *http://qibawiki.rsna.org/index.php/PET_Amyloid_Biomarker_Ctte*

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Appendix B: Background Information for Claim

Meta-analysis was performed as a groundwork project to determine the repeatability of amyloid PET imaging with ^{11}C-Pittsburgh Compound-B (^{11}C-PIB) and ^{18} Fluorine labeled radiotracers using the available literature. A total of 7 studies were included in this meta-analysis. Four studies evaluated the test-retest variability of ^{18} Fluorine labeled amyloid tracers (Florbetapir, AZD4694, Flutemetamol, Florbetaben). The test-retest amyloid PET studies were performed between 1 to 4 weeks apart. The pooled %RC for average cortical SUVR in patients with AD (n=26) was 10.36% (95% CI= 4.76-14.92). The pooled mean %RC for average cortical SUVR in HCs (n=22) was 10.41 (95% CI= 3.33-20.3). Three studies evaluated the test-retest variability of ^{11}C-PIB amyloid imaging. The test-retest amyloid PET studies were performed on the same day and up to 60 days apart. The pooled mean %RC for average cortical SUVR was 15.4% (95% CI= 8.49-20.05). The pooled mean %RC for average cortical SUVR in HCs (n=16) was 9.38% (95% CI= 7.55-10.92).

Appendix C: Conventions and Definitions

Convention Used to Represent Profile requirements

Requirements for adhering to this Profile are presented in tables/boxes as shown in the example below. Shaded boxes are intended future requirements, and are not at this time required for adhering to the Profile.

Illustrative example:

Parameter	Entity/Actor	Normative text: Clear boxes are current requirements Shaded boxes are intended for future requirements
Phantom tests: transaxial uniformity measurement	Imaging Site	Using ACR, uniform cylinder phantom or equivalent shall obtain an SUV for a large central ROI of 1.0 with an acceptable range of 0.9 to 1.1.
		Using ACR or uniform cylinder phantom or equivalent shall obtain an SUV for a large central ROI of 1.0 with an acceptable range of 0.95 to 1.05.

Items within tables are normative (i.e. required to be conformant with the QIBA Profile). The intent of the normative text is to be prescriptive and detailed to facilitate implementation. In general, the intent is to specify the final state or output, and not how that is to be achieved.

All other text outside of these tables is considered informative only.

Definitions

3D	Three-dimensional
11C	Carbon-11, an isotope of carbon
18F	Flourine-18, an isotope of fluorine
AB	Amyloid-B
AC	Attenuation Correction. Attenuation is an effect that occurs when photons emitted by the radiotracer inside the body are absorbed by intervening tissue. The result is that structures deep in the body are reconstructed as having falsely low (or even negative) tracer uptake. Contemporary PET/CT scanners estimate attenuation using integrated x-ray CT equipment. While attenuation-corrected images are generally faithful representations of radiotracer distribution, the correction process is itself susceptible to significant artifacts.
Accreditation	Approval by an independent body or group for broad clinical usage (requires ongoing QA/QC) e.g. ACR, IAC, TJC.
AD	Alzheimer’s Disease
ALARA	As Low As Reasonably Achievable
BBB	Blood Brain Barrier
BP_{ND}	Binding Potential. BP_{ND} is the ratio of the density of available receptors to the affinity of the tracer for the receptor, corrected for the free fraction of ligand in the non-displaceable compartment.
CLIA	Clinical Laboratory Improvement Amendments: Accreditation system for establishing quality standards for laboratory testing.
Co-57	Cobalt-57, an isotope of cobalt
Conformance	Meeting the list of requirements described in this document, which are necessary to meet the measurement claims for this QIBA Profile.
CRF	Case Report Form (CRF) is a paper or electronic questionnaire specifically used in clinical trial research. The CRF is used by the sponsor of the clinical trial (or designated CRO etc.) to collect data from each participating site. All data on each patient participating in a clinical trial are held and/or documented in the CRF, including adverse events.
CRO	Contract Research Organization. A commercial or not-for-profit organization designated to perform a centralized and standardized collection, analysis, and/or review of the data generated during a clinical trial. Additional activities which may be performed by an imaging core lab include training and qualification of imaging centers for the specific imaging required in a clinical trial, development of imaging acquisition manuals, development of independent imaging review charters, centralized

	collection and archiving of images received from study sites, performing pre-specified quality control checks/tests on incoming images and development and implementation of quality assurance processes and procedures to ensure that images submitted are in accord with imaging time points specified in the study protocol and consistent with the quality required to allow the protocol-specified analysis /assessments
Cs-137	Cesium-137, an isotope of Cesium
CSF	Cerebrospinal fluid
CT	X-ray computed tomography (CT) is a medical imaging technique that utilizes X-rays to produce tomographic images of the relative x-ray absorption, which is closely linked to tissue density.
CTDI	Computed tomography dose index
DICOM	Digital Imaging and Communications in Medicine (DICOM) is a set of standards for medical images and related information. It defines formats for medical images that can be exchanged in a manner that preserves the data and quality necessary for clinical use.
DLP	Dose length product
Dose	Can refer to either radiation dose or as a jargon term for 'total radioactivity'. For example, 10 mCi of 18F-FDG is often referred to as a 10 mCi dose.
DRO	Digital Reference Object
DVR	Distribution Volume Ratio
FDG	Fluorodeoxyglucose
FWHM	Full width at half maximum
HIPAA	Health Insurance Portability and Accountability Act
IAC	The Intersocietal Accreditation Commission (IAC) provides accreditation programs for Vascular Testing, Echocardiography, Nuclear/PET, MRI, CT/Dental, Carotid Stenting and Vein Center.
IAEA	International Atomic Energy Agency
IOD	Information Object Definition
kBq	Kilobecquerel
kVp	Peak kilovoltage
LBM	Lean Body Mass is calculated by subtracting body fat weight from total body weight. The Lean body mass (LBM) has been described as an index superior to total body weight for prescribing proper levels of medications and for assessing metabolic disorders.
mAs	Milliampere-seconds
MBq	Megabequerel. An SI-derived unit of radioactivity defined as 1.0 × 10^6 decays per second.
MCI	Mild Cognitive Impairment
mCi	millicuries. A non-SI unit of radioactivity, defined as 1 mCi = 3.7 × 10^7 decays per second. Clinical FDG-PET studies inject (typically) 5 to 15 mCi of 18F-FDG.
mpi	minutes post injection
MRI	Magnetic Resonance Imaging
NA	North America
NTP	Network Time Protocol
PACS	Picture archiving and communication system
PiB	Pittsburgh compound B, a radioactive analog of thioflavin T.
PET	Positron emission tomography (PET) is a tomographic imaging technique that produces an image of the in vivo distribution of a radiotracer, typically FDG.
PET/CT	Positron emission tomography / computed tomography (PET/CT) is a medical imaging system that combines in a single gantry system both Positron Emission Tomography (PET) and an x-ray Computed Tomography (CT) scanners, so that images acquired from both devices can be taken nearly-simultaneously.

PSF	Point Spread Function
PVEc	Partial Volume Effects Correction
QA	Quality Assurance. Proactive definition of the process or procedures for task performance. The maintenance of a desired level of quality in a service or product, esp. by means of attention to every stage of the process of delivery or production.
QC	Quality Control. Specific tests performed to ensure target requirements of a QA program are met. Typically, this is done by testing a sample of the output against the specification.
QIBA	Quantitative Imaging Biomarkers Alliance. The Quantitative Imaging Biomarkers Alliance (QIBA) was organized by RSNA in 2007 to unite researchers, healthcare professionals and industry stakeholders in the advancement of quantitative imaging and the use of biomarkers in clinical trials and practice.
Qualification	Approved by an independent body or group for either general participation in clinical research (ACRIN-CQIE, SNM-CTN others) or for a specific clinical trial (requires ongoing QA/QC). This includes CROs, ACRIN, SNM-CTN, CALGB and other core laboratories.
ROI	Region of interest. A region in an image that is specified in some manner, typically with user-controlled graphical elements that can be either 2D areas or 3D volumes. These elements include, but not limited to, ellipses, ellipsoids, rectangles, rectangular volumes, circles, cylinders, polygons, and free-form shapes. An ROI can also be defined by a segmentation algorithm that operates on the image. Segmentation algorithms include, but are not limited to, fixed-value thresholding, fixed-percentage thresholding, gradient edge detection, and Bayesian methods. With the definition of an ROI, metrics are then calculated for the portion of the image within the ROI. These metrics can include, but are not limited to, mean, maximum, standard deviation, and volume or area. Note that the term ROI can refer to a 2D area on a single image slice or a 3D volume. In some cases, the term ROI is used to refer to 2D area and the term volume of interest (VOI) is used to refer to a 3D volume. In this Profile, the term ROI is used to refer to both 2D areas and 3D volumes as needed.
SUV	Standardized Uptake Value. A measure of relative radiotracer uptake within the body. Typically defined for a time point t as
SUVmax	The maximum SUV within the ROI.
SUVmean	The average SUV within the ROI.
SUVpeak	The average SUV within a fixed-sized ROI, typically a 1 cm diameter sphere. The spheres location is adjusted such that the average SUV is maximized.
Tc-99m	Technetium-99m, an isotope of technetium
TOF	Time of Flight (TOF) is a PET imaging technique utilizing differential annihilation photon travel times to more accurately localize the in vivo distribution of a radiotracer.
USP	United States Pharmacopeial Convention establishes written and physical (reference) standards for medicines, food ingredients, dietary supplement products and ingredients in the U.S.
VOI	Volume of Interest

Organizations

AAPM	The American Association of Physicists in Medicine is a member society concerned with the topics of medical physics, radiation oncology, imaging physics. The AAPM is a scientific, educational, and professional organization of 8156 medical physicists.
ABNM	American Board of Nuclear Medicine
ABR	The American Board of Radiology

ABSNM	Nuclear Medicine Physics by the American Board of Science in Nuclear Medicine
ACR	The 36,000 members of |include radiologists, radiation oncologists, medical physicists, interventional radiologists, nuclear medicine physicians and allied health professionals.
ACRIN	The American College of Radiology Imaging Network (ACRIN) is a program of the American College of Radiology and a National Cancer Institute cooperative group. Focused on cancer-related research in clinical trials.
ANSI	American National Standards Institute
CQIE	The Centers of Quantitative Imaging Excellence (CQIE) program was developed by ACRIN in response to a solicitation for proposals issued in December 2009 by SAIC-Frederick on behalf of the National Cancer Institute (NCI). The primary objective of the CQIE Program is to establish a resource of 'trial ready' sites within the NCI Cancer Centers Program that are capable of conducting clinical trials in which there is an integral molecular and/or functional advanced imaging endpoint.
CRO	Contract Research Organization. A commercial or not-for-profit organization designated to perform a centralized and standardized collection, analysis, and/or review of the data generated during a clinical trial. Additional activities which may be performed by an imaging core lab include training and qualification of imaging centers for the specific imaging required in a clinical trial, development of imaging acquisition manuals, development of independent imaging review charters, centralized collection and archiving of images received from study sites, performing pre-specified quality control checks/tests on incoming images and development and implementation of quality assurance processes and procedures to ensure that images submitted are in accord with imaging time points specified in the study protocol and consistent with the quality required to allow the protocol-specified analysis /assessments
CTN	The Clinical Trials Network (CTN) was formed by SNMMI in 2008 to facilitate the effective use of molecular imaging biomarkers in clinical trials.
EANM	The European Association of Nuclear Medicine (EANM) constitutes the European umbrella organization of nuclear medicine in Europe
EARL	EANM Research Ltd (EARL) was formed by EANM in 2006 to promote multicenter nuclear medicine and research.
ECOG-ACRIN	A National Cancer Institute cooperative group formed from the 2012 merger of the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN).
EMA	European Medicines Agency is a European Union agency for the evaluation of medicinal products. Roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization.
EU	European Union
FDA	Food and Drug Administration is responsible for protecting and promoting public health in the U.S. through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, and veterinary products.
HIPAA	Health Insurance Portability and Accountability Act
IAC	The Intersocietal Accreditation Commission (IAC) provides accreditation programs for Vascular Testing, Echocardiography, Nuclear/PET, MRI, CT/Dental, Carotid Stenting and Vein Center.
IAEA	International Atomic Energy Agency
MITA	The Medical Imaging & Technology Alliance is a division NEMA that develops and promotes standards for medical imaging and radiation therapy equipment. These standards are voluntary guidelines that establish commonly accepted methods of design, production, testing and communication for imaging and cancer treatment products.

NEMA	National Electrical Manufacturers Association is a forum for the development of technical standards by electrical equipment manufacturers.
NIST	National Institute of Standards and Technology is a measurement standards laboratory which is a non-regulatory agency of the United States Department of Commerce.
QIBA	Quantitative Imaging Biomarkers Alliance. The Quantitative Imaging Biomarkers Alliance (QIBA) was organized by RSNA in 2007 to unite researchers, healthcare professionals and industry stakeholders in the advancement of quantitative imaging and the use of biomarkers in clinical trials and practice.
RSNA	Radiological Society of North America (RSNA). A professional medical imaging society with more than 47,000 members, including radiologists, radiation oncologists, medical physicists and allied scientists. The RSNA hosts the world's largest annual medical meeting.
SNMMI	Society of Nuclear Medicine and Molecular Imaging (formerly called the Society of Nuclear Medicine (SNM)). A nonprofit scientific and professional organization that promotes the science, technology and practical application of nuclear medicine and molecular imaging. SNMMI represents 18,000 nuclear and molecular imaging professionals worldwide. Members include physicians, technologists, physicists, pharmacists, scientists, laboratory professionals and more
TJC	The Joint Commission (TJC) accredits and certifies health care organizations and programs in the United States.
UPICT	Uniform Protocols for Imaging in Clinical Trials (UPICT). An RSNA-QIBA initiative that seeks to provide a library of annotated protocols that support clinical trials within institutions, cooperative groups, and trials consortia. The UPICT protocols are based on consensus standards that meet a minimum set of criteria to ensure imaging data quality.

Appendix D: Model-specific Instructions and Parameters

The presence of specific product models/versions in the following tables should not be taken to imply that those products are fully in conformance with the QIBA Profile. Conformance with a Profile involves meeting a variety of requirements of which operating by these parameters is just one. To determine if a product (and a specific model/version of that product) is conformant, please refer to the QIBA Conformance Document for that product.

D.1. Image Acquisition Parameters

The following technique tables list acquisition parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 3.6.4 ('Phantom Imaging').

These technique tables may have been prepared by the submitter of this imaging protocol document, the clinical trial organizer, the vendor of the equipment, and/or some other source. (Consequently, a given model/version may appear in more than one table.) The source is listed at the top of each table.

Sites using models listed here are encouraged to consider using these parameters for both simplicity and consistency. Sites using models not listed here may be able to devise their own acquisition parameters that result in data meeting the requirements of Section 3.6.4 and conform to the considerations in Section 4. In some cases, parameter sets may be available as an electronic file for direct implementation on the imaging platform.

D.2. Quality Assurance Procedures

Examples of recommend quality assurance procedures are shown for specific GE, Philips, and Siemens PET/CT scanners in the tables below.

QC procedures and schedules for Philips Gemini TF, V3.3 and V3.4			
Device	**QA Procedure**		**Frequency**
CT	Tube Calibration		Daily
	Air Calibration		Daily
	Noise. On head phantom		Daily
	Noise and Artifacts. On body phantom		Daily
	Contrast scale and artifacts		Monthly
	Impulse Response		Advanced test as needed
	Slice thickness		Advanced test as needed
PET	Daily PET CT	System Initialization	Daily
		Baseline collection (analog offsets of all photomultiplier channels)	Daily
		PMT gain calibration	Daily
		Energy test and analysis	Daily
		Timing test	Daily
		Emission sinogram collection and analysis	Daily
	AutoQC	Automated System Initialization	Daily, prescheduled to shorten daily QC
		Automated Baseline collection	Daily, prescheduled to shorten daily QC
	Uniformity check		Monthly
	SUV calibration		Every 6 months, after recalibration, when SUV validation shows discrepancy
	SUV validation		Every 2 months, when PM is performed

QA procedures and schedules for GE Discovery ST, STE, Rx and Discovery 600/700 series PET/CT systems			
Device	**QA Procedure**		**Frequency**
Computers	System reboot		Daily or as needed
CT	CT tube warm up		Daily or after 2 hours of inactivity
	Air calibrations (fast cals)		Daily
	Generator calibrations		Daily
	CT QA phantom	Contrast Scale	Acquire scans daily
		High Contrast Spatial Resolution	Acquire scans daily
		Low Contrast Detectability	Acquire scans daily
		Noise and Uniformity	Acquire scans daily
		Slice Thickness	Acquire scans daily
		Laser Light Accuracy	Acquire scans daily
	Full system calibration		Performed after tube replacement or as PM
PET	PET Daily Quality Assurance (DQA)	Coincidence	Daily
		PET coincidence mean	Daily
		PET coincidence variance	Daily
		Singles	Daily
		PET singles mean	Daily
		PET singles variance	Daily
		Deadtime	Daily
		PET mean deadtime	Daily
		Timing	Daily
		PET timing mean	Daily
		Energy	Daily
		PET energy shift	Daily
	PET singles update gain		Weekly
	Clean database		Weekly
	PET 2D normalization		Quarterly (if appropriate for the system)
	PET 2D well counter correction		Quarterly (if appropriate for the system)
	PET 3D normalization and well counter correction		Quarterly
	Establish new DQA baseline		Quarterly
	Ge-68 source pin replacement		Every 18 months

QA procedures and schedules for Siemens Biograph 6/16 Hi-Rez, Biograph 16 Truepoint, Biograph 16 Truepoint with TrueV, PET Syngo 2010A, Biograph mCT

Device	QA Procedure		Frequency
Computers	Restart computers		Daily at Startup
	Clear scheduler		Daily
	Clear network, local, and film queues		Four times daily
	Archive patient data		Daily
	System cleanup/defragmentation		Weekly
CT	CT Checkup/Calibration		Daily, after 60 minutes of full load, within 1 hour of patient scan
	CT Quality	Water HU	Daily
		Pixel noise	Daily
		Tube voltages	Daily
PET	PET Daily QC	Daily normalization	Daily
		Computation/ verification of the PET calibration factor (ECF)	Daily
		Normalization results display and sinogram inspection	Daily
		System quality report	Daily
		Partial detector setup: generate crystal region maps/energy profiles	Weekly
		Full detector setup and time alignment	Quarterly

Appendix E: Data fields to be recorded in the Common Data Format Mechanism

The list below comprises meta-information (i.e. in addition to image values of kBq/ml) that is necessary for quantitatively accurate (i.e. known and minimal uncertainties) of PET SUVs. The intent here is to list what information should be captured rather than the mechanism itself. The format and corresponding mechanism of data capture/presentation is currently unspecified, but ranges from paper notes, to scanned forms or electronic data records, to direct entry from the measurement equipment (i.e. the PET/CT scanner or auxiliary measurement devices such as the radionuclide calibrator) into pre-specified DICOM fields. Ideally all the specified meta-data will be captured by direct electronic entry to DICOM fields, after suitable modification of the DICOM format for PET imaging.

The concept endorsed here is that the needed meta-data is identified. Through revisions of this Profile, the DICOM standard, and technology the meta-data is inserted into the analysis stream (Figure 3) in a more direct manner and technology and accepted standards evolve.

- The needed information, where feasible, is listed in order from least frequently changing to most frequently changing.
- In all cases note whether measurements are made directly or estimated. If the latter case, note the source of information and the date and time (e.g. if subject cannot be moved from bed to measure weight or height).

Data fields to be recorded:

1. Site specific
    a. Site information (include name and/or other identifiers)
    b. Scanner make and model
    c. Hardware Version numbers
    d. Software Version numbers
    e. Confirmation that scanner used was previously qualified (or not)
2. Protocol specific

a. PET
    i. Duration per bed
    ii. Acquisition mode (3D)
    iii. Reconstruction method
b. CT technique (if PET/CT scan)

3. Scanner specific QA/QC
    a. Most recent calibration factors (scanner)
    b. Scanner daily check values
    c. most recent clock check
    d. most recent scanner QA/QC
4. Subject exam specific
    a. Weight (optional)
    b. Pre- and post-injection assayed activities and times of assay
    c. Injection time
    d. Site of injection (and assessment of infiltration)
    e. Net injected activity (calculated including decay correction)
    f. Uptake time

Appendix F: Testing PET Display and Analysis Systems with the UW-PET QIBA Amyloid Digital Reference Object (DRO) Series

The University of Washington-PET QIBA PET Amyloid DRO series is a synthetically generated set of DICOM image files of known voxel values for PET. The PET data were derived from a single subject's MRI scan (provided with the DRO series). The UW-PET QIBA DRO series is intended to test the computation of standardized uptake value ratios (SUVRs) by PET amyloid image analysis workstations (IAWs). This is motivated by vendor-specific variations in PET amyloid IAWs. The development of the UW-PET QIBA DRO series is supported by the Quantitative Imaging Biomarker Alliance (QIBA) and the University of Washington.

The primary goals and objectives of the UW-PET QIBA DRO series are to support the QIBA PET amyloid 'Performance Assessment: Image Analysis Workstation and Software' efforts for Profile development. This will be done by (1) visual evaluation of the target and reference region placement, (2) evaluation and validation of SUVR calculations with regards to reproducibility and linearity and (3) providing a common reference standard that can be adopted and modified by IAW manufacturers.

As mentioned above, the UW-PET QIBA PET Amyloid DRO series is based on a single segmented MRI scan of a patient. The MRI scan digitally had the skull and skin removed, and then was segmented into GM, WM, and CSF, which allows for different values of PET activity to be simulated in these regions.

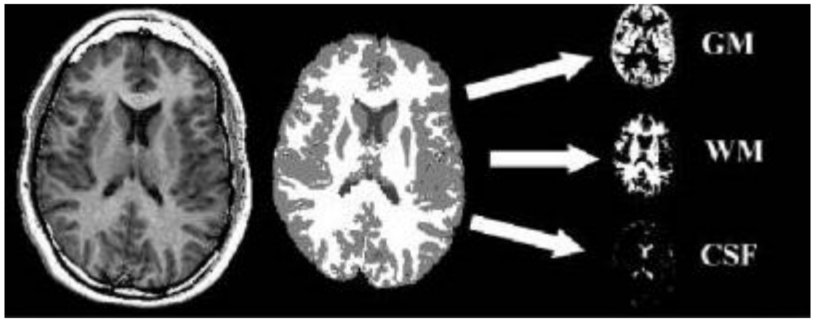


Illustration of how the DRO series was created.

Normally, a system of measurement would have assessments and conformance levels for bias, linearity and reproducibility. Since the claim in this Profile is a longitudinal claim (as opposed to a cross-sectional claim) and the same imaging methods shall be used at each time point, bias does not need to be assessed. Therefore, conformance assessment as detailed here will focus on linearity and reproducibility.

Linearity

The linearity of the IAW will be assessed by testing a range of different subjects, as defined by varying SUVR values. The table below gives more detail about the simulated subjects and their respective SUVR values. The activity in the CSF region will be set to 0.

Subject	GM Activity	WM Activity	GM/WM Ratio
1	0.9X	X	0.9
2	1.0X	X	1.0
3	1.1X	X	1.1
4	1.2X	X	1.2
5	1.3X	X	1.3
6	1.4X	X	1.4

Therefore, 6 subjects were simulated in the DRO series which will be later used to test the linearity of the IAW.

Reproducibility

The reproducibility of the IAW will be assessed by making multiple realizations of the same subject. This can be thought of as simulating test-retest multiple times on the same subject. The multiple realizations will be done by adding typical levels of clinical noise five times to each subject. Please see the figure below for a pictorial representation.

The DRO Series

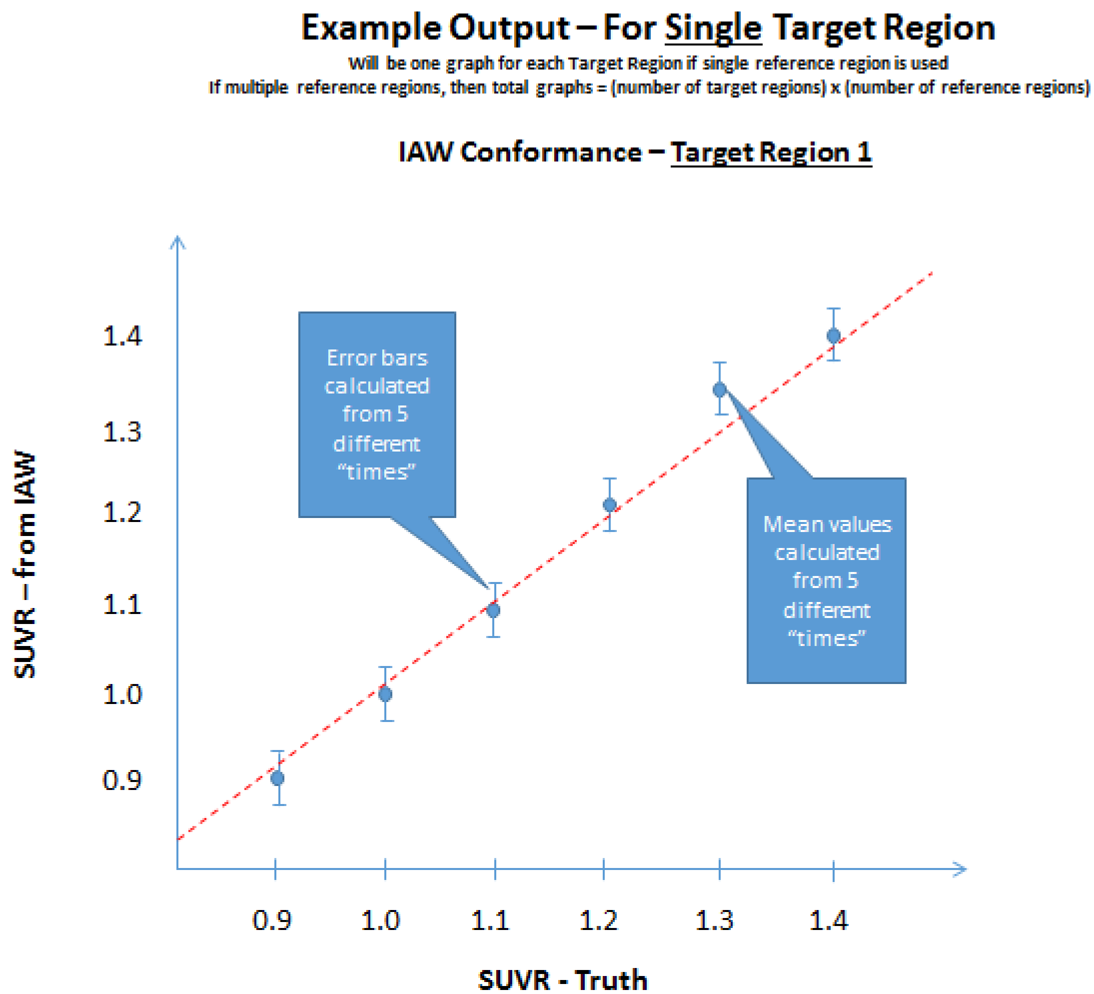
The simulation of six subjects and five realizations means that the DRO series will contain 30 simulated PET volumes. These volumes will be stored in DICOM format and can be downloaded from the Quantitative Imaging Data Warehouse (QIDW), with the link given below.

IAW Conformance Procedure

a. Download the UW-PET QIBA PET Amyloid DRO series from QIDW <give link when ready>.

b. Analyze the 30 volumes using the same procedure, target regions and reference regions as will be used with patient data.

c. For each target region for a fixed reference region, the information to form the graph below should be calculated, and will be called a given target's results, e.g. (Frontal Target/Whole Cerebellum Reference Region) Results:



4. If multiple reference regions will be used, generate the same information as in point 3 above using this new reference region. The final number of target results or graphs will be (number of target regions) x (number of reference regions).

5. The following statistical analysis should be performed on each target result.

   a. Fit an ordinary least squares (OLS) regression of the Y_i's on X_i's (where Y's are the SUV measurements from the IAW, and X's are the true SUV measurements). A quadratic term is first included in the model: $Y= \beta_o+\beta_1X+\beta_2X^2$.

      - The estimate of β_0, β_1 and β_2, *along with their 95% Confidence Intervals (CIs),* shall be reported as part of the assessment record (see last point below).

   b. Re-fit a linear model: $Y= A_o+A_1X$ (red dotted line on graph above).

- The estimate of A_0 and A_1, *along with their 95% CIs,* shall be reported as part of the assessment record (see last point below).
- R-squared (R^2) shall be >0.90 for the IAW to be compliant for the given target and reference regions.

c. For each of the 6 true SUVR values, calculate the mean (blue points in graph above) of the 5 measurements and the wSD (blue error bars in graph above) using the following equations where the summations are from J=1 to J=5:

$$\bar{Y}_i = \Sigma(Y_{ij})/J \text{ and } wSD_i^2 = \Sigma(Y_{ij} - \bar{Y}_i)^2/(J-1).$$

d. Estimate wCV using the equation, where N=6:

$$wCV = \sqrt{\Sigma_{i=1}^{N}(wSD_i^2/\bar{Y}_i^2)/N}.$$

f. Estimate the % Repeatability Coefficient (%RC) using the equation:

$$\widehat{\%RC} = 2.77 \times wCV \times 100.$$

- The %wCV shall be $\leq$ 2.6% for the IAW to be compliant for the given target and reference regions. (Note that this conformance criterion allows 95% confidence that the %RC of the IAW meets the Profile claim.)
- For future reference, the number of subjects and tests per subjects can be changed in the DRO series, which will change the wCV% threshold as per the table below.

# of Subjects (SUVRs)	# of Realizations (Tests per subject)	wCV% Threshold
6	5	2.6%
7	5	2.8%
9	5	2.9%
11	5	3.0%
6	10	3.1%

6. For each target's results, report the following in a format similar to the example table below.

Ref Region	Visual Placement Check	Target Region	Visual Placement Check	β_0	β_1	β_2	A_0	A_1	R^2	$R^2 >$ 0.90	wCV	%RC	%RC ≤ 2.6%
1	Pass	1	Pass	0.03	0.91	0.01	0.1	0.97	0.92	Pass	$7.6\text{x}10^{-3}$	2.1	Pass

1	Pass	2	Pass	0.05	0.9	0.02	0.07	0.95	0.91	Pass	1.05x10^{-2}	2.9	Fail
1	Pass	3	Fail	-	-	-	-	-	-	-	-	-	-
1	Pass	4	Pass	0.16	0.81	0.14	0.14	1.2	0.85	Fail	-	-	-
2	Fail	-	-	-	-	-	-	-	-	-	-	-	-
3	Pass	1	Pass	0.03	0.91	0.01	0.1	0.97	0.92	Pass	7.6x10^{-3}	2.1	Pass
3	Pass	2	Pass	0.04	0.95	0.04	0.03	0.92	0.93	Pass	8.0x10^{-3}	2.2	Pass
...	...	...	...	...	...	...	...	...	...	...	...	...	...

The table report above should be saved and archived with any PET amyloid patient study that is compliant with this Profile.

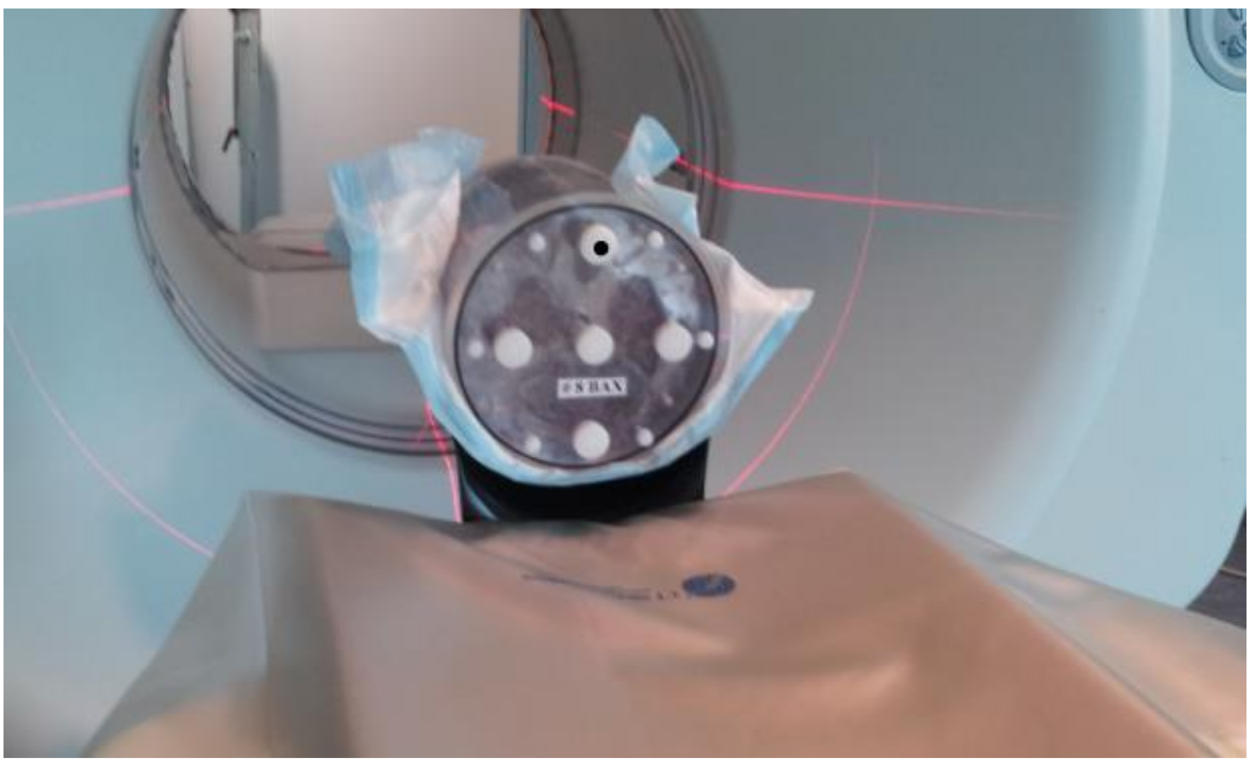
Appendix G: Best Practice Guidance for the Hoffman Brain Phantom

- Make sure that before the 18-F or 18-FDG is added, you start with a completely filled phantom (less ~100ml, described later). It is helpful to fill the phantom with water the day before to help remove small air bubbles.
- Purified or distilled water is preferred, normal tap water is OK.
- When you are filling, it helps to tip the phantom slightly (use a syringe or similar object underneath one side). It also helps to open more than one of the filling ports while filling. Once you have the phantom completely filled, then use a 50-60cc syringe to take out ~75-100ml before injecting with the FDG. This allows for better mixing.
- Prepare the F18 tracer (typically FDG) in a volume of **3-5ml,** calibrated for an injected amount of 0.5-0.6 mCi (18.5 – 22.2 MBq) at the projected time of scanning.

- Switch the needle on the syringe to a long, blunt tip needle. Insert through the top filling port (the brain's **anterior** side) until the tip of the needle is **approximately half way down through the phantom**. Rinse the syringe 2 or 3 times to reduce the residual in the syringe.
- To ensure there is no tracer left in the original (short) needle, attach that needle, and also rinse 2-3 times.
- Measure the residual in both needles and syringe. We suggest you place these in a surgical glove before placing in the dose calibrator to prevent contamination of the dose calibrator.

- Once injected, replace the cap and roll back and forth vigorously for about 5min. Occasionally, pick up and tip up and down the other way.
- Top off as best you can, filling through 1 or two of the ports (wherever bubbles are).
- Roll a 2nd time, briefly for about 1min. this will help to get bubbles out.
- Top off a 2nd time. The focus now is to remove any remaining air getting bubbles. An effective method is to hold upright (with filling ports up), and shake back and forth vigorously to make the bubbles rise. (Remember when filling to minimize spills. Wipe with a paper towel, and this goes to radioactive waste)
- Roll a final 3rd time. Then top off again to remove any remaining air bubbles.
- As a final check, look through the phantom at a bright light to check for bubbles. If there are some large bubbles (greater than ~3 mm), try another shaking/tapping/rolling/filling session.
- Finally, if you do the CT scan and notice there are big bubbles or air spaces, take the phantom and try to top off/remove the bubbles before doing the finally CT/Pet scans

Generally, this process takes about 10-20min.



Position the phantom on the scanner bed with the filling ports towards the foot of the bed, and the anterior filling port at 12 o'clock. (In this position, the cerebellar lobes should be visible at the bottom of the phantom, and should appear in the reconstructed image as if you were imaging a supine subject).

Appendix H: Detailed Example of Hoffman Phantom Data Analysis

The basic methodology in the quantitative analysis is to first align the test scan to the digital atlas using an affine registration, then to intensity normalize the data, and finally to find a smoothing factor for the digital atlas that best matches the spatial resolution of the test scan. Once a registered, the intensity normalized test image and smoothed gold standard are computed, and the difference image can be viewed visually and quantified by various methods described below to assess overall scan quality.

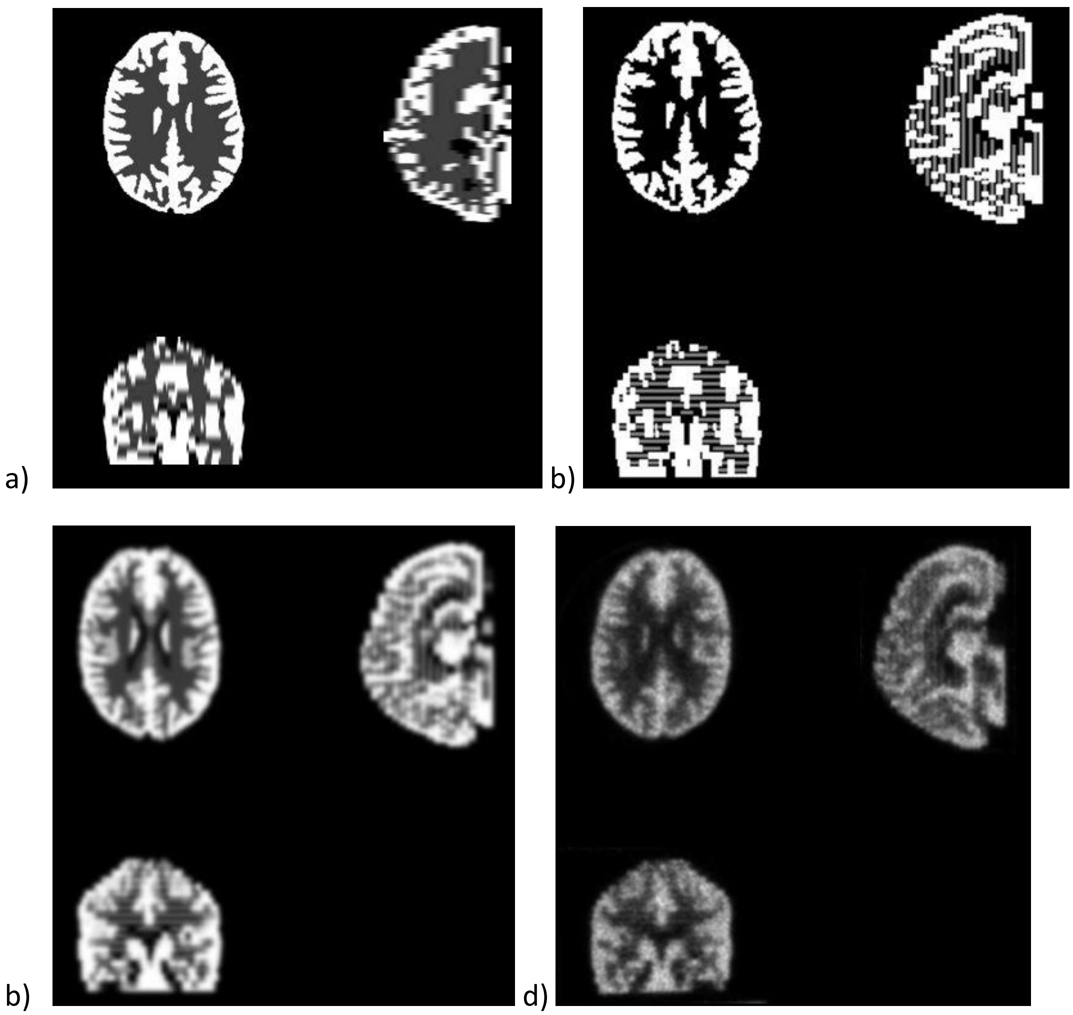


Figure 1. Digital Hoffman Phantom. a) 19-slice version supplied by Data Spectrum. b) 90-slice version modeling more accurately individual layers of each slice. c) smoothed version of the 90-slice digital phantom. d) sample real phantom data obtained from the high-resolution HRRT scanner.

Phantom Description

The interior of the Hoffman brain phantom is composed of 19 separate plexiglass plates, each 6.1 mm thick. To achieve the 4:1 gray:white uptake ratio via displacement of a uniform concentration of radioisotope solution, each plate is composed of a “sandwich” of eight separate layers, of “gray” slices (G), cut to the shape of modeled gray matter, and “white” slices (W), cut to the shape of modeled white matter. Areas of CSF are left completely void. Each layer is therefore composed of a “sandwich” in this order: GG|W|GG|W|GG. The most caudal slice and most cranial slice consist of just 4 gray layers (GG|GG).

Data Spectrum, who manufactures the phantom, supplies a 256x256x19 voxel digital atlas that models the phantom appearance as having one of 3 types of uniform areas in each 6.1 mm slice (gray=4, white=1, csf=0). See Figure 1a. Dr. Bob Koeppe from the University of Michigan, in collaboration with Data Spectrum and CTI (now Siemens) constructed a more accurate 160x160x90 voxel, 1.548x1.548x1.548 mm version of this phantom that models the individual layers between the slices. Each slice of this 90-slice phantom represents either a “GG” all gray layer with values either 0 or 1.0; or a “GW” layer with values either 0, 0.5 or 1.0. This digital phantom (Fig 1b,c) looks much more like data obtained from a high-resolution PET scanner (Fig 1d), and can be smoothed to approximate images from lower-resolution scanners. The individual layers can actually be seen in some higher resolution scanners, such as the Siemens HRRT.

One important item to note is that the actual phantom size, especially the actual physical slice thickness of each phantom, can vary slightly. Therefore, when comparing data, it is important to deal with the scaling appropriately. Alternatively, if comparisons are made between two acquisitions, one must insure that the identical phantom is used in the comparison. If there are multiple phantoms in use, it is good practice to track each phantom with an appropriate identification number.

Regarding smoothing, it is assumed that the PET scanner resolution can be modeled by smoothing with a Gaussian kernel with the same size in the transaxial direction (i.e. x and y direction), and another size in the axial direction (i.e. z direction). This is approximate, since blurring increases transaxially away from the center, and is different in the radial and tangential directions. Also, axial resolution is degraded in the outer end planes of the scanner. However, the uniform smoothing assumption is fairly reasonable for head imaging, where the field of view is fairly close to the center of the scanner.

Methods and Metrics

Method Overview

The method for quantitative analysis can be summarized by the following steps:

1) Sum a dynamic PET test image, which we will call the “Source Image” acquisition, to produce a single average PET volume
2) Register the averaged Source Image to the 90-slice digital reference using an affine transformation
3) Determine Gaussian smoothing factors FHWMxy, FWHMz, to be applied to the digital phantom so that it best matches the registered Source dataset.
4) Compute image metrics on differences between the matched smooth “gold standard” data, and the registered Source data.
5) Create different images and graphics to augment a visual assessment of image quality.

Relevant Data Files

The following input and reference files are used in the analysis:

<u>Reference Files</u>

ctiHoffman0.0_0.0.nii – This is the 160x160x90 digital gold standard data.

ctiHoffman5.0_5.0.nii – This is ctiHoffman0.0_0.0.nii smoothed by a Gaussian kernel 5.0 mm FWHM in the x, y, and z dimensions. This represents an image at about the resolution of the highest-resolution scanners, such as the HRRT.

HoffmanVOI5mm6Level.25_.95BrainMask.nii – This is a volume-of-interest (VOI) mask file with six levels created in PMOD using multi-level thresholding on the smoothed, phantom file, **ctiHoffman5.0_5.0.nii**. The resulting segmentation is seen in Figure 2. Idealized voxel intensities for CSF, white matter and gray matter are 0.0, .025, 1.0 respectively, but blurring of the digital phantom results in a partial volume effect so that voxel values vary continually between 0.0 – 1.0. Regions were defined with the following IDs and thresholding criteria as follows:

Region ID	Threshold	Description
1	Val < 0.01 outside brain contour	nonbrain
2	Val < 0.05	Pure CSF
3	0.05 < Val < .20	White/CSF mixture
4	0.20 < Val < .30	Mostly “pure” white
5	.30 < Val < .90	Gray/white mixture
6	.90 < Val	Mostly “pure” gray

Regions 4 and 6, which represent areas of mostly white and gray matter, respectively, are the main regions used for comparison in the analysis.

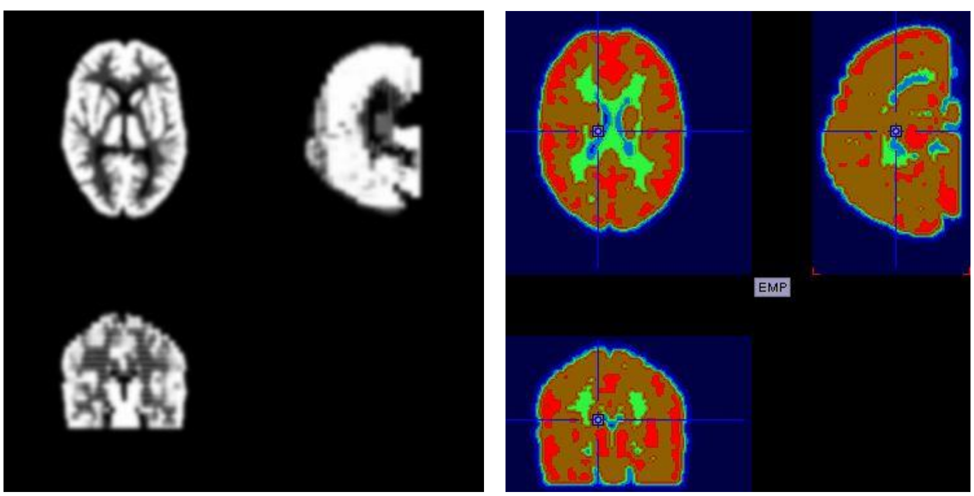


Figure 2. Six-region Volume of Interest mask. The smoothed digital reference (left), and the volume of interest mask volume created in PMOD using multi-thresholding segmention (right). The VOI mask is used to define areas representing primarily pure gray (shown in red) and pure white matter (shown in green). These regions are used for image intensity normalization and various image quality metrics.

Input files

SourceXXX – original dynamic PET data. Usually in DICOM format, and for this profile is recommended to be a 4 x 5 minute acquisition.

Intermediate Files

Avg **SourceXXX.nii –** summed dynamic data.

RegSourceXXX.nii – summed dynamic data registered to 160x160x90 voxel digital phantom template

RegSourceNorm.nii – version of **RegSourceXXX.nii** intensity normalized to values between 0 and 1.0.

Output Files

Volumes

RegSourceXXXFit.nii – smoothed version of the Hoffman digital template , **ctiHoffman0.0_0.0.nii** , that is the best fit to **RegSourceNorm.nii.**

RegSourceXXXAbsDiff.nii – absolute difference volume between **RegSourceFit.nii** and

Text

RegSourceXXXfit`.txt – summary output file`

JPG -

RegSourceXXXXplotAbsDiffProfile.jpg – profile of

RegSourceXXXXplotGrayWhiteProfile.jpg -

RegSourceXXXXplotImgDiff.jpg - central three orthogonal planes through **RegSourceXXXAbsDiff.nii**, gray scale set between -0.2 and 0.2.

RegSourceXXXXplotImgNorm.jpg – central three orthogonal planes through **RegSourceNorm.nii**, gray scale set between 0.0 and 1.0

Method Details – Processing Steps

1) Manual step: Load/visual check of image data. Add to PMOD batch file list
   Images need to be manually loaded to check visually that the orientation is correct. If the image loads using default parameters, it can be simply added to a PMOD file list for later batch processing. If the default settings do not work, the image must me manually loaded using the correct image reorientation switches, saved as a new dynamic file, then added to the PMOD batch file list.

2) Batch step: PMOD script: Dynamic Averaging, Affine Registration to Hoffman Digital reference
   This step sums the dynamic PET data to obtain an averaged PET source file, and then registers the averaged PET to the Hoffman reference image. It is assumed that there is no motion between image time frames, so a motion correction step is not necessary like it would be for a patient study. As a reference image, the version of the Hoffman reference smoothed with a 5 mm isotropic Gaussian filter is used (**ctiHoffman5.0_5.0.nii**). This represents the resolution of an image that would be expected from the highest resolution PET scanners. In PMOD's registration module, Normalized Mutual Information

and the “scale” option are selected to allow an affine match that will compensate for slightly different phantom actual sizes. No other pre-smoothing is used during the registration. The batch process saves the averaged and the registered dataset as two separate files. This step can be run on one or many different PET files. PMOD is not set up yet to record the reorientation matrix (I have requested this), so we do not have a full track of all operations.

3) <u>Batch step: Matlab script: Normalize PET, Fit Smoothing Model, Quantify Difference Image</u>
Once the PET source has been registered to the Hoffman reference, the following steps are carried out using a matlab script:

a) *Normalize the Registered PET source intensity.* The noiseless digital phantom has values ranging between 0.0 and 1.0. Rather than normalizing to maximum intensity of the source image, the following approach is taken which adjusts for the partial volume effect and for the expected Poisson-related variability around the mean for the expected values in the areas representing gray and white matter. Using the 6-level VOI mask, we use region 6, the area representing mostly pure gray matter, as a reference region. The mean intensity of voxel values in this region is computed in both the smoothed reference volume and the registered source volume. A scale term is computed as the ratio of reference volume gray region mean intensity / source volume gray region mean intensity. This results in the mean with the area representing pure gray area to be set to a voxel intensity of 1.0 in the normalized image.
b) *Fit Gaussian smoothing kernels, FWHMxy and FWHMz.*An unconstrained nonlinear estimation approach is use to find the Gaussian smoothing kernels that produce a smoothed version of the digital reference phantom best matching the normalized source volume. (using Matlab’s “fminsearch” function). We investigated various image difference measures: absolute difference, squared difference, correlation, and brain-masked differences, and the simple absolute difference appeared to work well. The code is written so that any of these options can be selected, but the default is the absolute difference.

2) <u>Calculation of Quality Metrics from the Normalized Source Image and Difference Image</u>
The difference between the normalized source image and the digital reference smoothed to fit the source image is the main basis for the comparison. Additionally, some measures can also be computed from the normalized source image alone. Basic ideas to consider in this analysis include:

- The ideal gray:white contrast ratio should be 4:1 in a noise free setting with perfect spatial resolution. We need to consider the partial volume effect, so most evaluations are made in comparison to global or VOI measures on the noise-free smoothed digital reference.
- For evaluations using a uniform phantom, the usual figure of merit for an acceptable measurement variance is +- 10% from the mean both in-plane and axially. Therefore, an absolute difference of about 10%, i.e. +- 0.1 intensity units would ideally be a maximum difference between the normalized source and the smoothed reference image.

Quality Metrics

a) Global Volume Metrics

i) **Comparison of fit smoothing parameters to published data from ADNI / Bob Koeppe’s group**. This value should be consistent for a given scanner type. Differences in Z-smoothing compared to ADNI results are expected due primarily to Z-scaling during the affine registration process. Based on empirical observation, there most likely is a problem if the fit smoothing parameters differ by more than 1 mm FWHM.

ii) **Average Global Absolute Difference – total image volume** : ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
iii) **Average Global Absolute Difference in the brain region only**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
iv) **Gray:White mater ratio in the source image**. Ideally, this should be 4.0. For scanners of lower resolution we would expect the value to be less.
v) **Ratio of Gray:White in the Source image compared to smoothed reference**. Ideally, this should be 1.0. Would expect at most a 10% variation.
vi) **Ratio of White matter intensity standard deviation in the Source imaging compared to the smoothed reference**: This measure gives an indication of image noise. By comparing to the reference volume, variation with the white matter region due to the partial volume effect should cancel out.
vii) **Ratio of Gray matter intensity standard deviation in the Source imaging compared to the smoothed reference**. : This measure gives an indication of image noise. By comparing to the reference volume, variation with the white matter region due to the partial volume effect should cancel out.

b) *Slice-by-slice Metrics (computed between planes 10-80, which represent the plane with brain data in the Hoffman reference volume)*
i) **Average Slice Absolute Difference – total slice**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
ii) **Average Slice Absolute Difference** – brain region only: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
iii) **Average Slice Absolute Difference – gray matter only (VOI region #6)**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
iv) **Average Slice Absolute Difference – white matter only (VOI region #4)**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
v) **Ratio of mean gray intensity in VOI region #6 for Source compared to smoothed reference**: ideally, this should be 1.0
vi) **Ratio of mean white intensity in VOI region #6 for Source compared to smoothed reference**. Ideally, this should be 1.0.
vii) **Profile Coefficient of Variation for Gray slice mean gray intensity.** This metric can be used as a sentinel for unacceptable variations in axial sensitivities.

3) <u>Outputs: Graphics, Text Summary and Imaging volumes</u>
a) <u>JPGs</u>
i) 3 orthogonal slices through the center of the difference volume – color bars set to +- 0.2 for all evaluations to highlight significant areas that differ from the reference volume. A
ii) 3 orthogonal slices through the normalized, registered source volume
iii) Slice-by-slice profiles of error measures between source and reference volumes
iv) Slice-by-slice profiles of the ratio of mean gray and white matter region intensity regions for the source volume compared to the reference volume.

b) <u>Text file</u>
i) Numerical values for the global and plane-by-plane metrics

c) <u>Image volumes</u>

i) Difference Volume
ii) Fit Smoothed Reference Volume

Note: Matlab Modules Used. In addition to the base Matlab package, the processing pipeline used the standard Matlab Image Processing Toolbox and the Optimization Toolbox. The pipeline also used the 3rd party Matlab package for reading, writing and displaying NIFTI files, “Tools for NIfTI and ANALYZE image”, found at http://www.rotman-baycrest.on.ca/~jimmy/NIfTI .

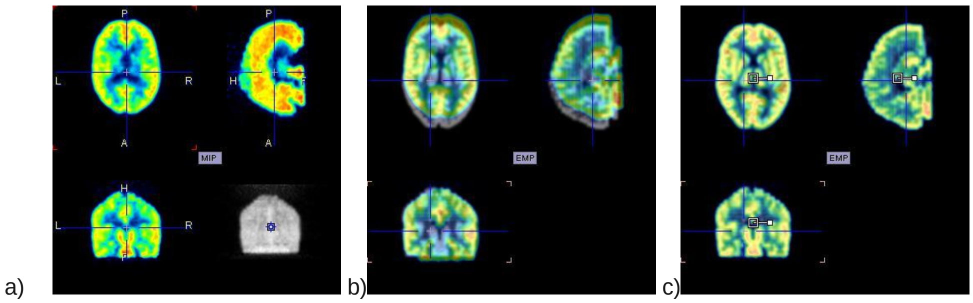
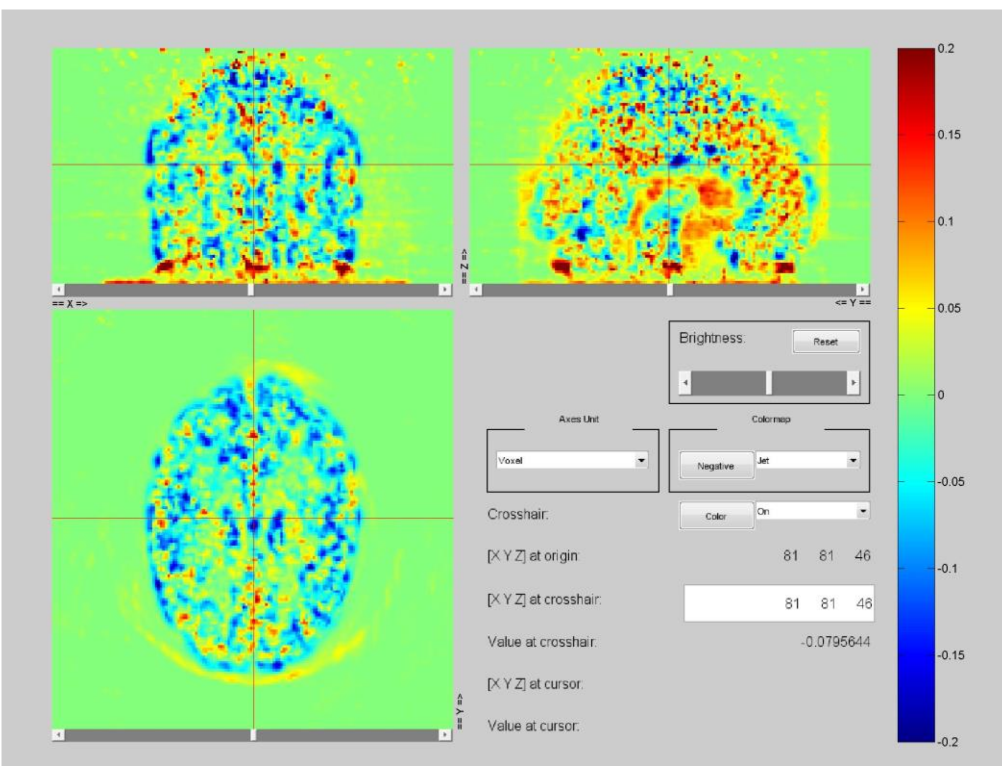
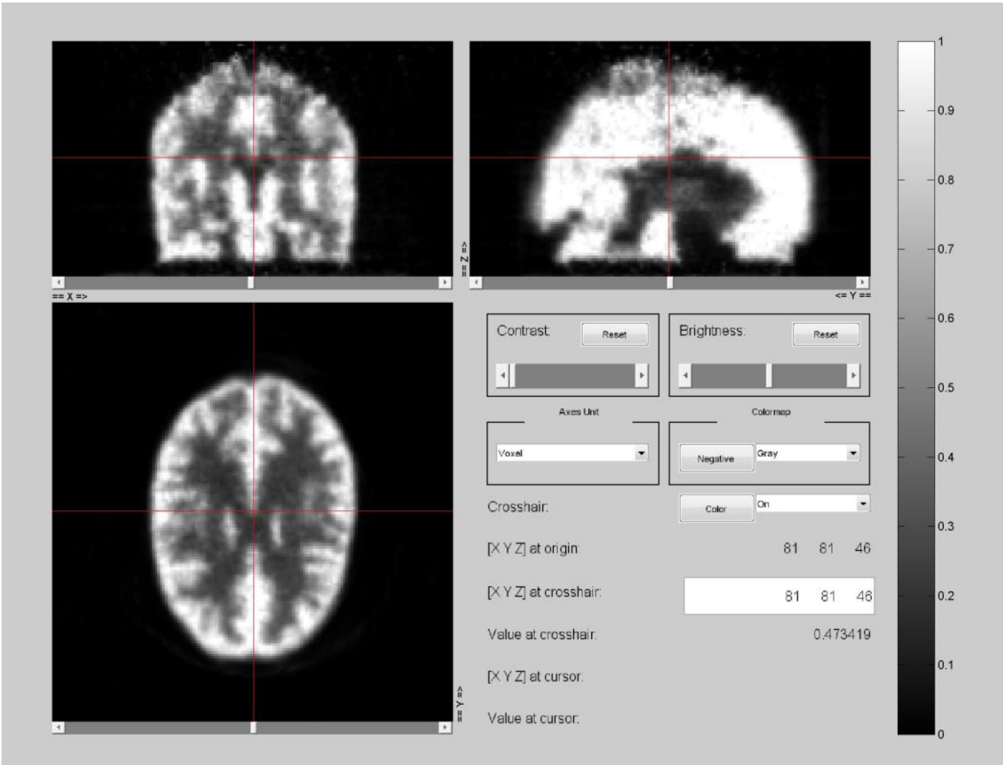


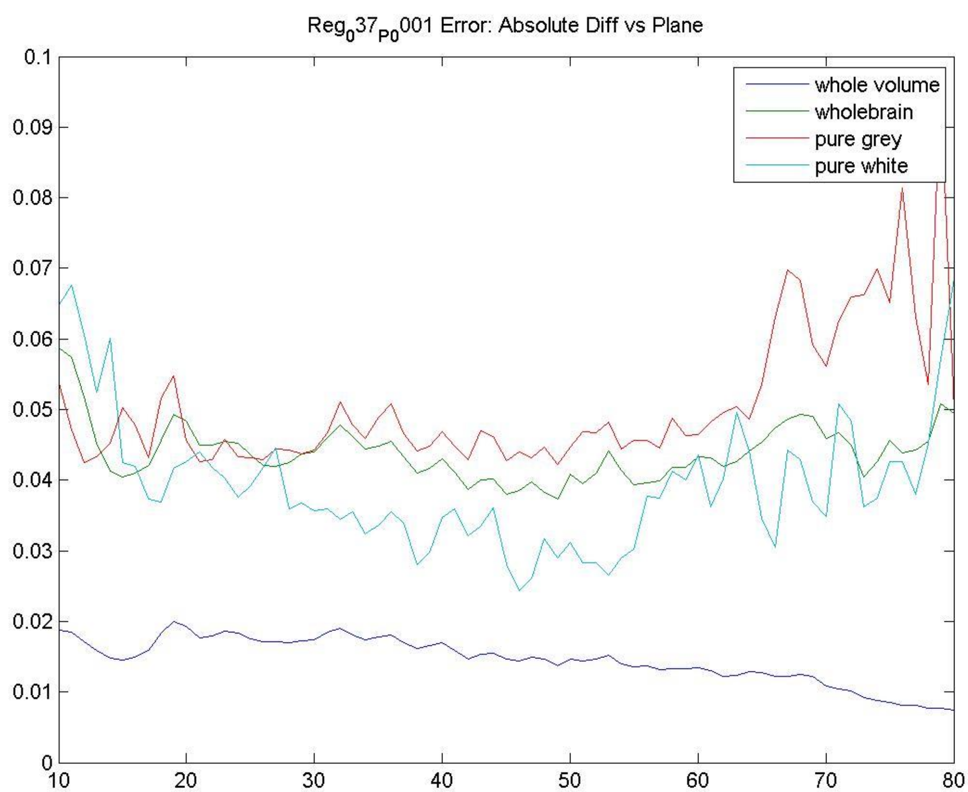
Figure 3. Affine Registration Process. Source image in original orientation (a). Source image (colored grayscale, and digital gold standard (grayscale) unregistered (b), and after registration in PMOD (c).

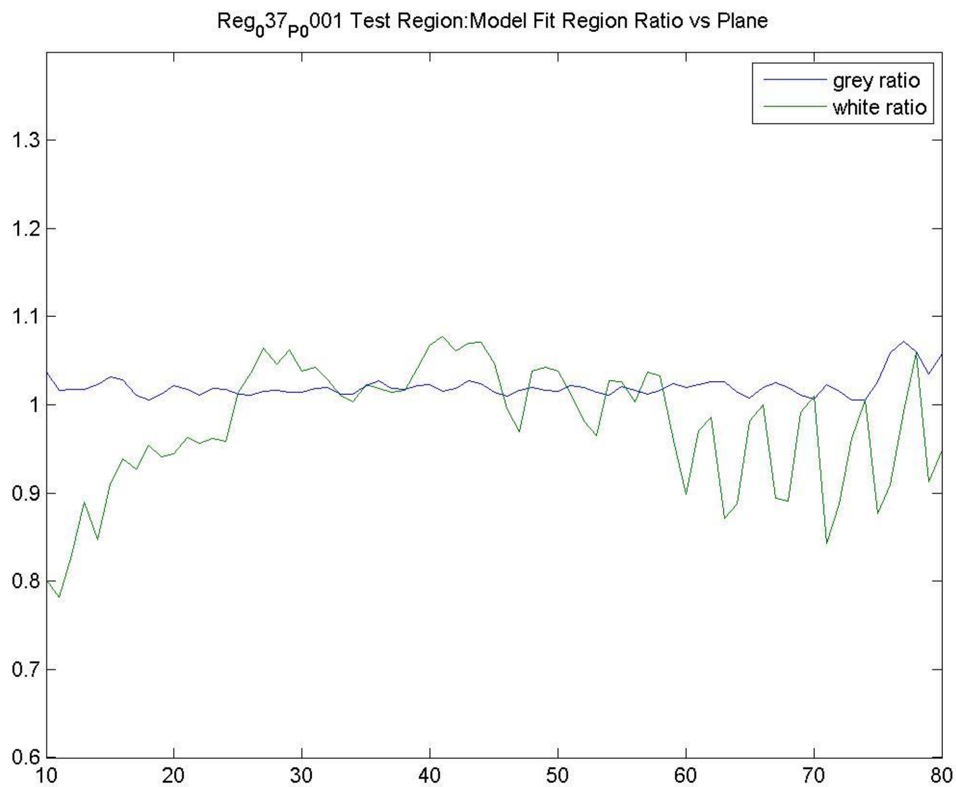
Example Results using the ADNI Hoffman Qualification Data

Example 1. Good quality scan. Siemens HIREZ (037_P_0001)

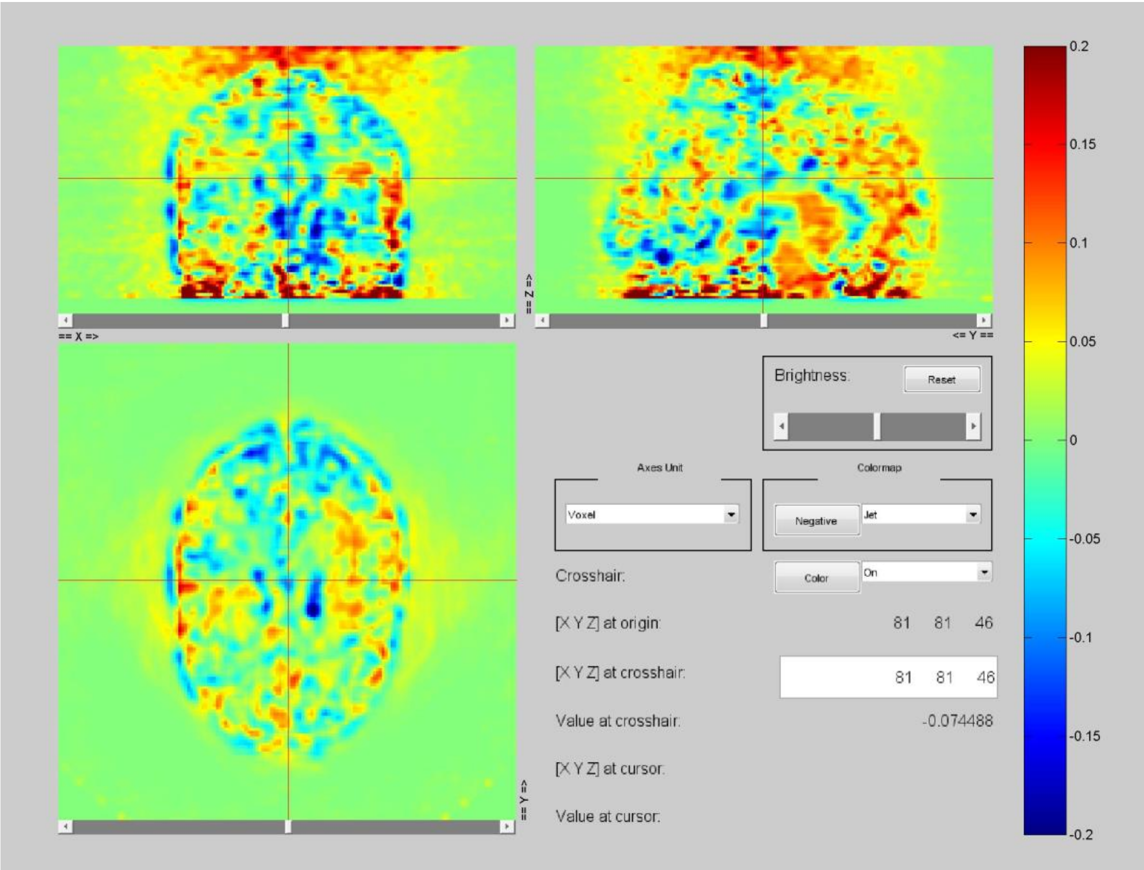


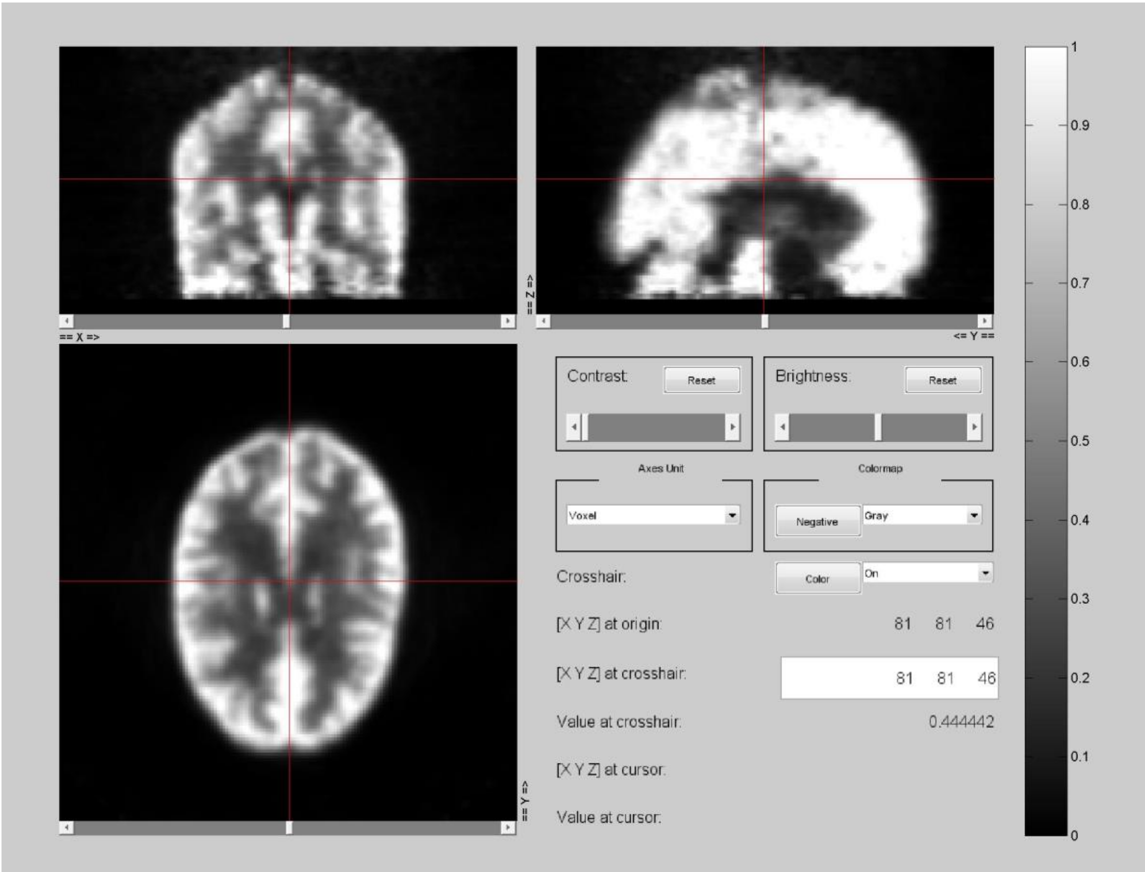

Contrast:
Reset
Brightness:
Reset
Axes Unit
Colormap
Voxel
Negative
Gray
Crosshair:
Color
On
[X Y Z] at origin: 81 81 46
[X Y Z] at crosshair: 81 81 46
Value at crosshair: 0.473419
[X Y Z] at cursor:
Value at cursor:
== X =>
== Z =>
<= Y ==
== Y =>
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

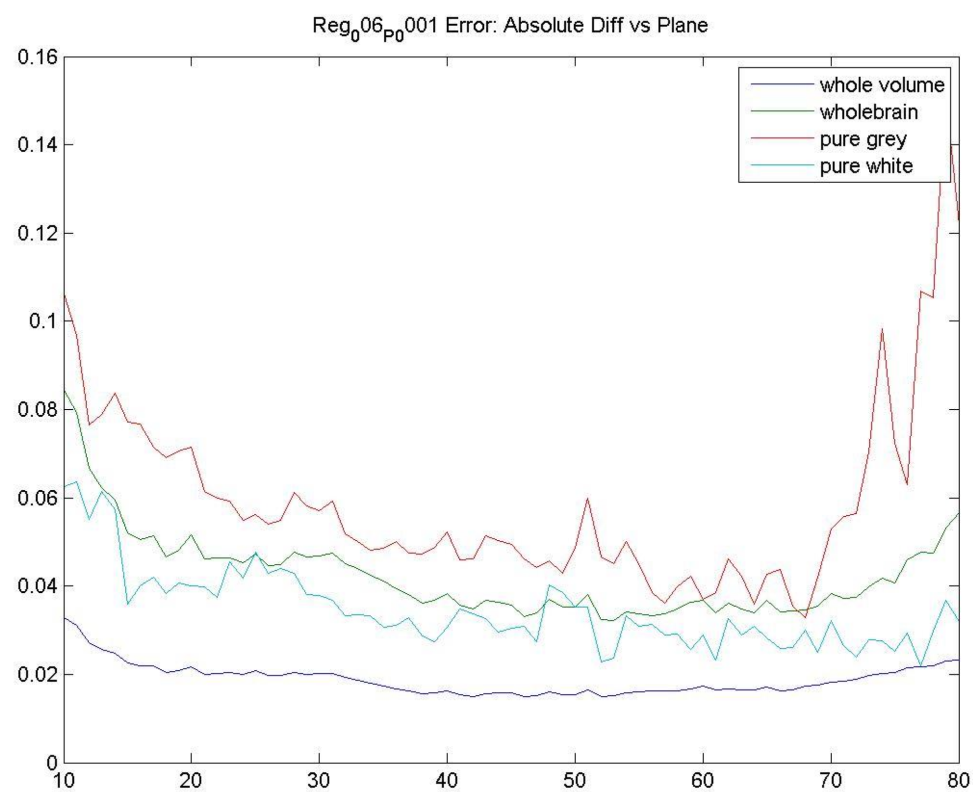

Reg0 37P0 001 Error: Absolute Diff vs Plane
whole volume
wholebrain
pure grey
pure white
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
10
20
30
40
50
60
70
80

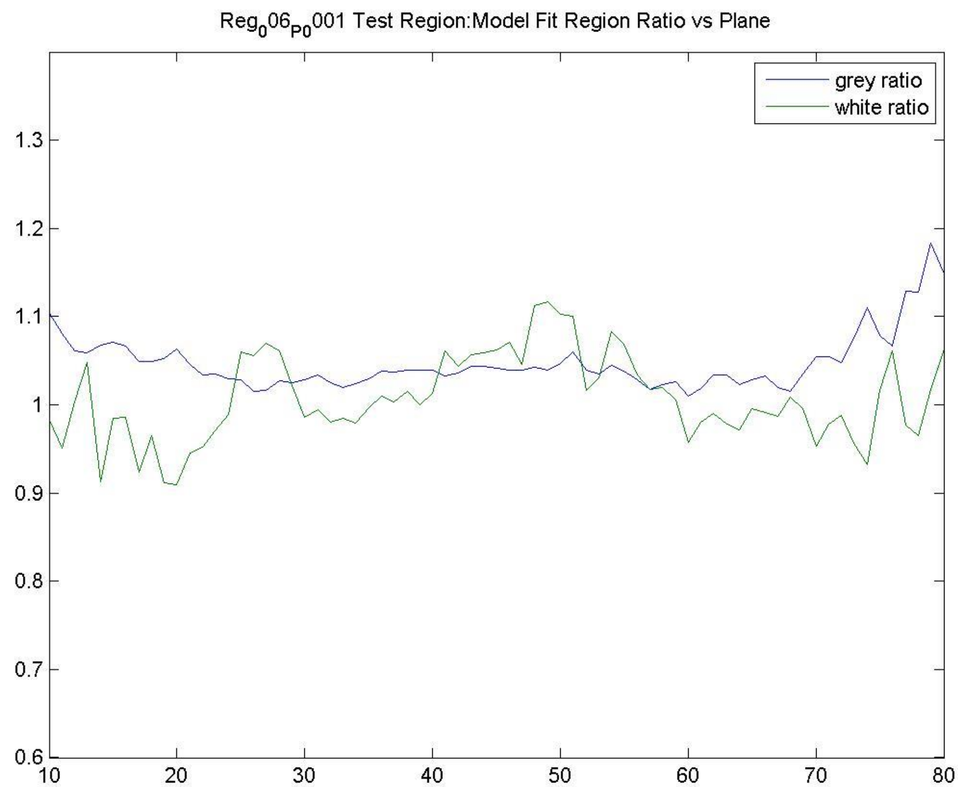

Reg037P0001 Test Region:Model Fit Region Ratio vs Plane
grey ratio
white ratio

Example #2. Another example of a good quality scan. ECAT HR+ (006_P_0001)

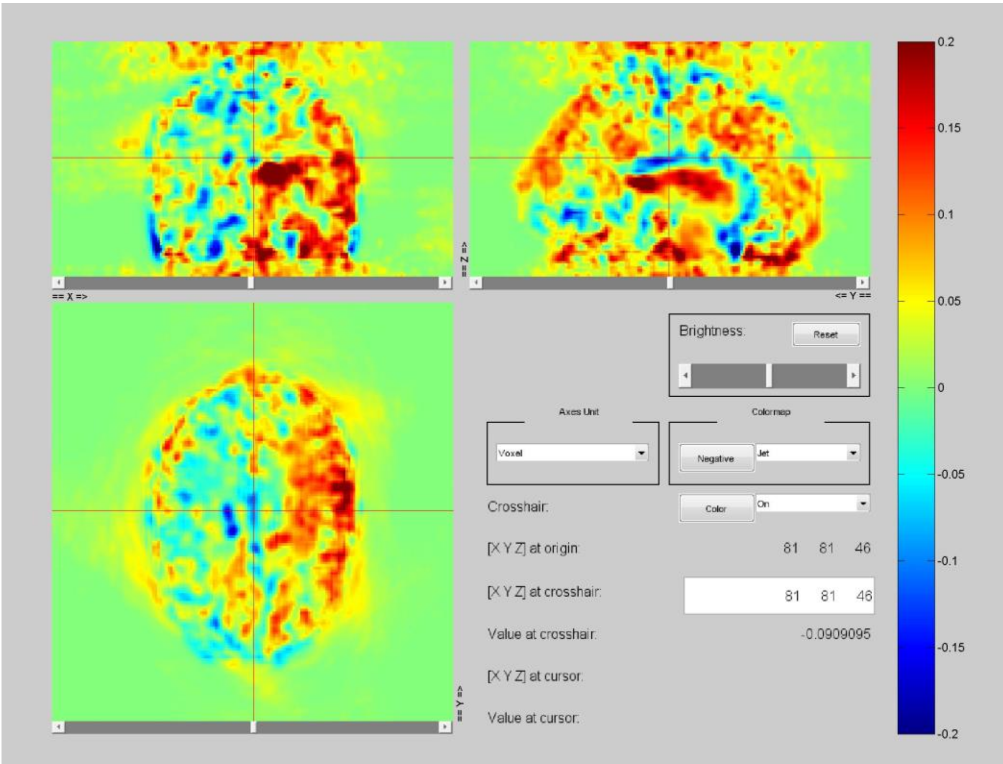


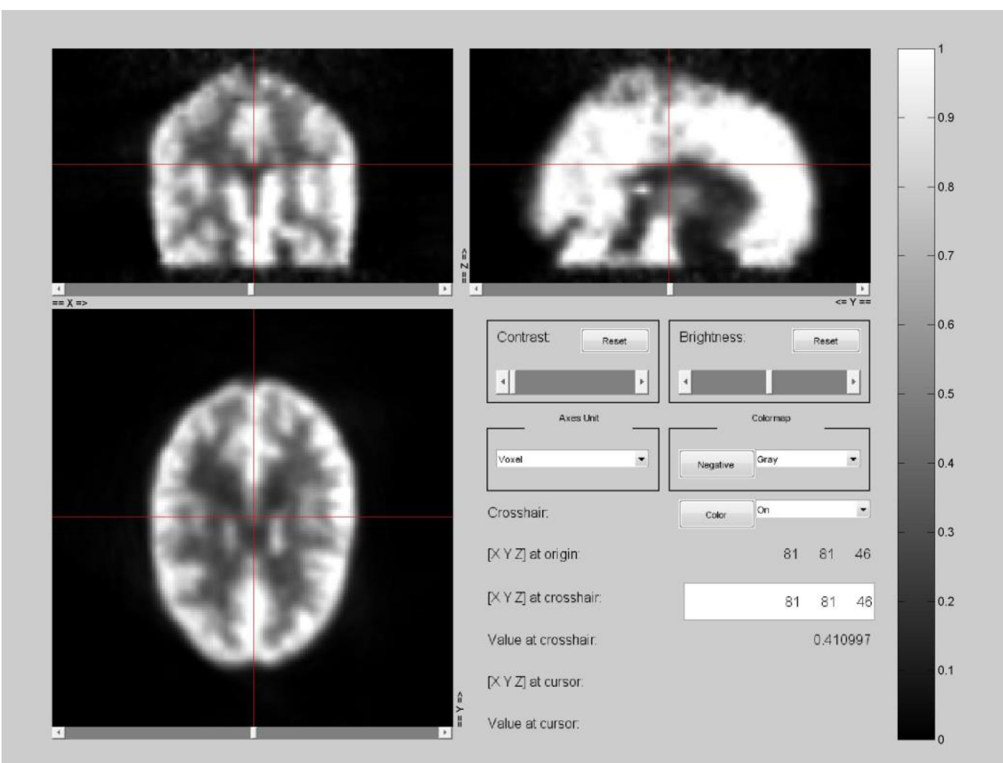

== X =>
<= Y ==
Contrast
Reset
Brightness
Reset
Axes Unit
Colormap
Voxel
Negative
Gray
Crosshair
Color
On
[X Y Z] at origin
81 81 46
[X Y Z] at crosshair
81 81 46
Value at crosshair
0.444442
[X Y Z] at cursor
Value at cursor
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

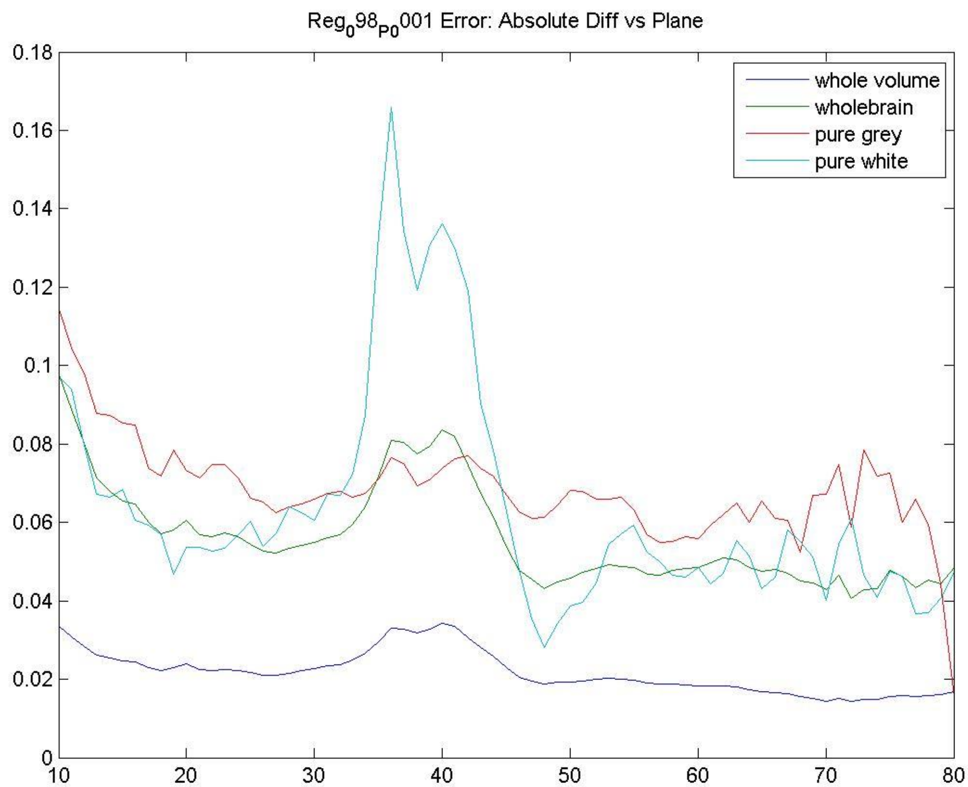

Reg0 06P0 001 Error: Absolute Diff vs Plane
whole volume
wholebrain
pure grey
pure white
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
10
20
30
40
50
60
70
80

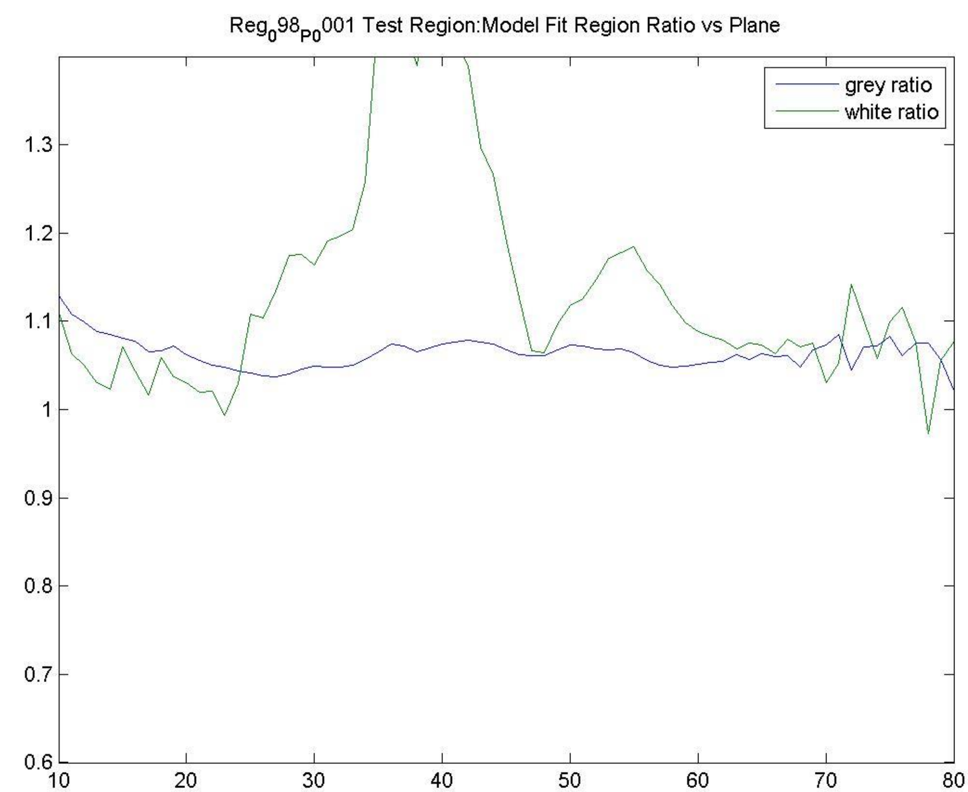

Reg006P0001 Test Region:Model Fit Region Ratio vs Plane
grey ratio
white ratio
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
10
20
30
40
50
60
70
80

Example #3. Siemens ECAT Accel (098_P_0002). Example with relatively poor image quality. Asymmetry seen between left and right side, and large errors between planes 30 and 50. But is this a function of poor scan quality, or a Hoffman phantom with extra space between plexiglass planes?

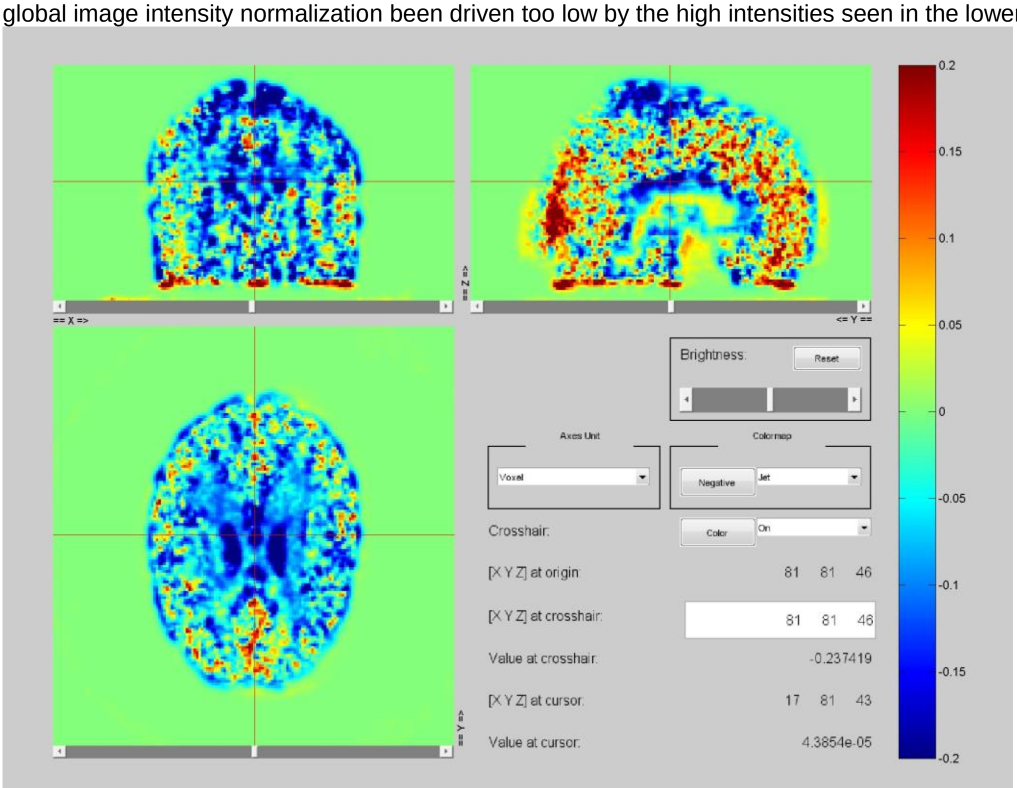


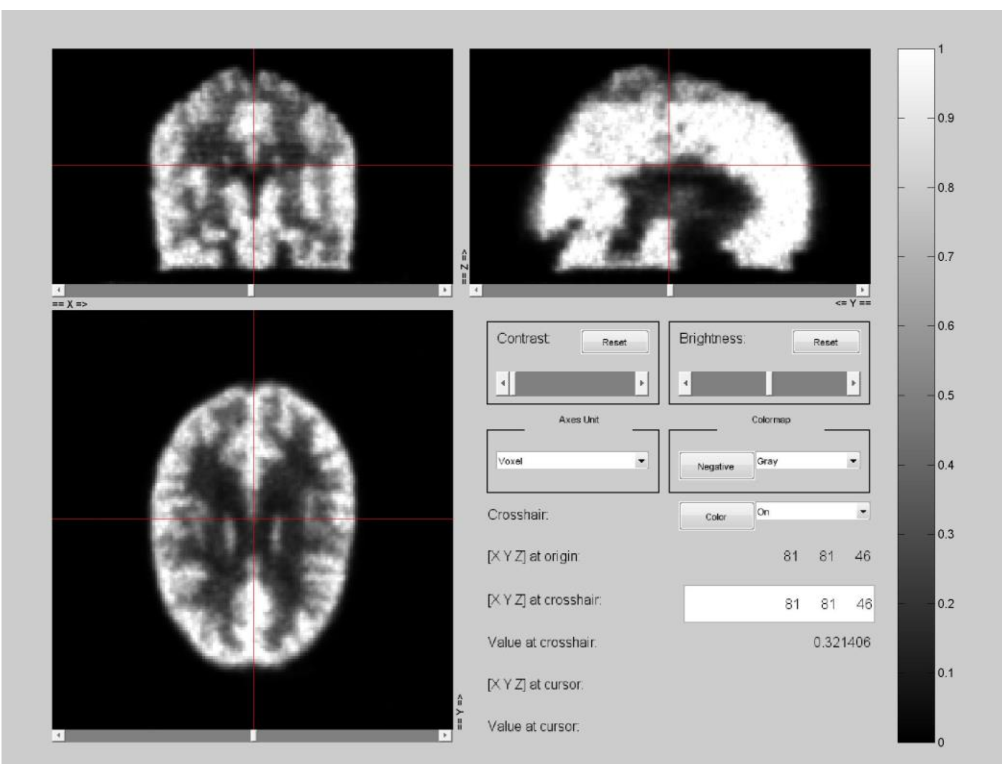


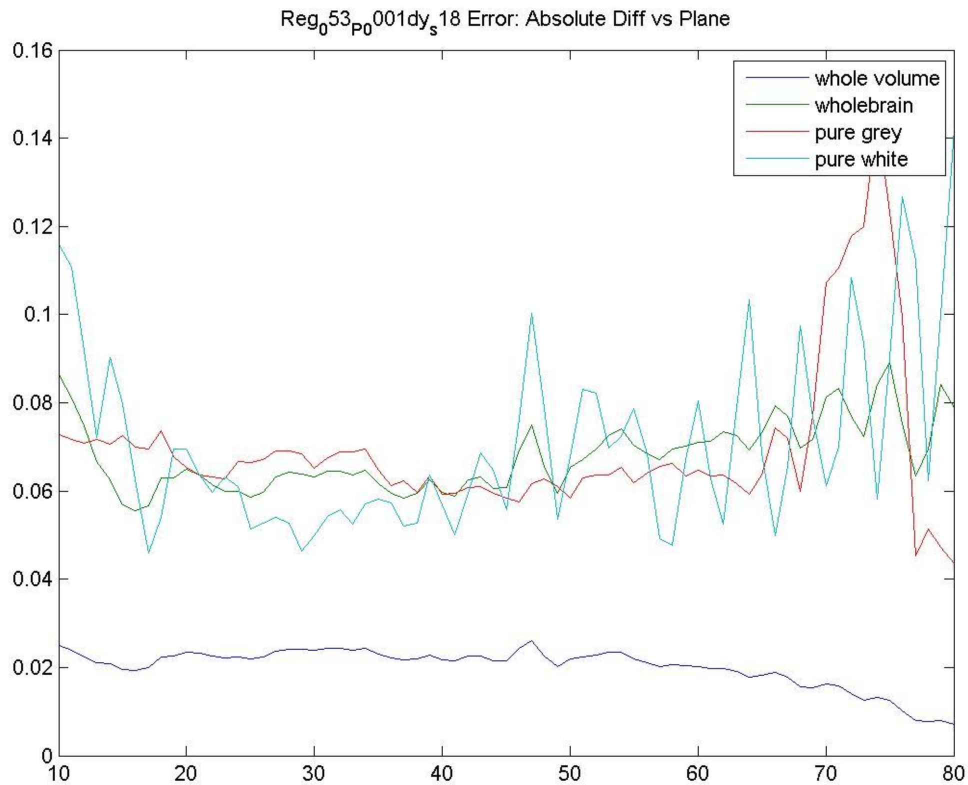

Reg098P0001 Error: Absolute Diff vs Plane
whole volume
wholebrain
pure grey
pure white
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
10
20
30
40
50
60
70
80

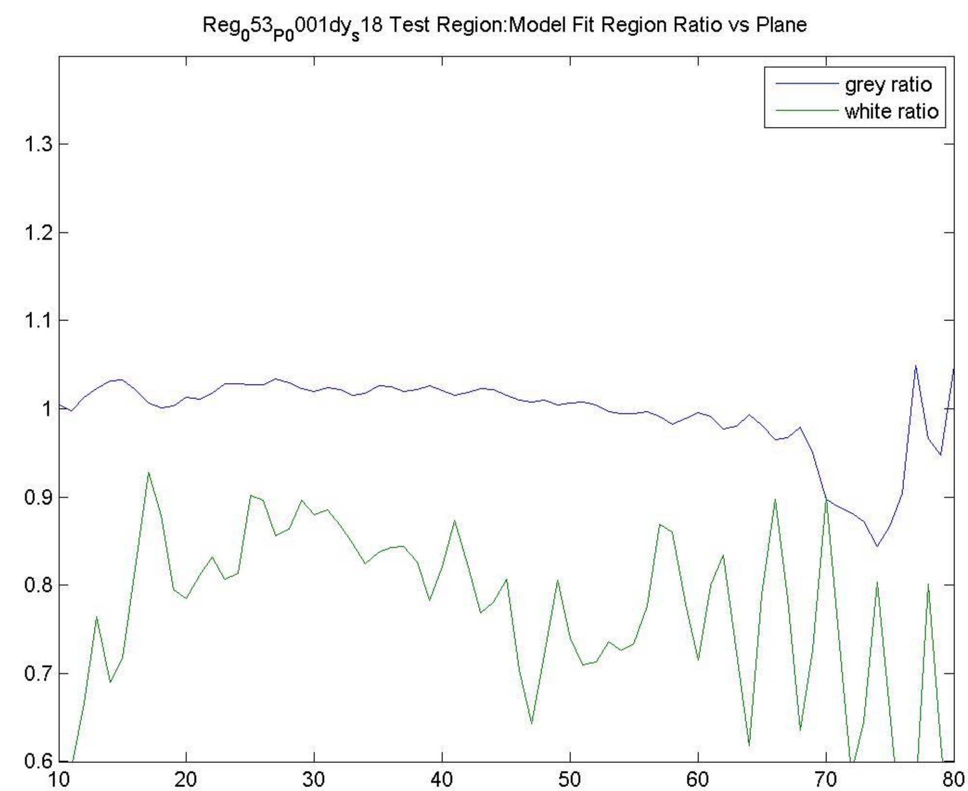

Reg098P0001 Test Region:Model Fit Region Ratio vs Plane
grey ratio
white ratio
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
10
20
30
40
50
60
70
80

Example #4. HRRT Example (128_P_0001). Poor performance at bottom of volume most likely due to scatter correction problems. Otherwise, the scan quality is reasonably good. Difference image for most of the brain is negative (blue regions) probably due to global image intensity normalization been driven too low by the high intensities seen in the lower planes.

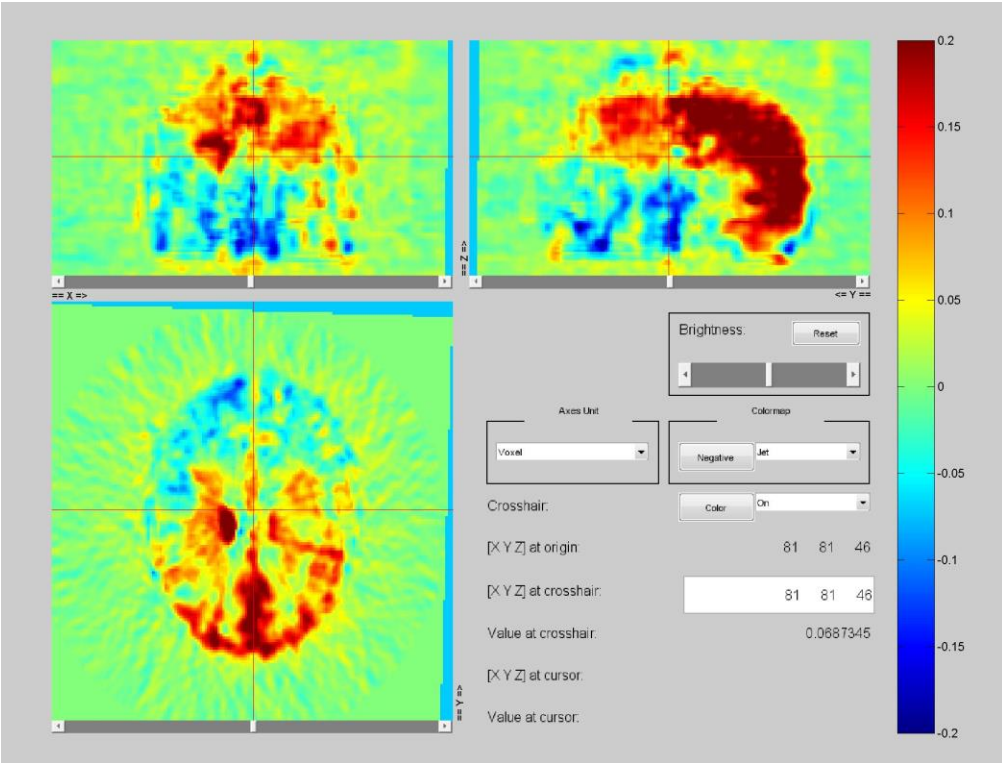


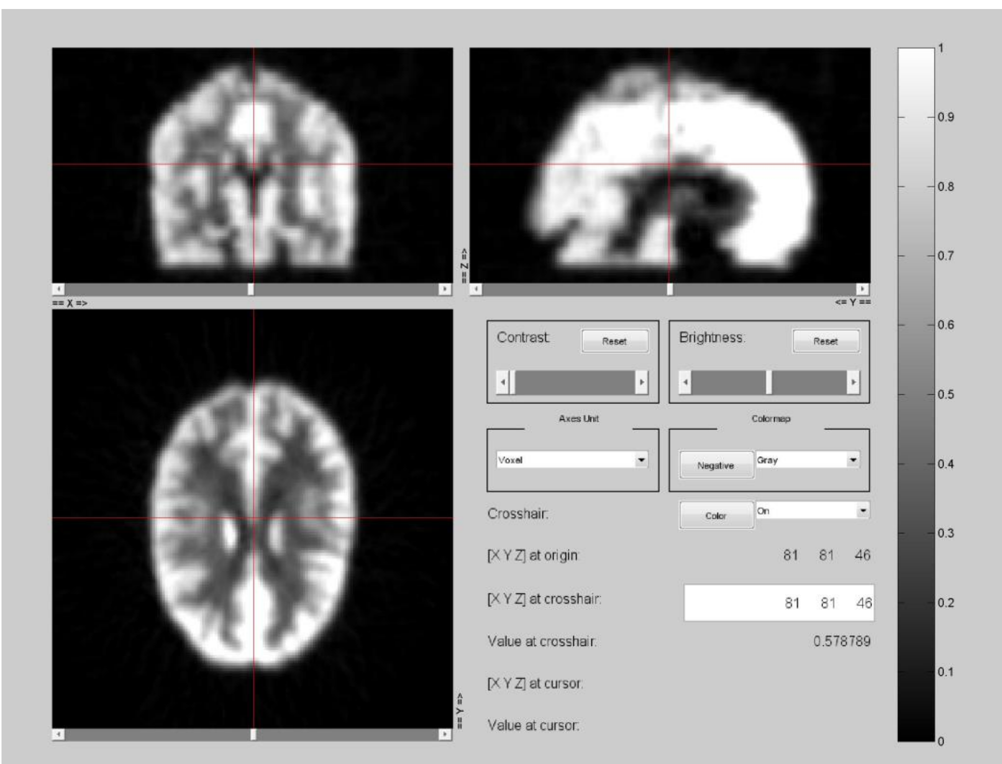


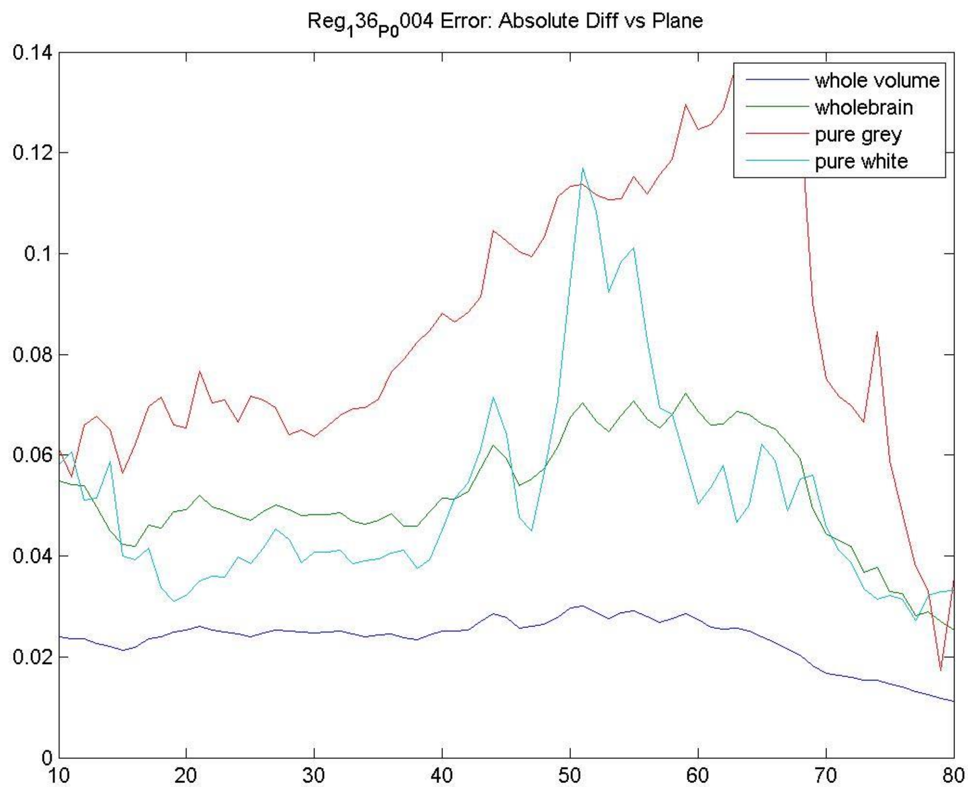

Reg$_0$53$_{P0}$001dy$_s$18 Error: Absolute Diff vs Plane
whole volume
wholebrain
pure grey
pure white
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
10
20
30
40
50
60
70
80


Reg$_0$53$_{P0}$001dy$_s$18 Test Region:Model Fit Region Ratio vs Plane
grey ratio
white ratio
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
10
20
30
40
50
60
70
80

Example #5. (136_P_0004) – GE Discovery ST. Poor Quality – likely fail. Very large errors in the frontal lobe regions. White matter values compared to reference very high.






Reg$_1$36$_{P0}$004 Error: Absolute Diff vs Plane
whole volume
wholebrain
pure grey
pure white
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
10
20
30
40
50
60
70
80