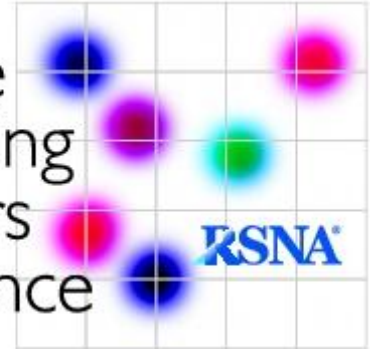


Quantitative
Imaging
Biomarkers
Alliance



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

Stage 2: Consensus Profile

20 June 2018

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Open Issues:

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47 This version incorporates text to address public comments received in response to the version of the Profile
48 dated June 2017.

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Modifications to address public comments

Modifications have been incorporated to address public comment and issues that were outstanding, including the Claim(s). These are subject to additional review.

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 in the process of being completed, funded as a NIBIB groundwork project.

Conformance Testing

Need to describe a study that actors need to perform to test that: 1) Their wCV is within the parameter stated in the Claim, 2) the wCV is constant over a prescribed range of SUVs, and 3) linearity with a slope of one is a reasonable assumption.

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53 1. Executive Summary

54 1.1 Overview

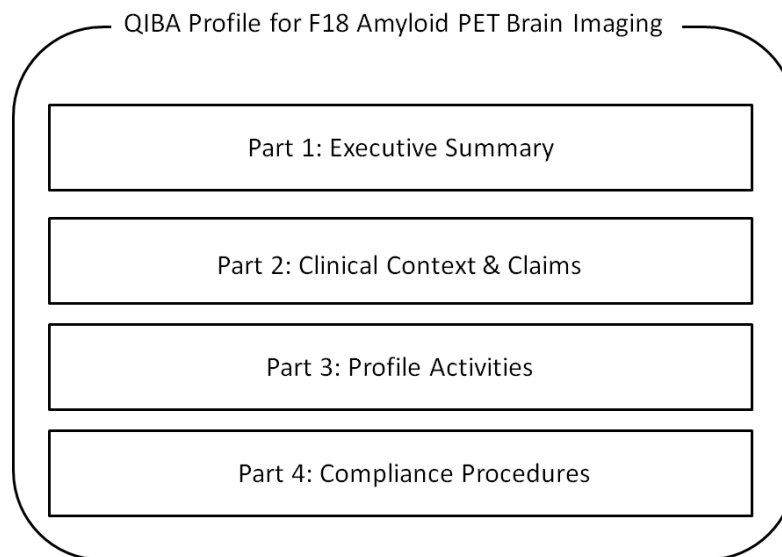
55 This QIBA Profile documents specifications and requirements to provide comparability and consistency for
56 the use of PET imaging using ¹⁸F labeled tracers that bind to fibrillar amyloid in the brain. Quantitative
57 measurement of amyloid, a hallmark pathology of Alzheimer’s disease, has become increasingly used in
58 clinical trials for patient inclusion, evaluation of disease progression, and assessment of treatment effects.

59 The Profile focuses on the use of Standardized Uptake Value Ratios (SUVRs) to measure amyloid burden,
60 while also describing benefits associated with the Distribution Volume Ratio (DVR) (kinetic modeling)
61 approach. The SUVR is determined using data acquired during a time window following a certain time
62 period after tracer injection that is intended to allow the tracer to reach “pseudo” equilibrium. This
63 approach has practical advantages, particularly for multi-site studies, due to the reduced time required for
64 the patient to be in the scanner (and for older scanners, the lesser amount of data acquired for a single
65 scan).

66 The guidance in this Profile can be applied for clinical trial use as well as individual patient management.

67 The document primarily addresses PET/CT imaging; however, a dedicated PET that has transmission
68 capabilities can also be used. PET/MR scanners are not strictly excluded in this version as long as the
69 repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the claims.

70 This Profile, developed through the efforts of the amyloid Profile writing group in the QIBA Nuclear
71 Medicine Technical Subcommittee, shares some content with the QIBA FDG-PET Profile, and includes
72 additional material focused on the devices and processes used to acquire and analyze amyloid tracer PET
73 data. The Profile is organized as follows:



74

75

Figure 1: Illustration of the Profile components

76 The Profile Part 3 is derived from multiple sources, including material contained in the work performed by
77 the Alzheimer’s Disease Neuroimaging Initiative (ADNI). The current version of the Profile focuses on a
78 longitudinal Claim, where the primary purpose is to assess change in amyloid load due to disease or

79 following an intervention. In this case, precision is most important as long as bias remains constant over
80 time. Characterization of measurement bias will be important for a cross-sectional Claim wherein the
81 amyloid tracer is used primarily to select amyloid positive subjects.

82 **1.2 Summary for Clinical Trial Use**

83 The QIBA Amyloid-PET Profile defines the technical and behavioral performance levels and quality control
84 specifications for brain amyloid tracer PET scans used in single- and multi-center clinical trials of neurologic
85 disease, particularly Alzheimer's disease. Examples of clinical application are detailed below in the Claims.

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

93 A motivation for the development of this Profile is that while a typical PET scanner measurement system
94 (including all supporting devices) may be stable over days or weeks; this stability cannot be expected over
95 the time that it takes to complete a clinical trial. In addition, there are well known differences between
96 scanners and/or the operation of the same type of scanner at different imaging sites. Particularly for
97 longitudinal studies, precise quality control of the scanner both daily and periodically for stability is of
98 paramount relevance. In addition, a process of harmonization is also of high relevance to make results
99 comparable between centers.

100 **1.3 Intended Audiences**

101 The intended audiences of this document include:

- 102 • Technical staff of software and device manufacturers who create products for this purpose.
- 103 • Biopharmaceutical companies, neurologists, and clinical trial scientists designing trials with imaging
104 endpoints.
- 105 • Clinical research professionals.
- 106 • Radiologists, nuclear medicine physicians, technologists, physicists and administrators at healthcare
107 institutions considering specifications for procuring new equipment for PET imaging.
- 108 • Radiologists, nuclear medicine physicians, technologists, and physicists designing PET/CT (and PET/MR)
109 acquisition protocols.
- 110 • Radiologists, nuclear medicine physicians, and other physicians or physicists making quantitative
111 measurements from PET images.
- 112 • Regulators, nuclear medicine physicians, neurologists, and others making decisions based on
113 quantitative image measurements.

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

2. Clinical Context and Claims

Accumulation of amyloid-B (AB) fibrils in the form of amyloid plaques in the brain is a 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 radiotracers (see Table in Section 3.1.3.1.2 for currently approved tracers) offer the potential of directly detecting and quantifying amyloid burden. Amyloid quantitation is being used to determine whether levels exceed a threshold for positivity (a cross sectional application) for patient inclusion in clinical trials and to measure changes in amyloid burden over time (a longitudinal application) to assess disease progression or modification by therapeutic intervention.

This QIBA Profile 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 to evaluate therapeutic drug response. A potential future clinical use is also in the individualization of therapeutic regimen based on the extent and degree of response as quantified by amyloid-PET. Quantitative assessment of amyloid burden at a single time point (cross sectional or bias Claim) is not part of the current Profile but may be included in a future version as bias reference data becomes available.

2.1. 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 (wCV) of $\leq 1.94\%$.

This technical performance claim is to be interpreted in the context of the considerations stated below.

2.2. Considerations for claim

The following important considerations are noted:

1. The technical performance claim was derived from a review of the literature summarized in Appendix B, where 18F amyloid PET tracers were used and data acquisition and processing procedures were considered to be adequately aligned with the recommendations in this profile. The constraint of a sixty day period (or less) for test-retest was applied in order to avoid the possible contribution of actual changes in amyloid burden. The wCV cited is the highest (“worst case”) of these short term test-retest studies, where wCV values ranged from 1.15% in healthy controls using a cerebellar cortex reference region to 1.94% in AD patients using a whole cerebellum reference region. A limitation is that only two relatively small studies covering three study groups (2 AD, 1 healthy control) satisfied the short term test-retest criteria and were aligned with profile recommendations. Given this limitation, and in order to assess the applicability of the short term wCV reference for typical clinical trial durations, the wCV values derived from two studies of amyloid negative normal controls from the larger ADNI data set over a 2 year period, using a variety of reference regions, were examined. The wCV values in these longer term studies ranged from 1.25% (white matter reference region) to 1.6% (whole cerebellum

reference region) in four of five cases, within the range stated by the claim. For the same set of images, the wCV in one group's analysis was 3.38% for one reference region vs. 1.37% for another. The important consideration of analysis methods is discussed in consideration number 2. The reference literature is discussed further in Appendix B.

2. Conformance to the Claim depends upon many factors, including minimized subject motion, alignment of Em/Tx scans, and stability in detection sensitivity from scan to scan in reference region slices compared to target region slices. In particular, choice of reference region, and the boundary definition of the reference region selected can greatly impact wCV due to the sensitivity of different regions to technical factors. A more extensive discussion of the considerations in selecting reference region is found in section 3.4.3.2.2.
3. This Claim is applicable for single or multi-center studies assuming that the same 18F-amyloid PET tracer, scanner, scanner software version, image acquisition parameters, image reconstruction method and parameters, and image processing methods including target and reference region definition and boundaries are used for each subject at each time point as described in the Profile.
4. 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). (The assumption of linearity and its demonstration are discussed further in section 4.4 and Appendix F.)
5. The SUVR has been selected due to its logistical feasibility in multi-site trials, and its use to date in large reference studies such as ADNI. However, from the fundamental kinetic properties of radiotracers it can be understood that 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) and/or tissue clearance (Carson RE et al, 1993). When random, this variability contributes to and is embedded in the wCV stated in the Claim. However, changes in perfusion and/or clearance can be systematic due to the action of certain pharmacological agents or due to disease progression, creating artificial change in amyloid SUVR. A published study using ADNI data suggests that the impact of regional cerebral blood flow changes on longitudinal change in SUVR can be on the order of 2% to 5% in late MCI/AD patients (Cselényi). This can be significant in studies of amyloid accumulation, prevention, or modest amyloid removal.

Whether or not a change in SUVR is affected by changes in perfusion and/or clearance ideally should be first demonstrated in a small (e.g. 20 subjects) cohort before SUVR is used in the larger clinical trial. These contributions can be quantified by applying kinetic modeling to a full image acquisition from time of tracer injection through late timeframes. These validation studies can help 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. Alternate approaches to assessing blood flow changes have also been proposed (e.g. arterial spin labeling MRI) though suitability remains to be validated. As a separate consideration, in the case of a new PET tracer, studies that include blood sampling should be conducted to confirm that the SUVR approach and use of a reference region are a suitable approach to measure tracer binding. For further details regarding considerations in kinetic modeling and a comparison to SUVR please see Appendix I.

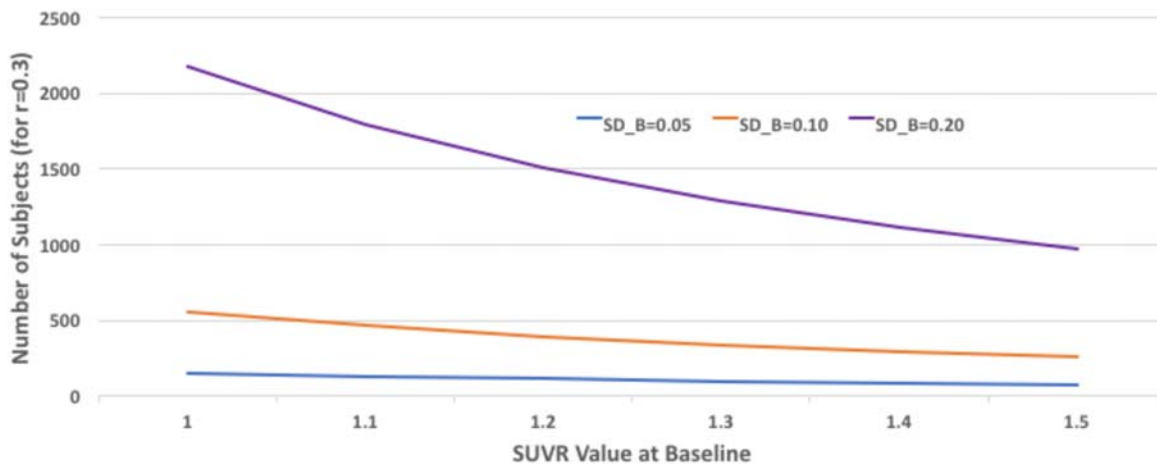
2.3. Clinical Trial Utilization

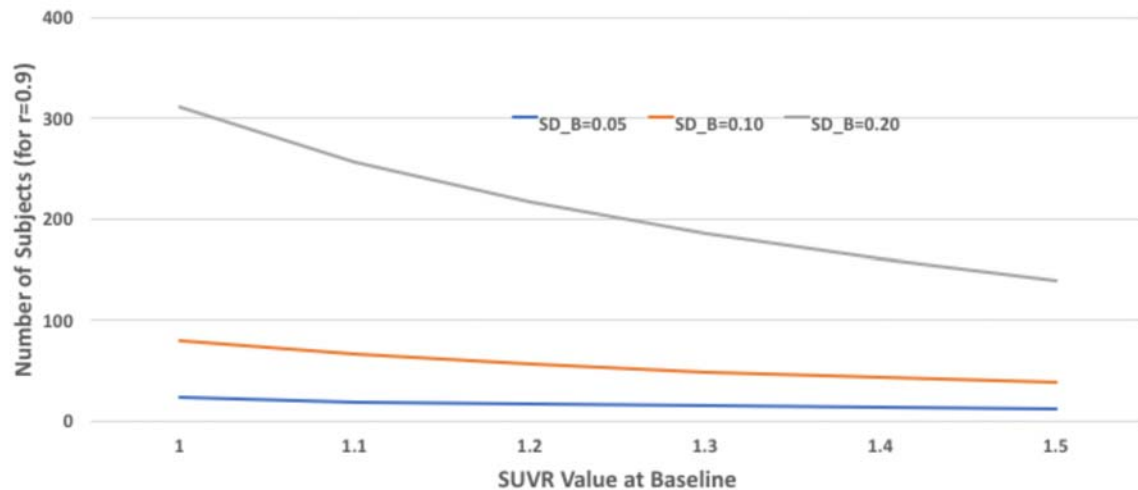
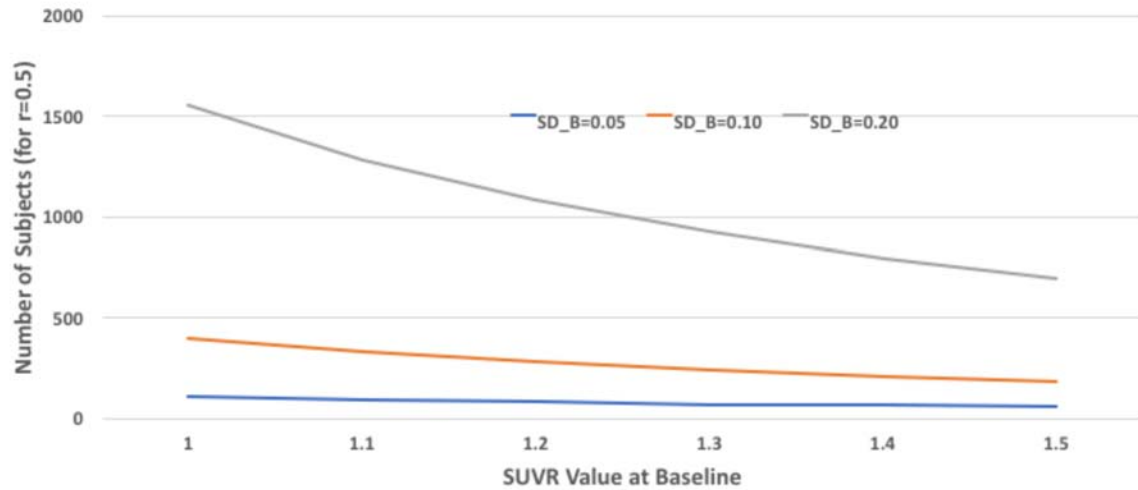
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201 Although the Claim is based on reference literature for a short duration, as suggested by the 2 year
202 comparison studies, the wCV should apply longer term pending the stated considerations.

203
204 The wCV stated in the technical performance Claim can be used to derive confidence intervals for individual
205 subject changes in amyloid burden. However, because amyloid accumulation rates reported in the
206 literature average from 1 percent to a few percent per year, SUVR confidence intervals derived from the
207 wCV may not be relevant to the assessment of individual change over the duration of a typical clinical trial.
208 In this case, the wCV value can be used to guide the number of subjects to include in clinical trials targeting
209 measurement of longitudinal change in amyloid SUVR. A few examples of practical uses of the Claim are
210 described below, and further guidance is found in the [“Statistical Planning for a Clinical Trial Guidance
211 document”](#) posted on the QIBA website, in development as a full manuscript.

- 212
213 1. **Powering a clinical trial to measure rate of amyloid accumulation.** As an example, suppose you want
214 to estimate the mean amount of amyloid accumulation in a two-year period for a cohort of patients.
215 You want to estimate the mean amount of accumulation to within $\pm 1\%$ (i.e. precision of 95% CI). We
216 considered mean SUVR values at baseline from 1.0-1.5, between-subject standard deviation (SD_B)
217 ranging from 0.05 to 0.30, and correlation between the paired measurements from a subject of $r=0.3$
218 (first figure panel), 0.5 (second panel), and 0.9 (third panel). The figure shows the number of subjects
219 needed if the likely rate of amyloid accumulation is 1.5% per year.

220
221 Note that the number of subjects required is greatly reduced as the correlation coefficient increases
222 between visits. For context, an internal (unpublished) analysis of florbetapir data available through
223 ADNI at baseline and 2 years suggests that the correlation between scans is higher for certain reference
224 regions than others. For example, using the composite of cerebellum and white matter or only white
225 matter as reference, R was 0.95 or 0.96 respectively for amyloid positive subjects (N=207) and 0.94 for
226 subjects close to the positivity threshold (N=51). However, using cerebellar cortex or whole cerebellum
227 as the reference, R values were 0.79 and 0.83 respectively for amyloid positive subjects and 0.33 and
228 0.48 respectively for subjects close to positivity threshold.





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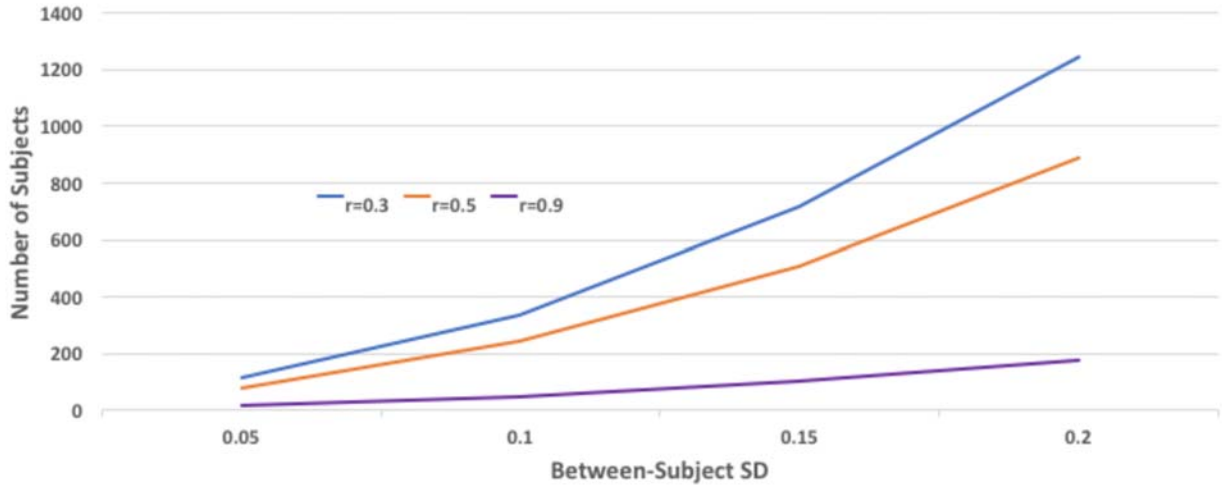
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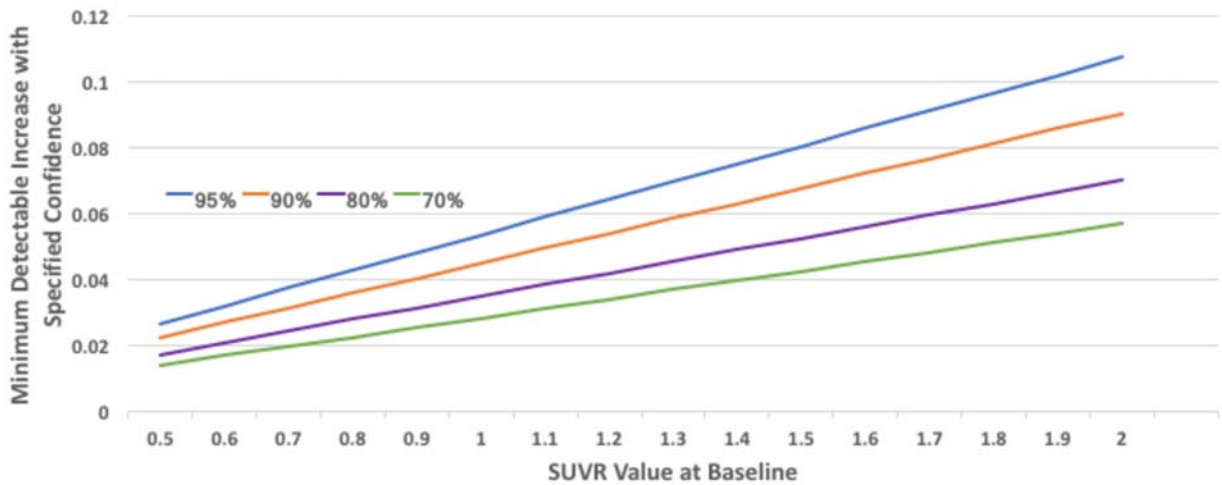
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2. **Powering a clinical trial to measure a reduction in the rate of amyloid accumulation (e.g. due to treatment intervention).** Consider a clinical trial comparing the accumulation in amyloid SUVR over time between two groups of subjects: those undergoing a new treatment vs. a control group. Alzheimer’s patients will be recruited and randomized to either the experimental intervention or the control group. SUVR will be measured in all subjects at baseline and two years later. The null hypothesis is that there is no difference in subjects’ mean amyloid accumulation between the two groups; the alternative hypothesis is that there is a difference (two-tailed hypothesis). If the likely rate of amyloid accumulation is 1.5% per year, the mean SUVR at baseline is 1.5, the between-subject standard deviation is between 0.05 and 0.2, and the correlation between the paired measurements from a subject is between 0.3 and 0.9, then the following figure illustrates the number of subjects needed per arm to detect a 50% reduction in the rate of accumulation over a 2-year period with 80% power.



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250

251 **3. Minimum detectable Increase for individual subject.** The smallest increase in SUVR that can be
 252 considered a real increase in amyloid accumulation for an individual subject (not just measurement
 253 error), with a certain confidence level, can be calculated as: $Y1 \times (0.0194) \times \sqrt{2} \times (z - value)$. The figure
 254 shows the minimum detectable increase for 70%, 80%, 90%, and 95% confidence for baseline SUVR
 255 values from 0.5-2.0.



256
257

258 **4. Confidence interval for an individual's true change.** For an individual's SUVR measurements of Y1 at
 259 baseline and Y2 at follow-up, the 95% confidence interval for the true change associated with the wCV
 260 of Claim 1 is given by the equation: $(Y2 - Y1) \pm 1.96 \times \sqrt{([Y1 \times 0.0194]^2 + [Y2 \times 0.0194]^2)}$.

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3. Profile Activities

The following figure provides a graphical depiction that describes the marker at a technical level. The resulting SUVR measure of amyloid burden is then interpreted per the thresholds and/or other criteria determined per the study (this differs from visual interpretation).

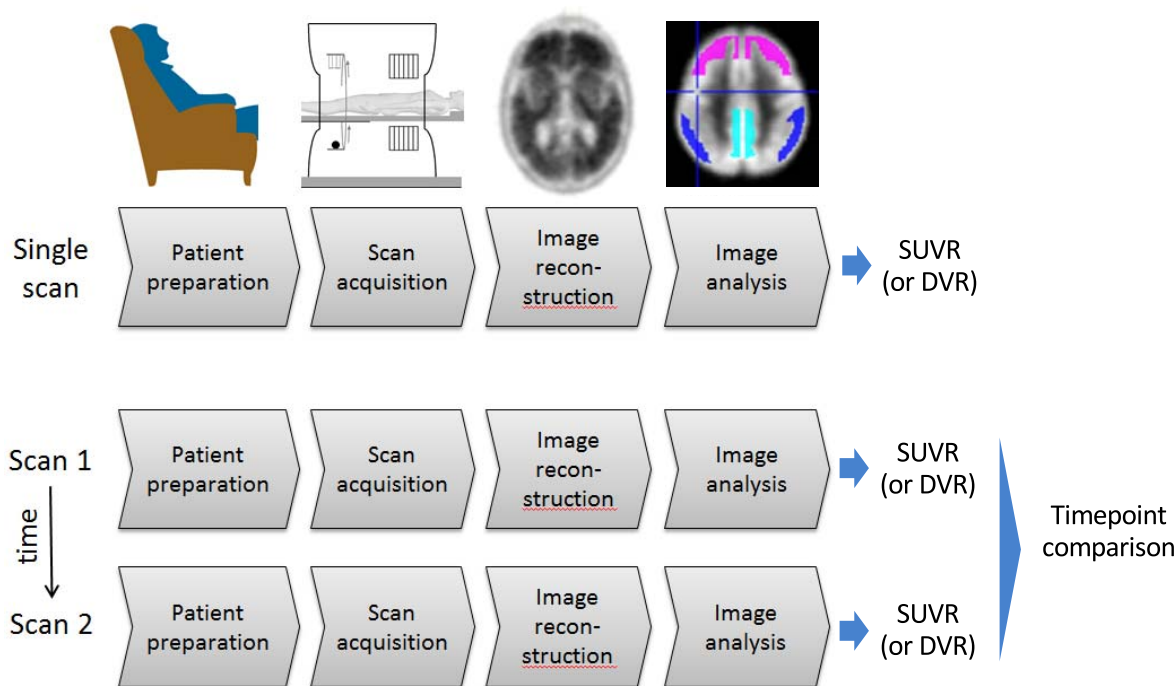


Figure 3: The method for computing and interpreting brain amyloid burden using PET may be viewed as a series of steps using either one scan (corresponding to a fit for use of a future ‘Cross-sectional’ Claim) or two or more scan sequences or time points (corresponding to a fit for use of the current 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 and/or different processing pipelines or measurement methods mapped to a standard range of numeric SUVR values (Klunk et al, 2015). At this time, the centiloid continues to undergo adoption and is not included in Profile requirements. Further, this Profile requires the use of a single radiotracer in a multi-center trial when pooling of data across centers is performed. For further description see section 3.4.3.3.3 of this Profile.

Patients may be selected or referred for amyloid-PET imaging through 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

- 288 bio-distribution and uptake of amyloid tracer. See Section 3.1.3.1.2 for ligand-specified timing.
- 289 2) Emission and transmission data are acquired (typically the PET scan and CT scan if a PET-CT
290 scanner).
- 291 3) Data correction terms are estimated and the attenuation and scatter corrected images are
292 reconstructed.
- 293 4) Images are assessed for quality control, and may separately be reviewed visually for qualitative
294 interpretation (outside of the scope of this profile).
- 295 5) Quantitative (and/or semi-quantitative) measurements are performed.

296 Note that steps 4 and 5 may occur in either order or at the same time, depending upon the context of the
297 review (clinical research versus clinical practice) with reference to the specifications described in each
298 tracer's package insert. Currently, the quantitative use of amyloid-PET tracers is not approved by any
299 regulatory authorities in clinical practice in the U.S. However, quantitation is available as part of various
300 scanner and workstation software packages and is used extensively in clinical trials. More details on the
301 requirements are given below.

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

304 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	Radiologist, Nuclear Medicine Physician, Image Analyst, or other qualified person with the necessary training to use one or more image Processing and Analysis Software tools
3.5	Image Interpretation	Radiologist, Nuclear Medicine Physician, or an individual meeting requirements designated for the study; note that qualitative image interpretation is not within the scope of this Profile

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

309 **3.1. Subject Handling**

310 This Profile will refer primarily to 'subjects', keeping in mind that the recommendations apply to patients in
311 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. Guidance for the use of amyloid to support diagnosis of symptomatic patients has been published in “Appropriate Use Criteria for Amyloid PET: A Report of the Amyloid Imaging Task Force”. Asymptomatic or other clinical trials are guided by study objectives. See tracer manufacturer guidance for additional information regarding patient exclusions.

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. (This is for comfort purposes and does not directly impact tracer uptake.)
- The subject should remain recumbent or may be comfortably seated. (This is for comfort purposes and does not directly impact tracer uptake.)
- After amyloid tracer injection, (and if not a full dynamic scan or early frame scan whereby acquisition begins immediately after injection, and if verified with tracer manufacturer's recommendations) 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 for the scan session (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. All tracers approved at the time of this Profile have a maximum of 10 ml. 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]
Tracer Admin Activity	370 MBq Max 50 mcg mass dose	185MBq Max 20 mcg mass dose	300 MBq Max 30 mcg mass dose

Parameter	Entity/Actor	Specification
Administered amyloid Radiotracer Activity	Imaging Technologist, Physician, Nurse, or other qualified Health Professional	The qualified Health Professional shall <ol style="list-style-type: none"> 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

Parameter	Entity/Actor	Specification
		<p>the time of measurement.</p> <p>4. Inject the quantity of radiotracer as prescribed in the protocol.</p> <p>These values shall be entered into the scanner during the PET/CT acquisition.</p> <p>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.</p> <p>All data described herein on activity administration shall be documented.</p>
		All data should be entered into the common data format mechanism (Appendix E).

416 3.1.3.1.3 Radiotracer Administration Route

417 Amyloid seeking radiotracer should be administered intravenously through an indwelling catheter (21
418 gauge or larger) into a large vein (e.g., antecubital vein). This is usually administered as a manual injection;
419 a power injector may be used especially for studies in which SUVR measures of amyloid load are compared
420 with dynamic measures (BP_{ND}). Intravenous ports should not be used, unless no other venous access is
421 available. If a port is used, an additional flush volume should be used. As reproducible and correct
422 administration of radiotracer is required for quantification purposes, extravasation or paravenous
423 administration should be avoided. It should be ensured, for both automated and manual injection, that the
424 radiotracer is not being diluted with saline before or during the injection process. Flushing with saline
425 should only occur after the injection and is recommended when using injection lines.

426 If an infiltration or extraneous leakage is suspected, the event should be recorded. The anatomical location
427 of the injection site should be documented on the appropriate case report form or in the Common Data
428 Format Mechanism (Appendix E).

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

Parameter	Entity/Actor	Specification
Amyloid radiotracer Administration	Technologist or Physician	<p>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.</p> <p>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.</p>
Suspected	Technologist	Technologist shall

Parameter	Entity/Actor	Specification
infiltration or extraneous leakage	and/or Physician or Physicist	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).

430 3.2. Image Data Acquisition

431 This section summarizes the imaging protocols and procedures that shall be performed for an amyloid-PET
432 exam by using either a PET/CT or a dedicated PET scanner with the requirement that a Germanium source
433 can be used to perform attenuation correction. Note that PET scanners that do not measure in some way
434 the attenuation of the brain and use a calculated algorithm for estimating the attenuation and scatter
435 corrections are excluded from this profile. PET/MR scanners are not strictly excluded in this version as long
436 as the repeatability of the SUVs from these scanners is conformant with the assumptions underlying the
437 Claims. This work was not yet published when this Profile was released. Since the claims of this profile are
438 only valid for the same patient being scanned on the same scanner with the same protocols and analysis,
439 only the repeatability of the PET/MR SUVs needs to be validated in the context of the Claims, and not the
440 difference in SUVs as compared to PET/CT scanners. Going forward in this document, PET scanner can
441 mean either a PET/CT or a dedicated PET scanner (or as stated above, PET/MR).

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

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

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

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

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

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

459 The issues described in this Section should be addressed in the clinical trial protocol, ideally with
460 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. The table below lists recommended tracer administration parameters at the time of this Profile for those tracers that have been approved by the FDA in the U.S. However, in all cases, the manufacturer's current labeling parameters should be consulted, as these may change over time. In addition, while the principles of this profile are fairly generalizable, the specifics apply to the tracers that have already been approved and for which data is available. Note that the durations shown in the table below should be considered minimum durations for image acquisition. For example, for florbetapir, the time window used by ADNI is 20 minutes rather than 10. A full dynamic protocol or longer imaging window (even if not full dynamic) can significantly improve the quality of the data. This will be particularly important for trials in preclinical AD.

Parameter	Florbetapir (Amyvid) [1]	Flutemetamol (Vizamyl) [2]	Florbetaben (Neuraceq) [3]
Tracer Uptake Time (mpi = mins post injection)	30 – 50 mpi	60 - 120 - mpi	45 - 130 mpi
Minimum Duration of Imaging Acquisition	10 min	10 - 20 min	15 – 20 min

Another amyloid tracer, AV4694, has not yet completed validation in phase III clinical trials and therefore dose and the following acquisition details are preliminary: uptake time 50-70 mpi, and an acquisition duration of 20 minutes.

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 subject on the PET or PET-CT scanner table so that their head and neck are relaxed. The head should ideally be positioned to have axial slices passing through the cerebellum without intersection with the posterior occipital lobe. This avoids contamination of the posterior cerebellar region by the occipital lobe and the tentorium. 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 place 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. Lasers are recommended to aid in horizontal and vertical centering. 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

527 region serves as a reference region for subsequent quantification.

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

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

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

535

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

536

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).

537

538

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 format mechanism (Appendix E).

539

540 3.2.1.3 Scanning Coverage and Direction

541 Anatomic coverage should include from the skull base to the skull vertex, ensuring complete inclusion of
542 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

Parameter	Entity/Actor	Specification
		specifications and the same for all time points.

543

544 **3.2.1.4 Scanner Acquisition Mode Parameters**

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

550 *PET Acquisition*

551 If possible, for SUVR measurement the PET data should be acquired in listmode format (for fullest flexibility
552 for correcting for head movement) or divided into multiple acquisitions with a maximum of 5 minutes each.
553 If there were no head motion during the scan, a single acquisition frame would be sufficient. However, this
554 is difficult to predict ahead of time, use of multiple time slices is critical for proper motion correction if the
555 subject does not remain still throughout the scan. A full dynamic scan would include additional frames but
556 should also provide for multiple time slices in the late timeframes. Individualized, site-specific acquisition
557 parameters should be determined upon calibration with the appropriate phantom (see below).

558

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.) <u>shall be specified</u> 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.) <u>shall be set as specified</u> by study protocol and used consistently for all patient scans.
		PET should be acquired in listmode format (best) or dynamic time frames of no more than 5 minutes each when possible in order to allow checking and correction for subject motion.

559

560 *CT Acquisition*

561 For the CT acquisition component of the PET/CT scan, this Profile only addresses the aspects related to the
562 quantitative accuracy of the PET image. In other words, aspects of CT diagnostic accuracy are not addressed
563 in this Profile. In principle, any CT technique (parameters include kVp, mAs, pitch, and collimation) will
564 suffice for accurate corrections for attenuation and scatter. However, it has been shown that for estimating
565 PET tracer uptake in bone, lower kVp CT acquisitions can be more biased. Thus higher kVp (greater than or

566 equal to 80 kVp) CT acquisitions are recommended in general (Abella et al). In addition, if there is the
 567 potential for artifacts in the CT image due to the choice of acquisition parameters (e.g., truncation of the CT
 568 field of view), then these parameters should be selected appropriately to minimize propagation of artifacts
 569 into the PET image through CT-based attenuation and scatter correction.

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

577

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 80 shall be used and used consistently for all subject scans.

578

579

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.

580

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

588 3.3. Imaging Data Reconstruction and Post-Processing

589 3.3.1 Imaging Data Reconstruction

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

595 The PET reconstruction parameters include the choice of reconstruction algorithm, number of iterations
 596 and subsets (for iterative algorithms), the type and amount of smoothing, the field of view, and voxel size.
 597 The quantitative accuracy of the PET image should be independent of the choice of CT reconstruction
 598 parameters, although this has not been uniformly validated. In addition if there is the potential for artifacts
 599 in the CT image due to the choice of processing parameters (e.g., compensation for truncation of the CT
 600 field of view), then these parameters should be selected appropriately to minimize propagation of artifacts
 601 into the PET image through CT-based attenuation and scatter correction. At the time of this profile version,
 602 most scanners have a z-slice thickness less than or equal to 3.27mm, although some older scanners have a
 603 slice thickness of 4.25mm.

604

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, the Point Spread Function (PSF) option can be used; the use or non-use of PSF must be consistent for a given subject across time points.

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 ≤ 4 mm in the z direction. 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.

505

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

510 3.3.2 Image Data Post-processing

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

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

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

523 3.3.2.1 Ensure image orientation

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

529

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

530

531 3.3.2.2 Create Static Image

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

542

543 3.3.2.2.1 Intra-scan inter-timeframe assessment and alignment

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

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

567 correction was performed on a frame by frame basis during image reconstruction, large values indicate that
568 emission-transmission scan misalignment error is also embedded in one or more frames.

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

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

589 3.3.2.2 Combine discrete timeframes

590 Once all or a subpopulation of the appropriately aligned timeframes have been identified, a composite
591

592 image is generated for further processing and analysis. For late timeframe scans, this is accomplished
 593 through averaging or summation of the timeframes into a single image volume. In full dynamic scanning, a
 594 “parametric” image can be created through a more complex procedure that involves measuring signal in
 595 amyloid “rich” (having high tracer binding) and amyloid “poor” (low tracer binding) regions, or using blood
 596 measurements if available, and solving simultaneous equations to determine voxel values. The parametric
 597 image can then be measured using the same Volume of Interest or other methods described below, with
 598 the difference that the measure becomes a Distribution Volume Ratio (DVR) rather than SUVR.
 599

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

701 3.3.3 Imaging Data Storage and Transfer

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

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

713 **Post-processed image data** are images that have been transformed after reconstruction in some manner.
 714 This is typically a stack of DICOM slices/files constituting a PET image volume that can still be analyzed on
 715 one or more of the following: PET scanner console, PET image display workstation, PACS system, etc.
 716 For archiving at the local site or imaging core lab (if relevant), the most important data are the original
 717 images, i.e. the image raw data. In the unlikely event that the scanner raw data (which should be archived
 718 by the local site) is required for later reprocessing; this should be made clear in the protocol.
 719

Parameter	Entity/Actor	Specification
Data archiving: raw images	Technologist	The originally reconstructed PET images (image raw data), with attenuation correction, and CT images shall always be archived at the local site. If scanner raw data need to be archived for future reprocessing, this should be defined prospectively in the Protocol.

Parameter	Entity/Actor	Specification
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.

720

721 **3.4. Image Analysis**

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

727 **3.4.1 Input Data**

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

734 **3.4.2 Image Quality Control and Preparation**

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

741 **3.4.2.1 Correction for Partial Volume Effects (PVE)**

742 Partial Volume Effects Correction (PVEc) is not recommended as a “by default” step in this Profile due to
 743 the fact that the process itself can introduce a great deal of variability, countering the tolerance goals of the
 744 Profile. However, we discuss this step here, as it may be included in certain study protocols particularly if
 745 methodology is systematically employed that does not increase variability. As background on this topic, due
 746 to the limits of PET scanner resolution, the signal measured at the borders of white and gray tissue, or
 747 tissue and cerebrospinal fluid (CSF) can contain contributions from both types of tissue within the
 748 boundaries of the same voxel. In particular, some amyloid PET tracers have high levels of nonspecific white
 749 matter uptake, producing high signal intensity that “spills into” neighboring gray tissue measures. In
 750 addition, neurodegenerative patients may exhibit substantial, progressive atrophy, increasing spill-in from
 751 CSF that can dilute increases or accentuate decreases originating from the atrophic tissue elements.
 752 Several different mathematical algorithms and approaches have been developed to correct or compensate
 753 for PVE and tissue atrophy. However, these approaches are not necessarily sensible in the setting of

754 amyloid imaging and quantification. Simply applying correction for the loss of cerebral gray matter results
 755 in upscaling of image signal intensity, and is most appropriate when the tissue origin of the signal is lost,
 756 resulting in the atrophy (such as loss of synaptic neuropil in [18F]2-fluoro-D-2-deoxyglucose (FDG) cerebral
 757 glucose metabolism imaging). In the case of amyloid deposition in neurodegenerative dementia, however,
 758 the deposits are not contained with normal cerebral gray matter elements. Amyloid plaques are
 759 extracellular accumulations and are unlikely to degenerate as gray matter atrophies due to losses of
 760 synapses and neurons ensues. Thus, applying gray matter atrophy-correction PVEc may inappropriately
 761 “upscale” the amyloid signal from atrophic cortical regions. Usual PVEc approaches result in a new image,
 762 typically containing only gray matter, and has been shown to increase the apparent amyloid in AD patients
 763 by as much as 30% to 56%. The most sensible approach to PVEc in amyloid images is to apply correction for
 764 spillover from subcortical white matter into the gray matter regions, which is likely to become increasingly
 765 problematic as the cortical gray matter becomes atrophic. Appropriate use of PVEc can potentially help to
 766 increase sensitivity to longitudinal change, and to reduce error associated with changes in atrophy or white
 767 matter uptake. However, PVEc methods can also introduce variability, and results are highly sensitive to
 768 subjective selections of the parameters used in calculating the correction. Effects upon measurement of
 769 longitudinal change have varied from no effect to an increase in measured change. The tradeoff between
 770 benefit vs. these considerations must be considered and the decision as to whether or not to use may be
 771 study dependent. The point in the process at which PVEc is applied may vary, for example either applied
 772 to spatially normalized images or to native images, prior to or after the creation of a SUVR image.

773 3.4.2.2 Image Smoothing

774 Depending upon whether more than one scanner and reconstruction software combination is being used to
 775 acquire patient data, and the objective of the image analysis, it may be necessary to smooth the image.
 776 Smoothing applies a mathematical filter to the image signal at each voxel to help compensate for
 777 differences in spatial resolution that exist between different scanners. Even if the same scanner is used for
 778 each visit by a particular subject, being able to compare the SUVR value to a threshold derived using images
 779 from multiple scanners, or to other study subjects whose data is collected on other scanners, requires
 780 adjustment for scanner differences. If not reconciled, these differences can cause a few percent difference
 781 in SUVR (Joshi et al, 2009).

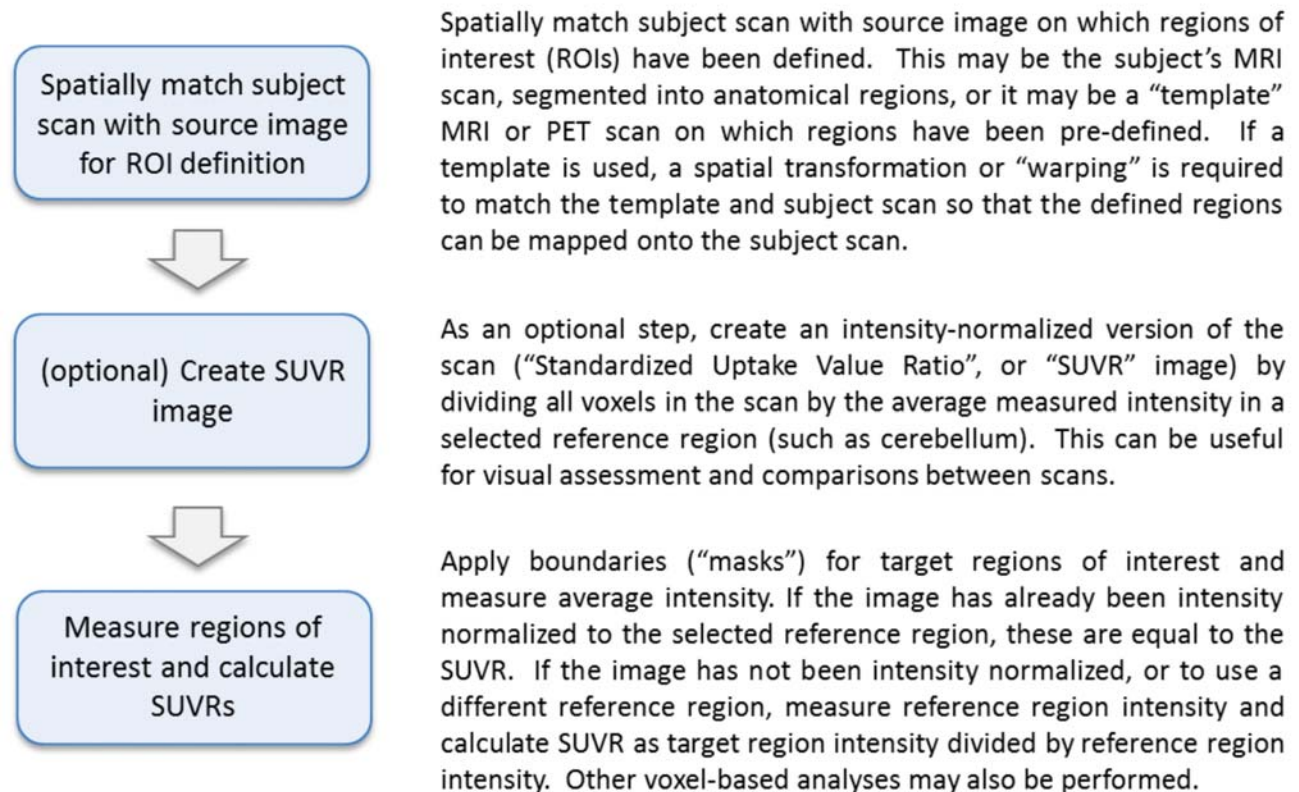
782 By “spreading” signal out, smoothing also helps to increase the spatial overlap of amyloid accumulation
 783 across different subjects, increasing the ability to identify group effects in voxel-based comparisons.
 784 However, smoothing also dilutes signal, particularly in small structures, and can also increase the mixing of
 785 white, gray, and CSF signal.
 786

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.

788 3.4.3 Methods to Be Used

789 The methodology and sequence of tasks used to perform amyloid tracer analysis have historically varied

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



301

302

303

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

304

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

308 3.4.3.1 Spatially Match Subject and Template

309 The fitting of Volumes of Interest (VOIs) to a scan for amyloid studies has typically been performed by
 310 automated software, reducing the subjectivity, inter-reader differences, and labor intensity of manual
 311 delineation. In order to measure pre-defined VOIs for SUVR calculation (or DVR in the case of full dynamic
 312 scanning), it is necessary to map these spatial boundaries to the subject’s specific brain morphology or vice

313 versa.

314 3.4.3.1.1 “Fuse” MRI and PET images

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

327 Since mapping operations performed on the MRI will be applied to its co-registered PET scan, it is critical to
 328 ensure that the PET and MRI have been properly aligned to one another. Visual inspection should be
 329 conducted with careful attention to proper left-right orientation and alignment in all three planes
 330 (transaxial, sagittal, and coronal) ; quantitative goodness of fit measures can also be applied. Successful
 331 fusion may be indirectly checked through verification of correct VOI placement and/or correct spatial
 332 normalization. However, if misalignment occurs, one must backtrack to determine where in the process
 333 this happened, and verification of each step is recommended. Automated methods to assure goodness of
 334 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.

337 3.4.3.1.2 Longitudinal PET co-registration

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

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

348 It is noted here that some studies (unpublished, multiple groups) have shown that a superior longitudinal

349 alignment of sequential PET scans can be achieved when co-registering the series of PET scans together
 350 rather than separately co-registering each PET to the MRI. However, it is also noted that in cases of
 351 substantial longitudinal atrophy or ventricular expansion, care must be taken in ensuring that the VOIs
 352 applied to each scan account for the actual gray tissue present in the brain.

353 In addition, it is also noted that although not ordinarily expected, it is possible for longitudinal structural
 354 changes (abnormalities) to occur that impact the ability to use a common mapping across scans. One such
 355 example is cerebellar encephalomalacia. However, such an event is not within the scope of this profile
 356 version and it is rather recommended to exclude the subject in this case or to use target and reference
 357 regions that are unaffected by the abnormality.

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

361 The following approaches can be applied for spatial mapping:

362 (a) Spatial mapping (“warping”) of individual brain scans to a template brain having pre-defined VOI
 363 boundaries. The VOIs are then measured in “template space”, with some spatial distortion to the original
 364 brain tissue. The goodness of fit of subject to template depends upon multiple factors including: the spatial
 365 warping algorithm applied, the parameters selected for the warping algorithm, and the template selected.
 366 For example, scans acquired in an aging, atrophic population may warp in a superior manner to a template
 367 that was also derived from an aging, atrophic population.

368 (b) Spatial mapping of the template brain and pre-defined VOI boundaries to the individual brain scans. In
 369 this case, the VOIs are still probabilistic but are mapped to the subject's original morphology.

370 (c) Use of segmentation algorithms that identify each anatomical structure of interest within the subject's
 371 native morphology using the subject's MRI (e.g., Freesurfer). The resulting segmentation (i.e. the
 372 identification of various gray tissue regions) can vary depending upon several factors including: the
 373 segmentation software and version applied, the operating system on which the software is run, the
 374 parameters selected in the segmentation software, the MRI sequence used, and .

375 The mapping between subject image and template image is accomplished through automated spatial
 376 normalization or warping software algorithms. When an MRI is used, the transformation is determined
 377 though a “warp” between subject MRI and template, and the same mathematical transform is applied to
 378 the coregistered PET scan (if transforming to template space) and/or to the ROIs (if transforming to the
 379 native subject scan). The accuracy of the spatial transformation depends upon the algorithm. Certain
 380 software and software versions have shown superior alignment of cerebellum, deep structures such as
 381 putamen and medial temporal regions, and ventricles as compared to older algorithms (Klein et al, 2009).
 382 In addition, the template to which images are warped can impact goodness of fit and optimization for the
 383 study population may be of use.

384 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 to 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

358 field of view). In head rotation and in emission-transmission scan misalignment, the posterior edge of the
359 cerebellar cortex can be particularly impacted. In addition, slight shifts in position can cause a blending of
360 white and gray tissue that will impact the reference measurement. Further, the cerebellum is located in
361 transaxial slices that are not in proximity to several typical target VOIs, and signal in those slices may not
362 change in the same way due to technical factors. In longitudinal studies, for one radiotracer, the cerebellar
363 cortex has been demonstrated to show stability over time (Villemagne, AAIC 2015) while for others
364 variability with regard to measured change has been shown, decreasing statistical power. Even in cross-
365 sectional measurements, technical noise embedded in the cerebellum (or any reference region) may cause
366 a subject whose amyloid burden is at the threshold of positivity to “tip” in one direction or another. If the
367 reference regions does include the cerebellum, it is recommended to omit the superior portions of the
368 cerebellum to avoid radiotracer contamination from surrounding structures such as the occipital cortex or
369 the fusiform gyrus and to omit the lowest slices that exhibit greatest variability. These strategies have been
370 employed in various studies (Shcherbinin et al, 2016; Barrtet et al, 2016; Pontecorvo et al, 2017; Hahn et al,
371 2017). Alternate reference region comparisons are also recommended to ensure that noise has not driven
372 the SUVR result.

373 Use of whole cerebellum has been specified as a reference of choice with some PET tracers (such as
374 florbetapir), and can reduce variability arising from shifts that include more white matter (Joshi, JNM 2015),
375 since white matter is already included. However, the same issues with spatial location, edge noise, and
376 lower average signal still apply. As an alternative reference, the pons has been applied in multiple studies,
377 and found to have a slightly lower variability. Its advantages include higher signal due to white matter
378 inclusion, and more central location in the brain at a slightly further distance from the edge of the scanner
379 transaxial field of view. Some studies using florbetapir, flutemetamol and 11C-PIB have found that the pons
380 exhibited lower longitudinal variability than a cerebellar reference region (Thurfjell et al, 2014; Shokouhi et
381 al, 2016; Edison et al, 2012). However, the narrow cylindrical size and shape of the pons make it vulnerable
382 to subject motion, and it, too, can be affected by technical variability. Subcortical white matter provides
383 another alternate reference region, with the advantages of higher signal, larger measurement volume,
384 transaxial alignment with target regions of interest. Studies have demonstrated benefit in lower variability
385 using subcortical white matter, and thus greater statistical power in measuring longitudinal change, relative
386 to other reference regions (Chen et al, 2015; Brendel et al, 2015; Schwarz et al, 2016; Blautzik et al, 2017).
387 One consideration in the use of a white matter reference is that the kinetic properties of white matter
388 differ from those of the gray tissue target regions, with unclear impact upon measurement validity. There
389 is not yet a published full dynamic modeling study of white matter as a reference. White matter axonal
390 integrity may decline with AD progression and age, potentially increasing advantageous cross sectional
391 differences between AD and Normal, and introducing possible variability over time. However, findings
392 support the ability to detect increases in amyloid positive populations as expected and seen with gray
393 tissue reference regions, yet with lower variability (ideally this would be compared to full kinetic modeling
394 results to demonstrate accuracy). When white matter is used, careful definition based upon the MRI, with
395 erosion from neighboring gray tissue, is recommended. Combinations of whole cerebellum, pons, and
396 subcortical white matter, or cerebellar white matter and pons, or “amyloid poor” gray regions other than
397 cerebellum have also been applied with reductions in longitudinal variability (for florbetapir) resulting in
398 increased statistical power (Tryputsen et al, 2015; Landau et al, 2015). It is finally noted that regions
399 comprised of both gray and white matter, whether whole cerebellum or composite regions, may include
400 divergent changes over time. These may be a suitable match for probabilistic target regions that include
401 both gray and white matter, or given white matter spillover into gray tissue. However, for “pure” gray
402 target regions, their longitudinal use may introduce some non-amyloid related variability. All of this must
403 be weighed against other sources of variability arising from use of a pure cerebellar cortex reference due to

low signal, scatter, subject motion, and differences in the axial placement from scan to scan.

“Amyloid poor” gray tissue in the same axial plane as the target regions can provide the dual benefit of co-location, protecting against sometimes major changes arising from differences in slice sensitivity in a scanner, as well as matching of gray tissue perfusion rates. A caveat is that if these regions slowly accumulate amyloid or do have amyloid accumulation that can be removed during an anti-amyloid drug study, reference stability may be compromised.

With the above caveats in mind, the use of a combined reference, subcortical white matter, or other stable “amyloid poor” regions proximal to target regions may be advised, depending on the radiotracer, 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

Parameter	Entity/Actor	Specification
		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.

034

035 **3.4.3.2.4 Generate SUVR Image**

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

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

042 **3.4.3.3 Create SUVR**

043 **3.4.3.3.1 Measure Regional Values**

044 The mean value within each VOI is calculated as the numerator for the SUVR. A cortical average may be
 045 calculated as the average of multiple VOIs, or weighted by the number of voxels in each VOI. While the
 046 selection of which regions to include and how to combine them is dependent upon the study objectives,
 047 minimizing variation due to numerous technical factors (including subject motion, axial variability, and
 048 image alignment) is best achieved when using an average of multiple regions. The performance claim is
 049 derived from published studies in which a non-weighted average of cingulate, frontal, lateral temporal, and
 050 lateral parietal regions was applied.

051 **3.4.3.3.2 Calculate SUVR**

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

055 **3.4.3.3.3 Relating SUVR values to other studies: the Centiloid**

056 Different protocols involve different tracers, target regions, and reference regions, and all of these
 057 contribute to how the SUVR can be interpreted with regard to amyloid burden. A value of 1.2, for example,
 058 can be amyloid positive using one tracer and/or set of regions for analysis, but amyloid negative using a
 059 different tracer and/or regions. In order to reconcile findings across data acquisition, processing, and
 060 analysis protocols, the concept of the Centiloid was developed (Klunk et al, 2015). The Centiloid is not
 061 intended to dictate the method for acquiring and processing data, but rather to provide a way to equate
 062 results obtained with a broad variety of protocol parameters. The basis for the Centiloid is a “gold
 063 standard” set of results derived from young healthy controls and elderly AD patients. These results have
 064 been generated using the radiotracer ¹¹C-PiB and a defined set of target region, reference region, and
 065 image processing and analysis steps. A linear progression of values from 0 (no amyloid) to 100 (mean for
 066 amyloid positive sporadic AD patients) has been established using this approach. 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 required to be 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 Centiloid values can be replicated with a correlation (r^2) exceeding 0.98. 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 directly applied to new studies using the same conversion parameters. PiB, flutemetamol, fluorbetaben and other image, SUVR and conversion data are available on the GAAIN website: <http://www.gaain.org/centiloid-project>.

It is noted that while the Centiloid can be used to reconcile values across tracers and methods, its use does not change the within-method variability or error that is already present (Su et al, 2018).

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

In the context of this quantitative Profile, interpretation refers to the way in which the quantitative SUVR or DVR measurements are used, rather than to a visual interpretation of the scan. Reporting of SUVR or DVR values is subject to the requirements of the study.

Parameter	Entity/Actor	Specification
Image Reporting	Imaging Facility	Imaging reports shall conform to the requirements of the study protocol.

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 and Molecular Imaging Technologists Section (SNMMI-TS) 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 have board certification by the American Board of Nuclear Medicine (ABNM) and/or the American Board of Radiology (ABR) (Diagnostic and/or Nuclear Radiology) 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 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 or may already be included in this Profile if the repeatability of the SUVs from these scanners is conformant with the assumptions underlying the claims. 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

Parameter	Entity/Actor	Specification
		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 $\pm 2.5\%$ 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 $\pm 2.5\%$ 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 $\pm 2.5\%$ 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.

176

177 3.6.3.1.2 Scales and stadiometers

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

179

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 $\pm 2.5\%$ from expected values using NIST-traceable or equivalent standards.

180

181 3.6.3.1.4 Clocks and timing devices

182 The PET and CT scanner computers and all clocks in an imaging facility used to record activity/injection
183 measurements should be synchronized to standard time reference within ± 1 minute. These include any
184 clocks or timekeeping systems that are connected with a subject's amyloid-PET study, in particular those
185 associated with the radionuclide calibrator, the injection room, the scanner, and the acquisition
186 computer(s). The synchronization of all clocks (to date, time of day and to time zone) should be monitored

187 periodically as part of ongoing QA program. In particular, clocks should be inspected immediately after
 188 power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur). Correct synchronization
 189 could be achieved using the Consistent Time Integration Profile as defined in the IHE IT Infrastructure
 190 Technical Framework. The Consistent Time Profile requires the use of the Network Time Protocol (NTP)
 191 (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.

193 **3.6.4 Phantom Imaging**

194 **3.6.4.1 Uniformity and Calibration**

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

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

Parameter	Entity/Actor	Specification
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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	<p>At least quarterly and following software upgrades, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom.</p> <ol style="list-style-type: none"> 1. Visual check that no streak artifacts or axial plane non-uniformities are present. 2. The standard deviation of a large central 2D ROI (3D when drawn on multiple slices) 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 (resulting in a 3D VOI) 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 $\leq 1\%$ qualify for use (e.g. some of the end planes may not qualify). (Note that if the historical 10% tolerance is applied rather than 1%, a similar error can be introduced into longitudinal SUVR measurement and the reference region and target region must be in the same axial slices from scan to scan.)
		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.

214 **3.6.4.2 Resolution**

215 The assessment of adequate resolution should include both a qualitative evaluation (using clinical or
216 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.

217

218 **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 $\mu\text{C}/\text{ml}$), 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.

219

220 **3.6.4.4 Amyloid-PET Specific Phantom Measurements**

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

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

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

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

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

- 238 • Spatial resolution – PET scanner hardware, reconstruction methods and reconstruction parameter
239 selections can result in dramatically different spatial resolutions in the reconstructed images.
240 Because partial volume effects (especially between gray and white matter regions) can bias many
241 amyloid PET measurands, it is essential to calibrate the spatial resolution of each scanner using the
242 acquisition and reconstruction protocol planned for patient imaging. A post-reconstruction
243 smoothing operation can then be applied for calculation of a measurand at a uniform spatial
244 resolution between scanners.
- 245 • Uniformity – In-plane and axial uniformity of the purpose-specific phantom should be within 1%
246 throughout the scanner field of view to be used in the calculation of the amyloid PET measurand.
247 Note that the historical axial uniformity tolerance of 10% has the implication that if a subject is
248 imaged in one axial location for one scan, and in a different axial location (e.g. a few cm different)
249 for the next scan, then the slices used to calculate each reference or target region value may change
250 DIFFERENTLY. This can introduce error of a few percent to many percent into the longitudinal SUVR
251 change. Selection of reference region and target region in the same axial slices can help to mitigate
252 this potential source of noise, as the differences cancel out.
- 253 • Absence of reconstruction artifacts – Reconstructed purpose-specific phantom data should be
254 visually free of reconstruction artifacts, such as streaks due to failing detectors or axial plane non-
255 uniformities due to errors in normalization.
- 256 • Qualitative and quantitative accuracy – Measurands using ratios, such as the SUVR must
257 demonstrate accuracy with 10% of an analytical or otherwise known gold standard.

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

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

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

278 The normative list below is based on the Hoffman anthropomorphic, NEMA Image Quality, ACR, and
 279 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.

280

281

282 3.6.4.5 Phantom imaging data analysis

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

287

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.

4. Conformance Procedures

Relation of this Profile to Expectations for QIBA Profile Conformance

Definitions (from Appendix C):

Qualified: 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.

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

Conformant: 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,

- 324 • Appropriately trained image analysts, with oversight by a Radiologist or Nuclear Medicine Physician,
- 325 • Medical Physics support to ensure appropriate scanner and equipment calibration, and to address
- 326 issues relating to quantification such as attenuation maps or movement
- 327 • Processes that assure imaging QIBA Profile-conformant image generation in appropriate time window

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

340

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 (for example, a Ge-68 cylinder if applicable) 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.

341

342 4.2. Performance Assessment: PET Acquisition Device

343 Distinct from the performance specifications and frequency of testing described in Section 4.1, which apply
 344 to quality control of the Acquisition Device at the imaging facility, this Section defines performance

345 specifications of the Acquisition Device to be met upon leaving the manufacturing facility. In order to be in
346 conformance with this Profile, the Acquisition Device should be held to the same standard whether a
347 mobile utility or a fixed installation; a mobile scanner may require additional calibration to achieve this
348 performance.

349 The PET scanner should use DICOM attributes to follow version numbers of software for: 1 Acquisition, 2
350 Reconstruction, 3 Post-processing, 4 Display/ROI analysis, 5 Dynamic Analysis. Performance requirements
351 regarding software version identification, documentation and tracking across time are described in Section
352 4.5.

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

357
358 All needed information for fully corrected administered activity (e.g., residual activity, injection time,
359 calibration time) is required. Note that use of the term administered activity below refers to fully corrected
360 net radioactivity.

361
362 Baseline level conformance requires that the DICOM image set from the subject's PET scan and necessary
363 metadata (that is not currently captured by all PET scanner acquisition processes) is captured in trial
364 documentation, e.g., case report forms. The metadata is required to perform the quantitative analysis and
365 perform quality control on SUV covariates. This includes for example, post-injection residual activity and
366 subject height. This data should be captured in the 'Common Data Format Mechanism' as described in
367 Appendix E.

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

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

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

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

391

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	<p>Shall be able to be calibrated according to the following specifications:</p> <ul style="list-style-type: none"> 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 <p>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).</p> <p>Slice-to-slice variability shall be no more than $\pm 5\%$. (not including end slices, as per ACRPET Core Lab).</p>
		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.
		<p>Patient weight shall be specifiable with 4 significant digits.</p> <p>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.</p>
BMI	Acquisition Device	Depending upon the study requirements, BMI shall be specified.
Height	Acquisition	Shall be able to record patient height in feet/inches or cm/m as supplied from the modality worklist and/or operator entry into

Parameter	Entity/Actor	Specification
	Device	<p>scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard.</p> <p>Patient height shall be specifiable with 3 significant digits.</p> <p>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.</p>
Administered Radionuclide	Acquisition Device	<p>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.</p> <p>Shall be able to enter the radionuclide type (i.e., F-18) by operator entry into the scanner interface.</p> <p>Shall be recorded in Radionuclide Code Sequence (0054,0300) in the DICOM image header (e.g., (C-111A1, SRT, “¹⁸Fluorine”)).</p>
		<p>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.</p>
Administered Radiotracer	Acquisition Device	<p>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 F¹⁸”).</p>
Administered Radiotracer radioactivity	Acquisition Device	<p>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.</p>
		<p>Shall be able to record with separate entry fields on scanner interface:</p> <ol style="list-style-type: none"> (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 <p>Shall automatically calculate the administered radioactivity and store in the Radionuclide Total Dose field (0018,1074) in the DICOM image header.</p> <p>Alternatively, shall be able to receive this information as per DICOM</p>

Parameter	Entity/Actor	Specification
		Supplement 159.
		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

Parameter	Entity/Actor	Specification
		Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation Time, Exposure and Slice Width in the DICOM image header.
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

Parameter	Entity/Actor	Specification
		<p>distance from defined landmark site (e.g., vertex, EAM). (both the landmark location (anatomically) and the distance scanned from landmark) would require DICOM tags).</p> <p>Shall be able to be reportable for future scanning sessions.</p> <p>The Acquisition Device shall record the z-axis FOV which represents the actual distance of scan anatomic coverage (cm).</p>
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).
Events	Acquisition Device	Shall record any events such as patient stopped scanning session or got up out of scanner during scanning session. (These events are to be recorded on the scanning session CRF at a minimum.)
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	<p>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.</p> <p>PET images shall be transferred and stored without any form of lossy compression.</p>

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

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394 4.3. Performance Assessment: Reconstruction Software

395 Reconstruction Software shall propagate the information collected at the prior Subject Handling and
 396 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.

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

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

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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.

Parameter	Entity/Actor	Specification
		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 parameters	Reconstruction software	Shall allow the user to control image noise and spatial resolution by adjusting reconstruction parameters, e.g., number of iterations, post-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.

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4.3. Performance Assessment: Image Analysis Workstation

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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.

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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.

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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: <ul style="list-style-type: none"> slope (\hat{A}_1) between 0.95 and 1.05 R-squared (R^2) >0.90

Parameter	Entity/Actor	Specification
		See Appendix F.

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

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 SUVs 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.

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

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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.

Parameter	Entity/Actor	Specification
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 workstation	Shall be able to apply a 3D smoothing filter if indicated as 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)

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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).

Parameter	Entity/Actor	Specification
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.
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.

4.3. 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.

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Test-Retest Papers

Inter-scan period less than 60 days

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(See also Schwarz below as a review of other comparisons of longitudinal variability)

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577 **Note that U.S. prescribing information is listed below for approved tracers. However, this profile is not**
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579 **outside of the U.S.**

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713 Appendices

714 Appendix A: Acknowledgements and Attributions

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

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726

727 **Appendix B: Background Information for Claim**

728

729 A meta-analysis of published data was performed to determine the repeatability of amyloid PET imaging
730 with ¹⁸ Fluorine labeled radiotracers. Two types of repeatability studies were considered. The first of these
731 restricted the test-retest period to less than 60 days, over which factors such as longer term scanner drift or
732 appreciable amyloid accumulation would not occur. These studies provided the basis of the wCV value used
733 in the technical performance Claim. The second set of studies compared baseline values to those acquired
734 after a two year period, a typical clinical trial duration. Since amyloid accumulation is unlikely to occur in a
735 majority (though not all) of amyloid negative cognitively normal subjects, longitudinal values in this group
736 were examined. These studies were not used to determine the wCV but did provide a practical indicator of
737 longer term technical variance given a population presumed to be fairly stable with regard to amyloid
738 pathology.

739

740 **Test-Retest studies:** Test-retest amyloid PET studies were identified for the tracers florbetapir (Joshi et al,
741 2012, scans within 4 weeks) and flutemetamol (Vandenberghe et al, 2010, scans 7 to 13 days apart). Other
742 available studies with images acquired during this time period were excluded for reasons including: a) use
743 of 11C-PIB and a 60 to 90 minute timeframe at the end of a full dynamic scanning session where greater
744 technical variability is observed; this can be due to subject motion and also to low signal whereby decay
745 correction amplifies the noise contribution; and b) intentional varying of administered radioactivity during
746 the study to test the impact of that parameter. The study by Joshi et al acquired florbetapir PET images in
747 10 AD patients and 10 healthy controls (HC) over a time window of 50 to 70 minutes post injection, and
748 used whole cerebellum as the reference region. Mean Repeatability Coefficient (RC) and 95% confidence

749 intervals (CI) were 5.38% (3.76% to 9.44%) for AD subjects and 3.32% (2.32% to 5.84%) for HC. Values for
 750 wCV were 1.94% and 1.20% respectively. The study by Vandenberghe et al acquired flutemetamol PET
 751 images in 5 AD patients over a time period of 85 to 115 minutes post injection, and used cerebellar cortex
 752 as the reference region. Mean Repeatability Coefficient (RC) was 3.18% with a 95% CI of 1.99% to 7.81%.
 753 The value for wCV was 1.15%. The greatest (“worst”) value of 1.94% from these studies was applied to the
 754 Claim. F As noted in the Claim Considerations, the number of short term test-retest studies was a
 755 limitation, and for this reason and for practical context, this value was also compared to the wCVs
 756 calculated for the longer term studies described below.

757
 758 **Longer term longitudinal variability:** Several studies have examined the effects of applying different
 759 reference regions or other parameters to amyloid SUVR data acquired over one or two years. Two studies
 760 were identified that measured amyloid SUVR in florbetapir PET scans acquired in subjects from the
 761 Alzheimer’s Disease Neuroimaging Initiative (ADNI) at baseline and after 2 years. This period is
 762 representative of a clinical trial duration. The table below shows the RC means and 95% CI for these
 763 studies, using different reference regions. The mean RC in four of the five cases ranged from 3.45% to
 764 4.45%, within the range of 3.18% to 5.38% of the short term test-retest studies described above (Joshi,
 765 Vandenberghe). In the Brendel analyses, SUVRs measured using the same subjects but two different
 766 reference regions resulted in an RC% of 9.37% that was more than 2x larger when using a whole (full)
 767 cerebellum reference as that using white matter as a reference. This was also double the RC% measured by
 768 Chen using a different subset of ADNI scans across three different reference regions: pons, cerebellar
 769 cortex, and subcortical white matter. These comparisons suggest the following: 1) even over a longitudinal
 770 period of 2 years, it is feasible to achieve the wCV identified through the short term test retest studies
 771 above; and 2) choice of reference region coupled with analysis methods can materially impact the RC% and
 772 wCV, using the same subject scans.

Author	Chen et al 2015	Chen et al 2015	Chen et al 2015	Brendel et al 2015	Brendel et al 2015
Population	CN	CN	CN	CN	CN
Number of subjects	88	88	88	62	62
Amyloid status	Negative	Negative	Negative	Negative	Negative
Time between scans	2 years	2 years	2 years	2 years	2 years
Reference Region	Pons	Cerebellum	White	Full cerebellum	White
RC%	3.45%	4.45%	4.28%	9.37%	3.81%
95% CI - lower	3.01%	3.87%	3.73%	7.97%	3.24%
95% CI - upper	4.05%	5.21%	5.02%	11.36%	4.61%

774 CN = cognitively normal

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	Milliamperere-seconds
MBq	Megabecquerel. 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 $1 \text{ mCi} = 3.7 \times 10^7$ 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
SUV_{max}	The maximum SUV within the ROI.
SUV_{mean}	The average SUV within the ROI.
SUV_{peak}	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

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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.

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796 **Appendix D: Model-specific Instructions and Parameters**

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

302 ***D.1. Image Acquisition Parameters***

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

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

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

313 ***D.2. Quality Assurance Procedures***

314 Examples of recommend quality assurance procedures are shown for specific GE, Philips, and Siemens
315 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
	AutoQC	Emission sinogram collection and analysis	Daily
		Automated System Initialization	Daily, prescheduled to shorten daily QC
	Uniformity check	Automated Baseline collection	Daily, prescheduled to shorten daily QC
			Monthly
	SUV calibration		Every 6 months, after recalibration, when SUV validation shows discrepancy
SUV validation		Every 2 months, when PM is performed	

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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		

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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

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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

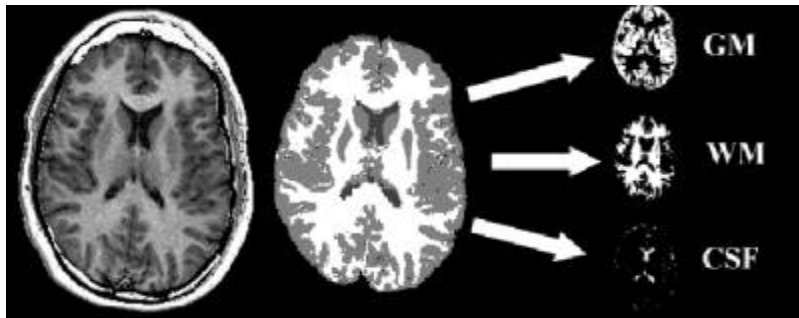
365

366 **Appendix F: Testing PET Display and Analysis Systems with the UW-PET QIBA** 367 **Amyloid Digital Reference Object (DRO) Series**

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

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

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



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Illustration of how the DRO series was created.

385

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

390 **Linearity**

391 The linearity of the IAW will be assessed by testing a range of different subjects, as defined by varying SUVR
392 values. The table below gives more detail about the simulated subjects and their respective SUVR values.
393 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

394

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

397 **Reproducibility**

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

302 **The DRO Series**

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

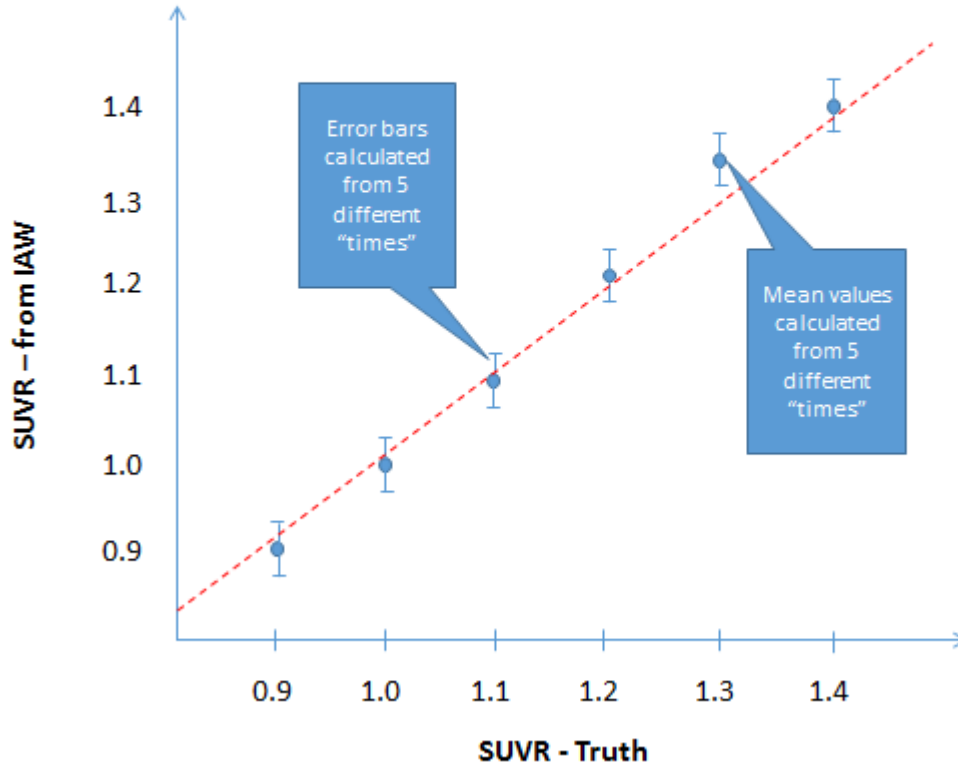
306 **IAW Conformance Procedure**

- 307 a. Download the UW-PET QIBA PET Amyloid DRO series from QIDW [<give link when ready>](#).
- 308 b. Analyze the 30 volumes using the same procedure, target regions and reference regions as will be
309 used with patient data.
- 310 c. For each target region for a fixed reference region, the information to form the graph below should
311 be calculated, and will be called a given target's results, e.g. (Frontal Target/Whole Cerebellum
312 Reference Region) Results:

Example Output – For Single Target Region

Will be one graph for each Target Region if single reference region is used
If multiple reference regions, then total graphs = (number of target regions) x (number of reference regions)

IAW Conformance – Target Region 1



- 913
- 914 4. If multiple reference regions will be used, generate the same information as in point 3 above using
- 915 this new reference region. The final number of target results or graphs will be (number of target
- 916 regions) x (number of reference regions).
- 917 5. The following statistical analysis should be performed on each target result.
- 918 a. Fit an ordinary least squares (OLS) regression of the Y_i 's on X_i 's (where Y 's are the SUV
- 919 measurements from the IAW, and X 's are the true SUV measurements). A quadratic term is
- 920 first included in the model: $Y = \beta_0 + \beta_1 X + \beta_2 X^2$.
- 921 • The estimate of β_0 , β_1 and β_2 , along with their 95% Confidence Intervals (CIs), shall be
- 922 reported as part of the assessment record (see last point below).
- 923 b. Re-fit a linear model: $Y = A_0 + A_1 X$ (red dotted line on graph above).
- 924 • The estimate of A_0 and A_1 , along with their 95% CIs, shall be reported as part of the
- 925 assessment record (see last point below).
- 926 • R-squared (R^2) shall be >0.90 for the IAW to be compliant for the given target and
- 927 reference regions.
- 928 c. For each of the 6 true SUV values, calculate the mean (blue points in graph above) of the 5
- 929 measurements and the wSD (blue error bars in graph above) using the following equations

where the summations are from J=1 to J=5:

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

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

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

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	θ_0	θ_1	θ_2	A_0	A_1	R^2	$R^2 > 0.90$	wCV	%RC	%RC $\leq 2.6\%$
1	Pass	1	Pass	0.03	0.91	0.01	0.1	0.97	0.92	Pass	7.6×10^{-3}	2.1	Pass
1	Pass	2	Pass	0.05	0.9	0.02	0.07	0.95	0.91	Pass	1.05×10^{-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	7.6×10^{-3}	2.1	Pass
3	Pass	2	Pass	0.04	0.95	0.04	0.03	0.92	0.93	Pass	8.0×10^{-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

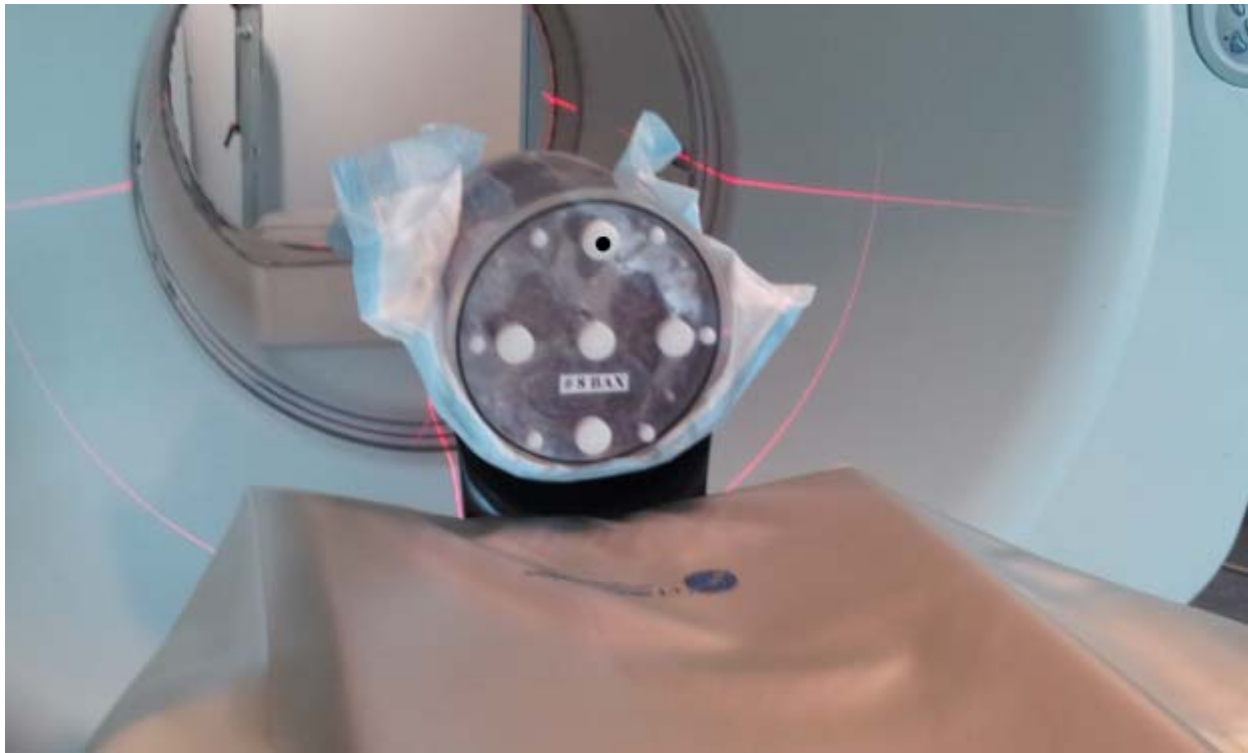
- Make sure that before the 18-F or 18-FDG is added, you start with a completely filled phantom (less ~100ml, described later). It is helpful to fill the phantom with water the day before to help remove small air bubbles.
- Purified or distilled water is preferred, normal tap water is OK.
- When you 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.

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- 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

384 Generally, this process takes about 10-20min.



386

387 Position the phantom on the scanner bed with the filling ports towards the foot of the bed, and the

388 anterior filling port at 12 o'clock. (In this position, the cerebellar lobes should be visible at the bottom of

389 the phantom, and should appear in the reconstructed image as if you were imaging a supine subject).

390

391

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.

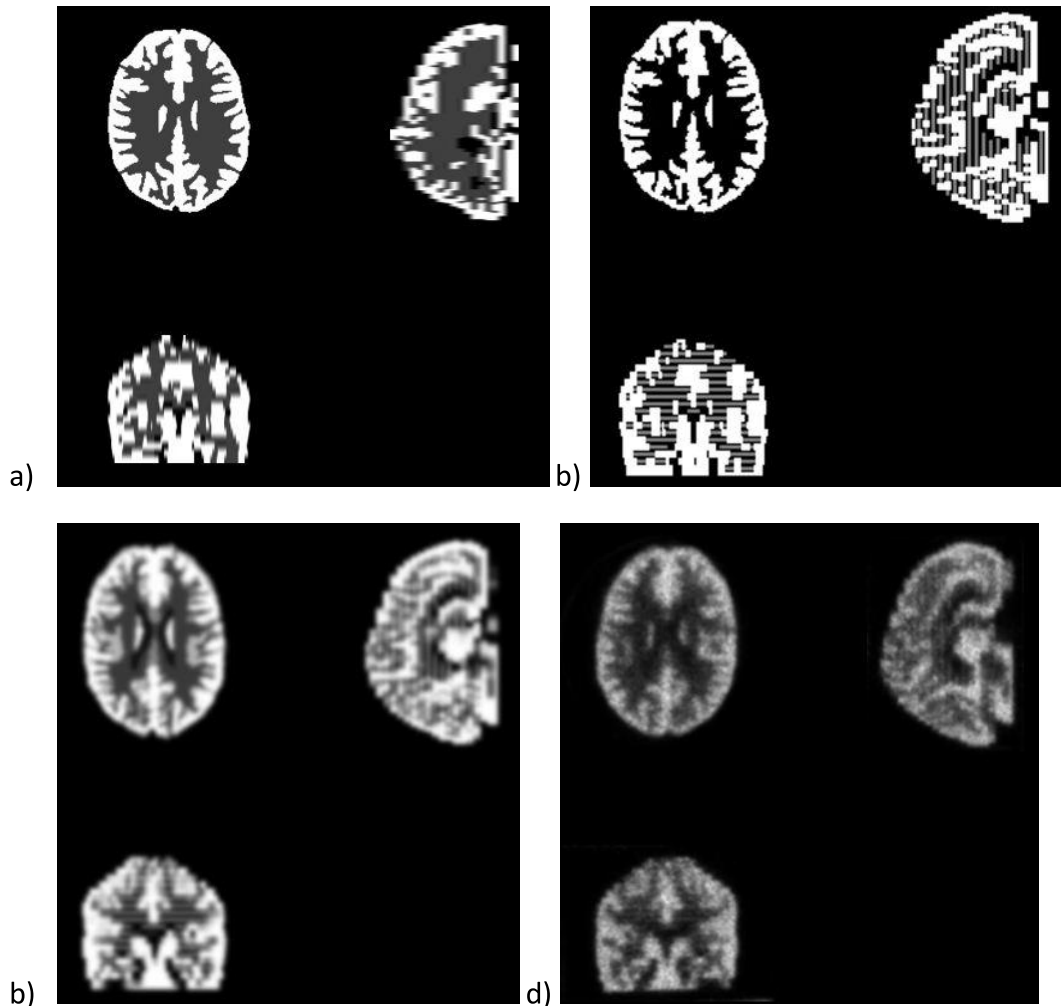


Figure 1. Digital Hoffman Phantom. a) 19-slice version supplied by Data Spectrum. b) 90-slice version modeling more accurately individual layers of each slice. c) smoothed version of the 90-slice digital phantom. d) sample real phantom data obtained from the high-resolution HRRT scanner.

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).

012
013 Data Spectrum, who manufactures the phantom, supplies a 256x256x19 voxel digital atlas that models the
014 phantom appearance as having one of 3 types of uniform areas in each 6.1 mm slice (gray=4, white=1,
015 csf=0). See Figure 1a. Dr. Bob Koeppel from the University of Michigan, in collaboration with Data Spectrum
016 and CTI (now Siemens) constructed a more accurate 160x160x90 voxel, 1.548x1.548x1.548 mm version of
017 this phantom that models the individual layers between the slices. Each slice of this 90-slice phantom
018 represents either a “GG” all gray layer with values either 0 or 1.0; or a “GW” layer with values either 0, 0.5
019 or 1.0. This digital phantom (Fig 1b,c) looks much more like data obtained from a high-resolution PET
020 scanner (Fig 1d), and can be smoothed to approximate images from lower-resolution scanners. The
021 individual layers can actually be seen in some higher resolution scanners, such as the Siemens HRRT.
022

023 One important item to note is that the actual phantom size, especially the actual physical slice thickness of
024 each phantom, can vary slightly. Therefore, when comparing data, it is important to deal with the scaling
025 appropriately. Alternatively, if comparisons are made between two acquisitions, one must insure that the
026 identical phantom is used in the comparison. If there are multiple phantoms in use, it is good practice to
027 track each phantom with an appropriate identification number.
028

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

035 ***Methods and Metrics***

036 **Method Overview**

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

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

046 **Relevant Data Files**

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

048 Reference Files

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

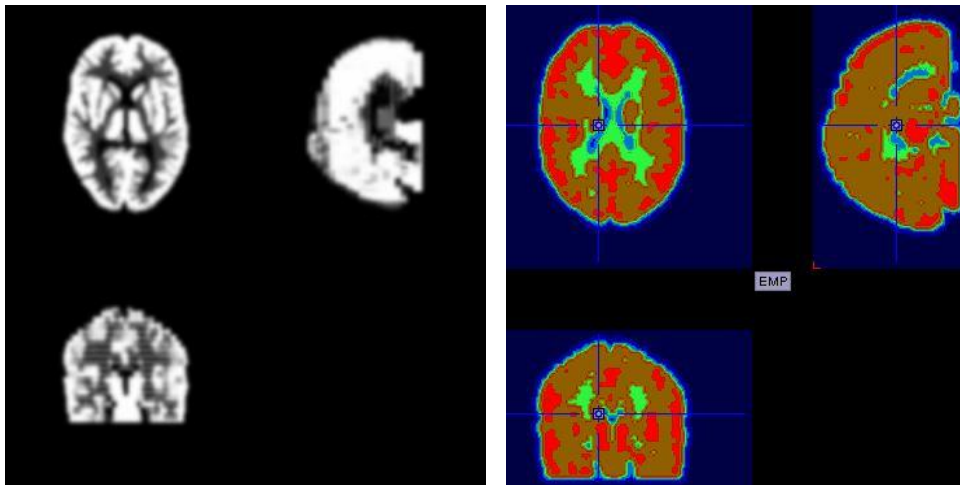
050 **ctiHoffman5.0_5.0.nii** – This is ctiHoffman0.0_0.0.nii smoothed by a Gaussian kernel 5.0 mm FWHM in the
051 x, y, and z dimensions. This represents an image at about the resolution of the highest-resolution scanners,
052 such as the HRRT.

053 **HoffmanVOI5mm6Level.25_.95BrainMask.nii** – This is a volume-of-interest (VOI) mask file with six levels
 054 created in PMOD using multi-level thresholding on the smoothed, phantom file, **ctiHoffman5.0_5.0.nii**. The
 055 resulting segmentation is seen in Figure 2. Idealized voxel intensities for CSF, white matter and gray matter
 056 are 0.0, .025, 1.0 respectively, but blurring of the digital phantom results in a partial volume effect so that
 057 voxel values vary continually between 0.0 – 1.0. Regions were defined with the following IDs and
 058 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

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

061



062

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

067 Input files

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

070

071 Intermediate Files

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

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

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

075

076 Output Files

077 *Volumes*

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

080 **RegSourceXXXAbsDiff.nii** – absolute difference volume between **RegSourceXXXFit.nii** and
081 **RegSourceNorm.nii**

082

083 *Text*

084 **RegSourceXXXfit.txt** – summary output file

085

086 *JPG -*

087 **RegSourceXXXplotAbsDiffProfile.jpg** – plot showing slices-by-slice profiles of ROI absolute difference
088 sums vs image plane number in the **RegSourceXXXAbsDiff.nii** volume for these four ROIs: whole volume,
089 whole brain, pure grey ROI, pure white ROI (see example plot < >)

090 **RegSourceXXXplotGrayWhiteProfile.jpg** - plot showing slice-by-slice profiles of ROI # 4 (pure white
091 matter) and #6 (pure grey matter)" ratios between the reference data (**RegSourceXXXFit.nii**) and the test
092 data (**RegSourceNorm.nii**) (see example plot < >)

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

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

097

098 ***Method Details: Processing Steps***

099

100 1) Manual step: Load/visual check of image data. Add to PMOD batch file list

101 Images need to be manually loaded to check visually that the orientation is correct. If the image loads
102 using default parameters, it can be simply added to a PMOD file list for later batch processing. If the
103 default settings do not work, the image must be manually loaded using the correct image reorientation
104 switches, saved as a new dynamic file, then added to the PMOD batch file list.

105 2) Batch step: PMOD script: Dynamic Averaging, Affine Registration to Hoffman Digital reference

106 This step sums the dynamic PET data to obtain an averaged PET source file, and then registers the
107 averaged PET to the Hoffman reference image. It is assumed that there is no motion between image
108 time frames, so a motion correction step is not necessary like it would be for a patient study. As a
109 reference image, the version of the Hoffman reference smoothed with a 5 mm isotropic Gaussian filter
110 is used (**ctiHoffman5.0_5.0.nii**). This represents the resolution of an image that would be expected from
111 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) Batch step: Matlab script: Normalize PET, Fit Smoothing Model, Quantify Difference Image

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, FWHM_{xy} and FWHM_z.* An unconstrained nonlinear estimation approach is used 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) Calculation of Quality Metrics from the Normalized Source Image and Difference Image

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 Koeppel’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.

- 155 ii) **Average Global Absolute Difference – total image volume** : ideally, this should be less than
 156 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
 157 iii) **Average Global Absolute Difference in the brain region only**: ideally, this should be less than
 158 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
 159 iv) **Gray:White mater ratio in the source image**. Ideally, this should be 4.0. For scanners of lower
 160 resolution we would expect the value to be less.
 161 v) **Ratio of Gray:White in the Source image compared to smoothed reference**. Ideally, this should
 162 be 1.0. Would expect at most a 10% variation.
 163 vi) **Ratio of White matter intensity standard deviation in the Source imaging compared to the**
 164 **smoothed reference**: This measure gives an indication of image noise. By comparing to the
 165 reference volume, variation with the white matter region due to the partial volume effect
 166 should cancel out.
 167 vii) **Ratio of Gray matter intensity standard deviation in the Source imaging compared to the**
 168 **smoothed reference**. : This measure gives an indication of image noise. By comparing to the
 169 reference volume, variation with the white matter region due to the partial volume effect
 170 should cancel out.
 171 b) *Slice-by-slice Metrics (computed between planes 10-80, which represent the plane with brain data in*
 172 *the Hoffman reference volume)*
 173 i) **Average Slice Absolute Difference – total slice**: ideally, this should be less than 10%, therefore
 174 less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
 175 ii) **Average Slice Absolute Difference – brain region only**: ideally, this should be less than 10%,
 176 therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
 177 iii) **Average Slice Absolute Difference – gray matter only (VOI region #6)**: ideally, this should be
 178 less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0
 179 and 1.0.
 180 iv) **Average Slice Absolute Difference – white matter only (VOI region #4)**: ideally, this should be
 181 less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0
 182 and 1.0.
 183 v) **Ratio of mean gray intensity in VOI region #6 for Source compared to smoothed reference**:
 184 ideally, this should be 1.0
 185 vi) **Ratio of mean white intensity in VOI region #6 for Source compared to smoothed reference**.
 186 Ideally, this should be 1.0.
 187 vii) **Profile Coefficient of Variation for Gray slice mean gray intensity**. This metric can be used as a
 188 sentinel for unacceptable variations in axial sensitivities.
 189

190 3) Outputs: Graphics, Text Summary and Imaging volumes

- 191 a) JPGs
 192 i) 3 orthogonal slices through the center of the difference volume – color bars set to +/- 0.2 for all
 193 evaluations to highlight significant areas that differ from the reference volume. A
 194 ii) 3 orthogonal slices through the normalized, registered source volume
 195 iii) Slice-by-slice profiles of error measures between source and reference volumes
 196 iv) Slice-by-slice profiles of the ratio of mean gray and white matter region intensity regions for the
 197 source volume compared to the reference volume.
 198 b) Text file
 199 i) Numerical values for the global and plane-by-plane metrics
 200 c) Image volumes

- 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> .

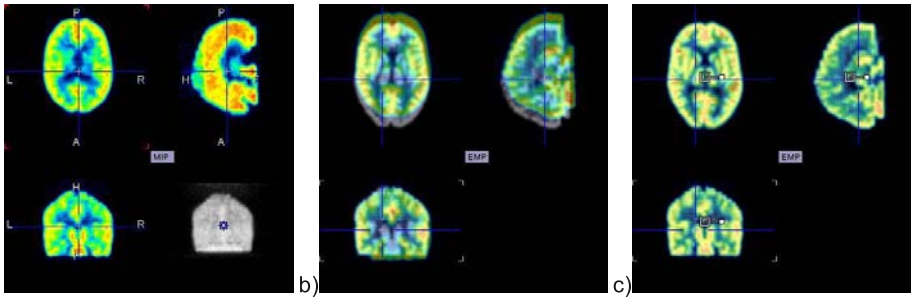
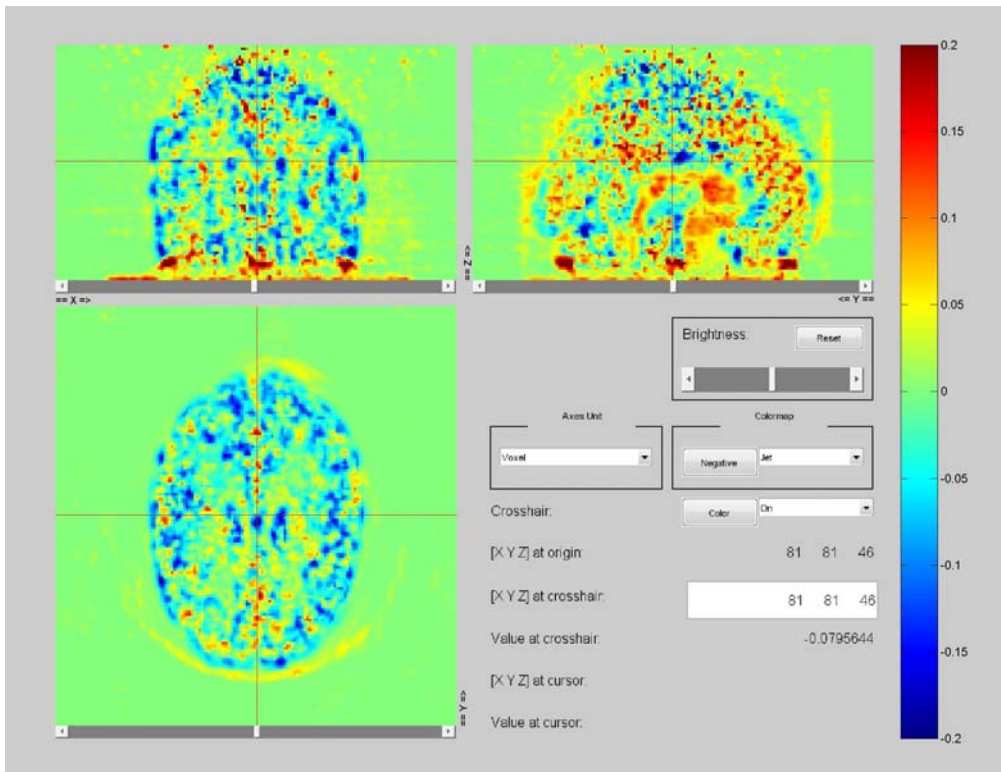
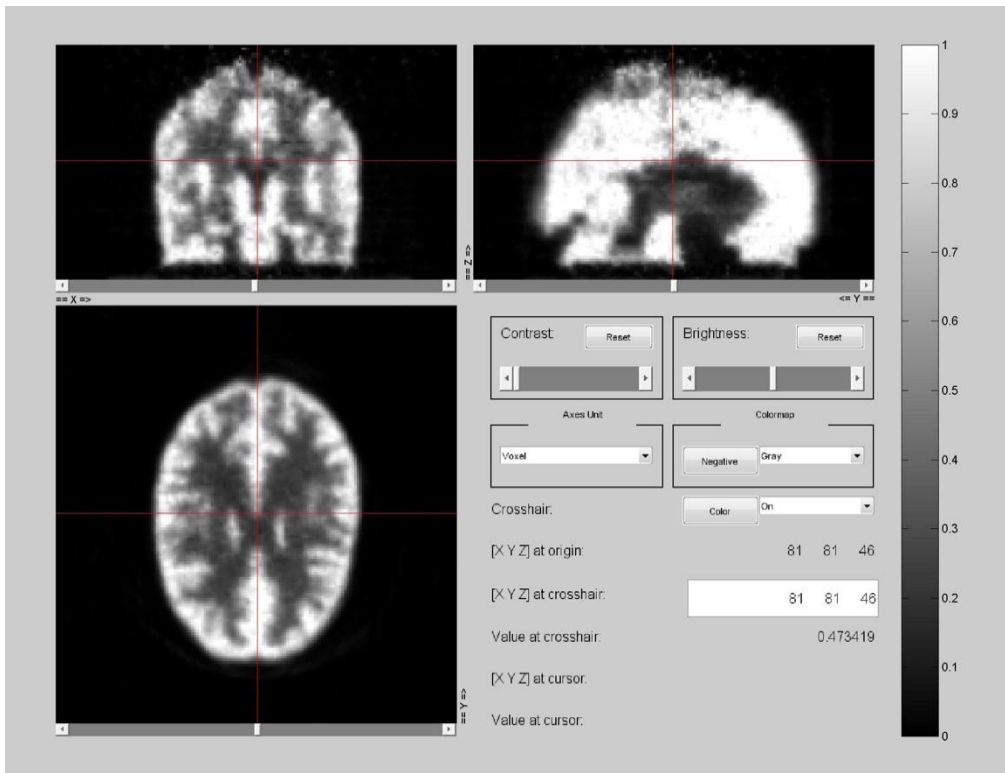


Figure 3. Affine Registration Process. Source image in original orientation (a). Source image (colored grayscale, and digital gold standard (grayscale) unregistered (b), and after registration in PMOD (c).

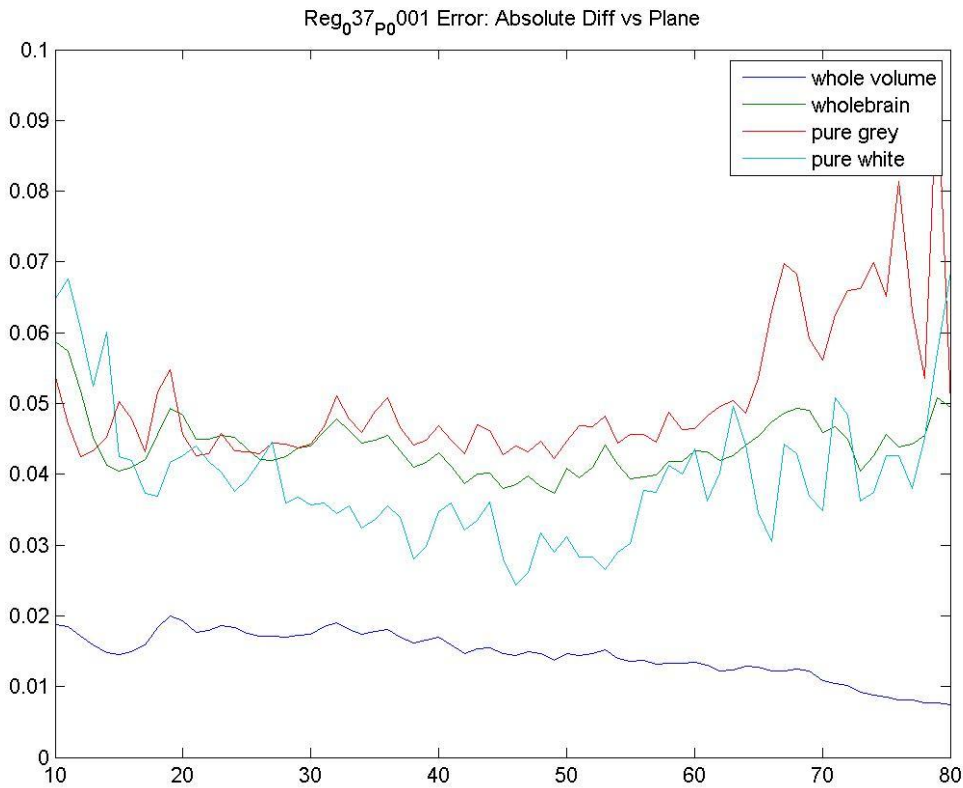
Example Results using the ADNI Hoffman Qualification Data

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

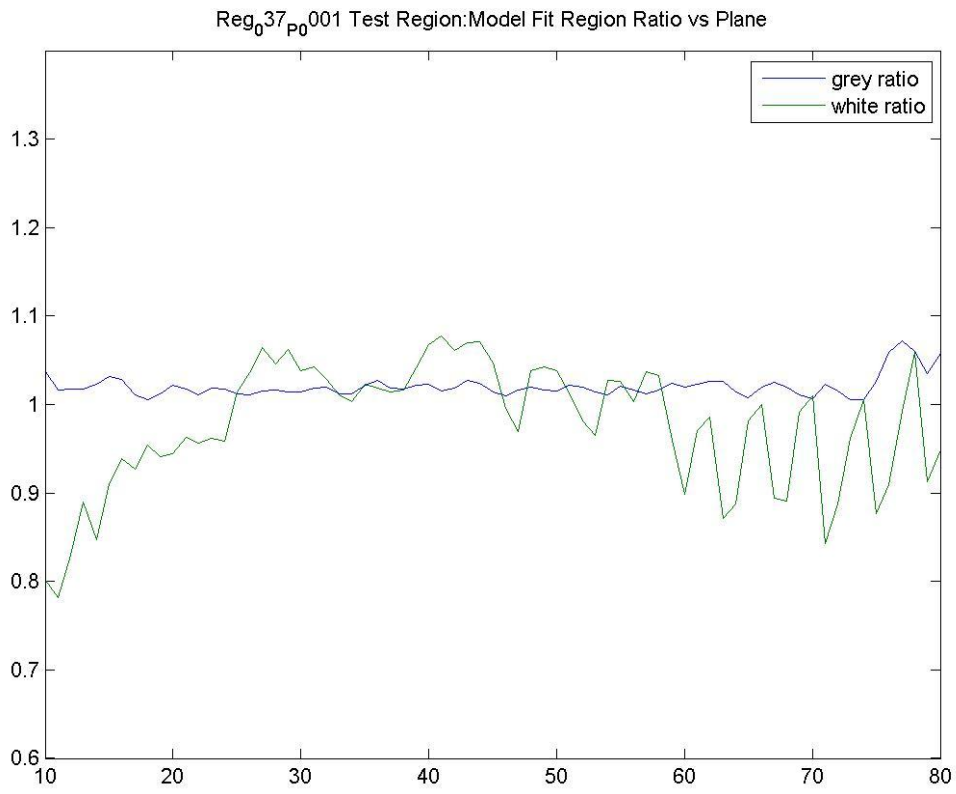




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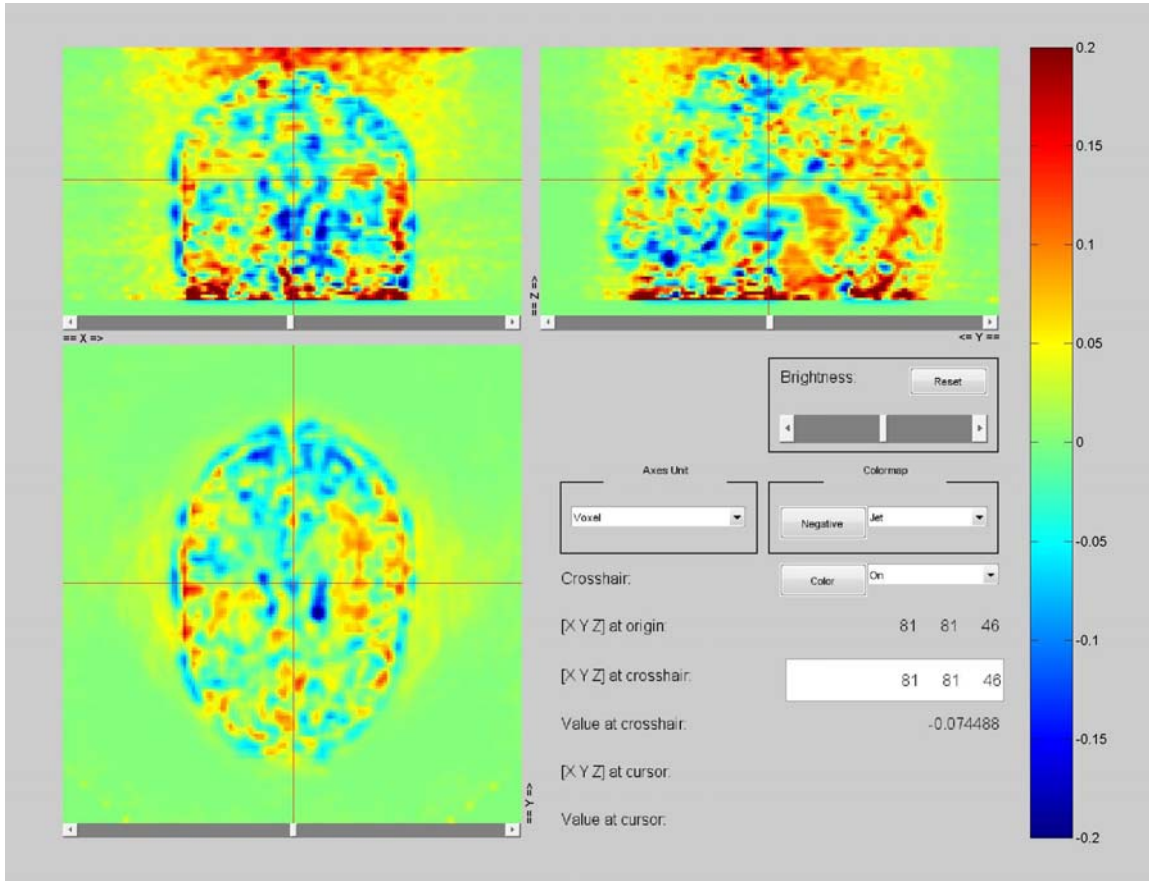


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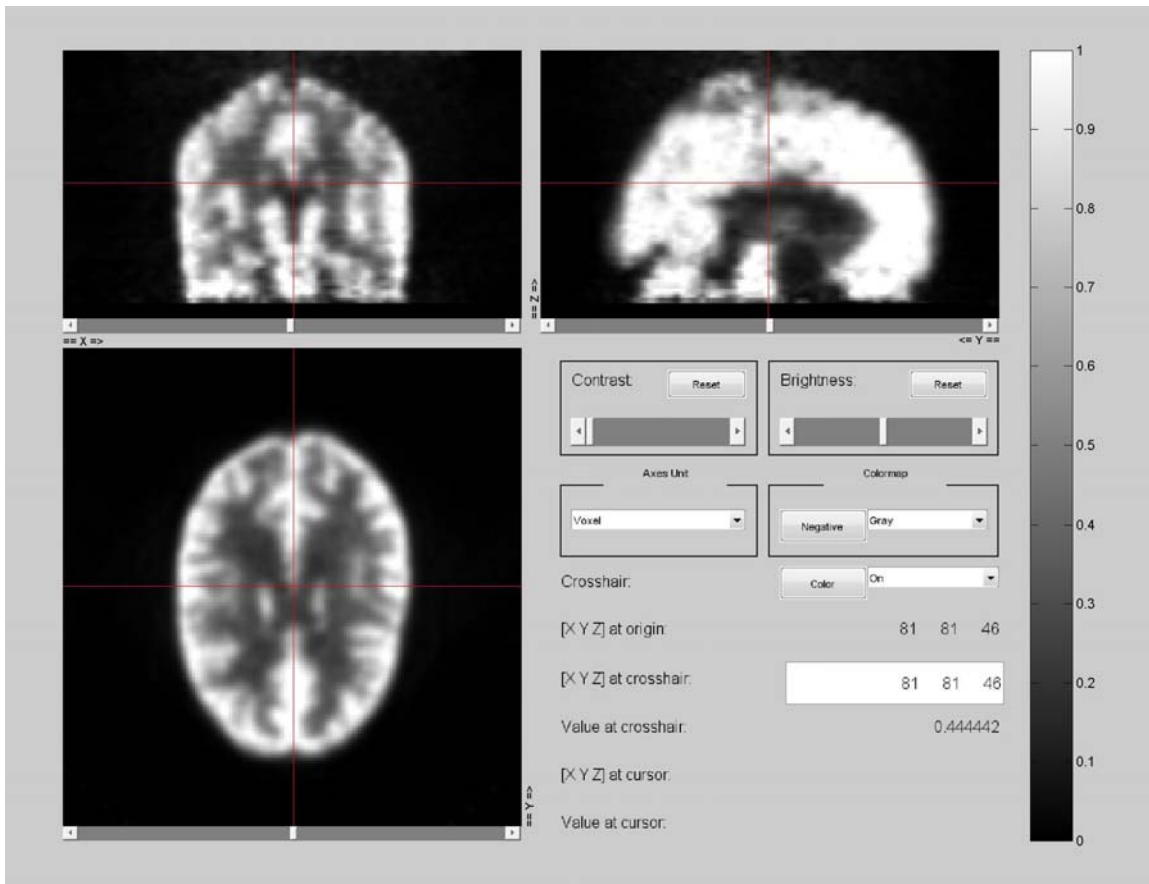


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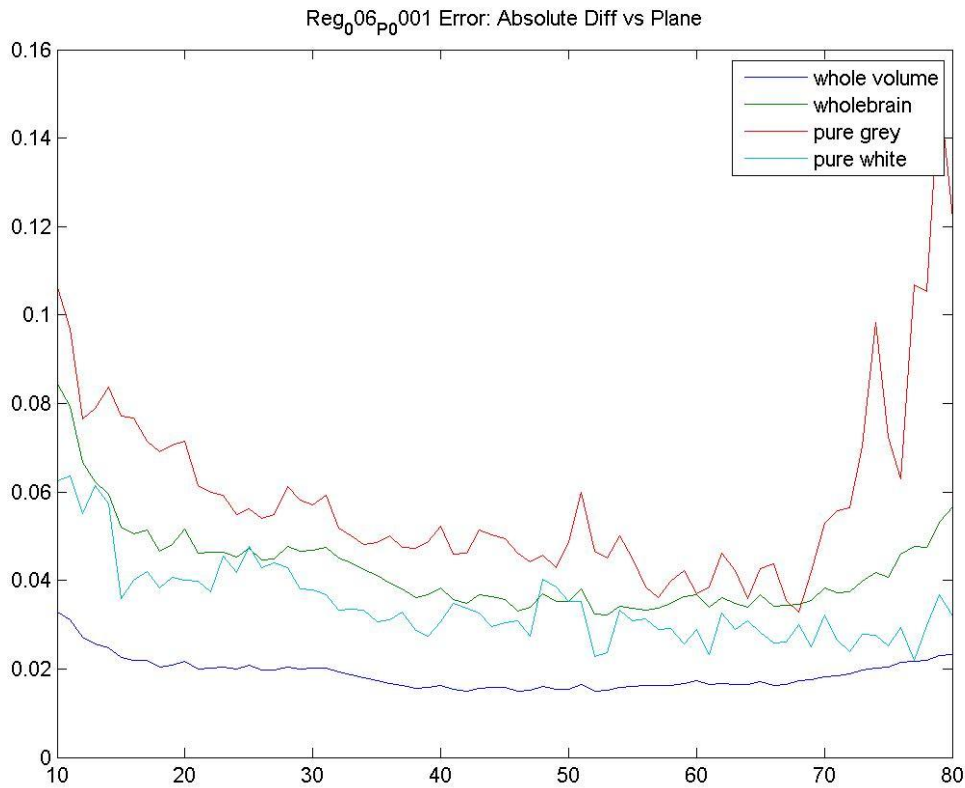
221 Example #2. Another example of a good quality scan. ECAT HR+ (006_P_0001)



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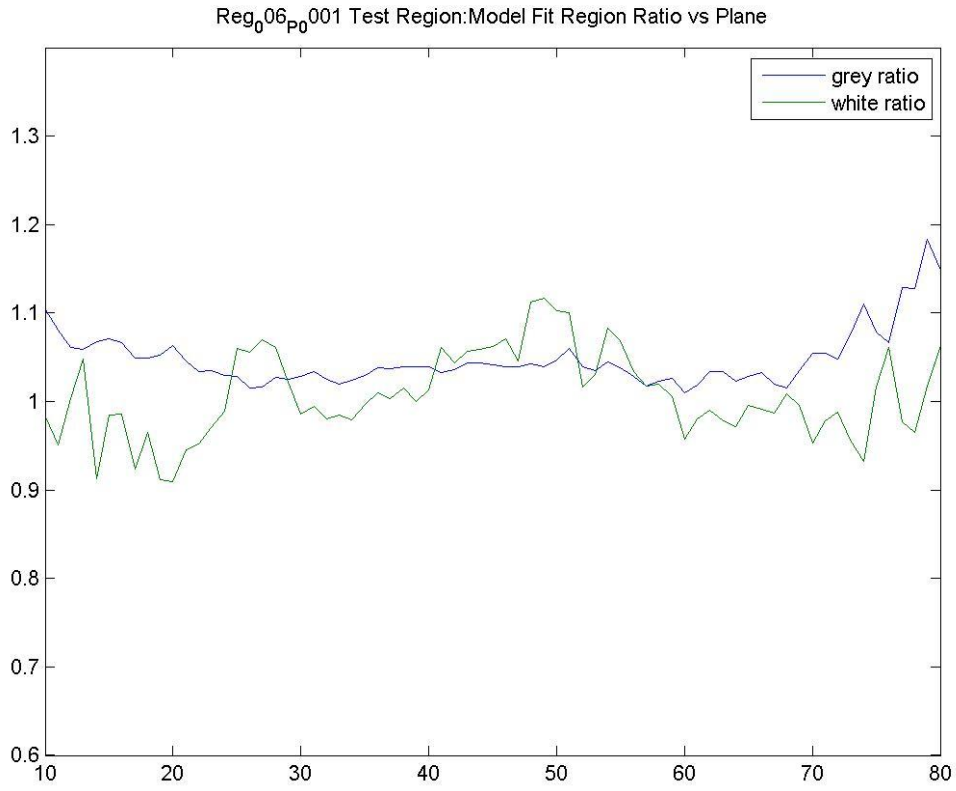


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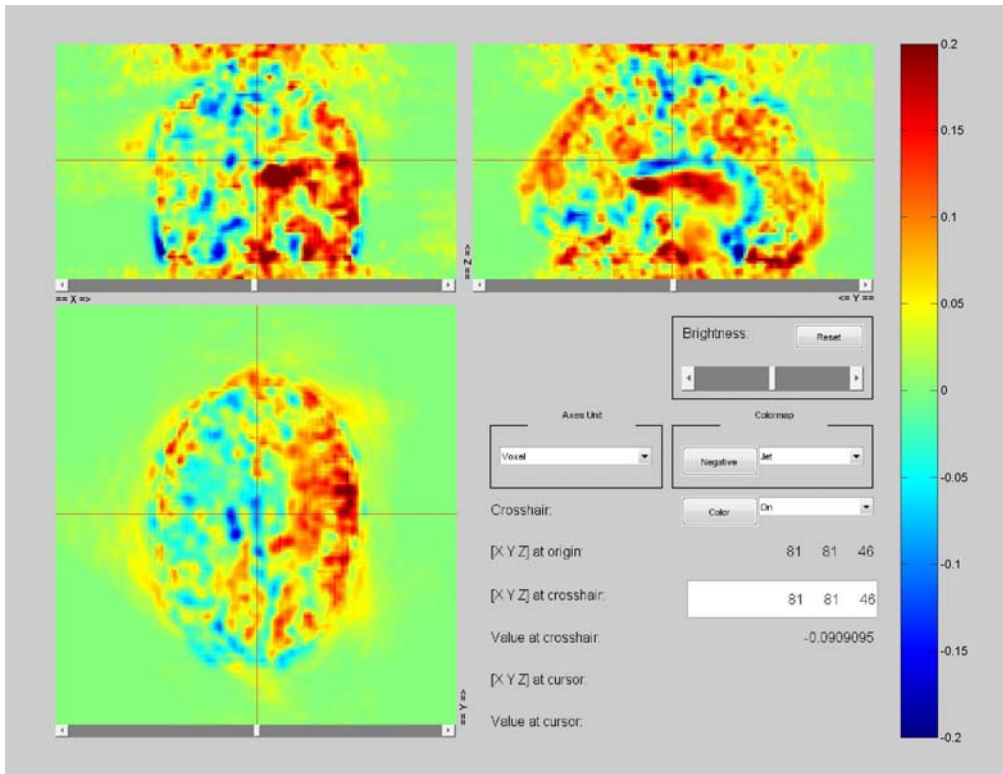


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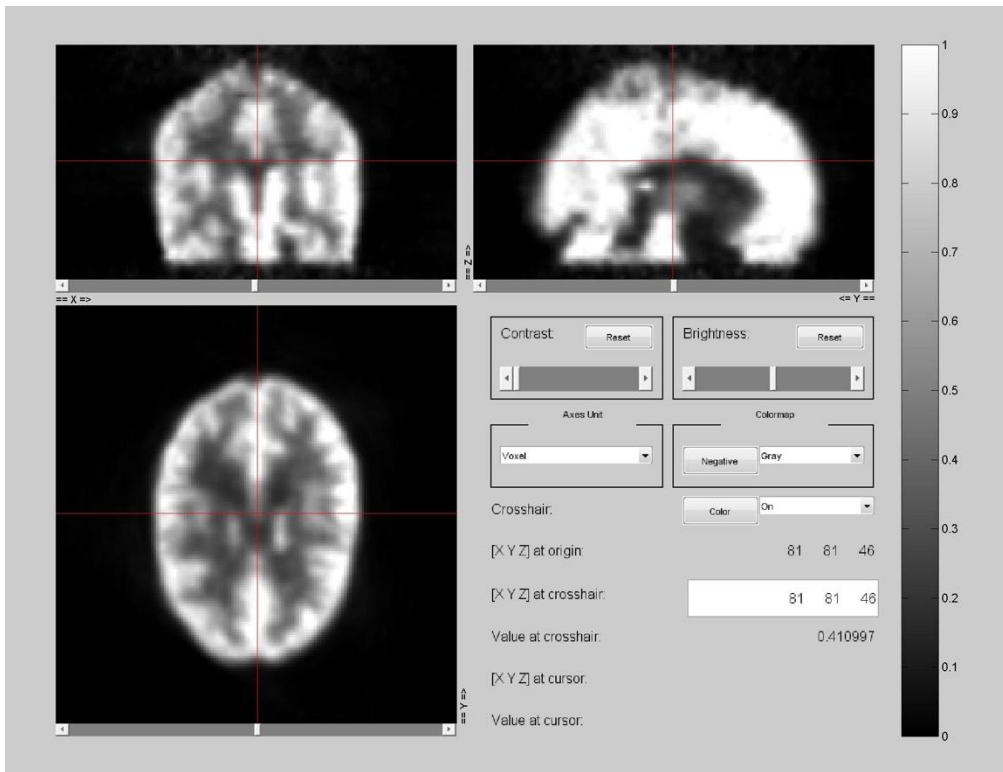
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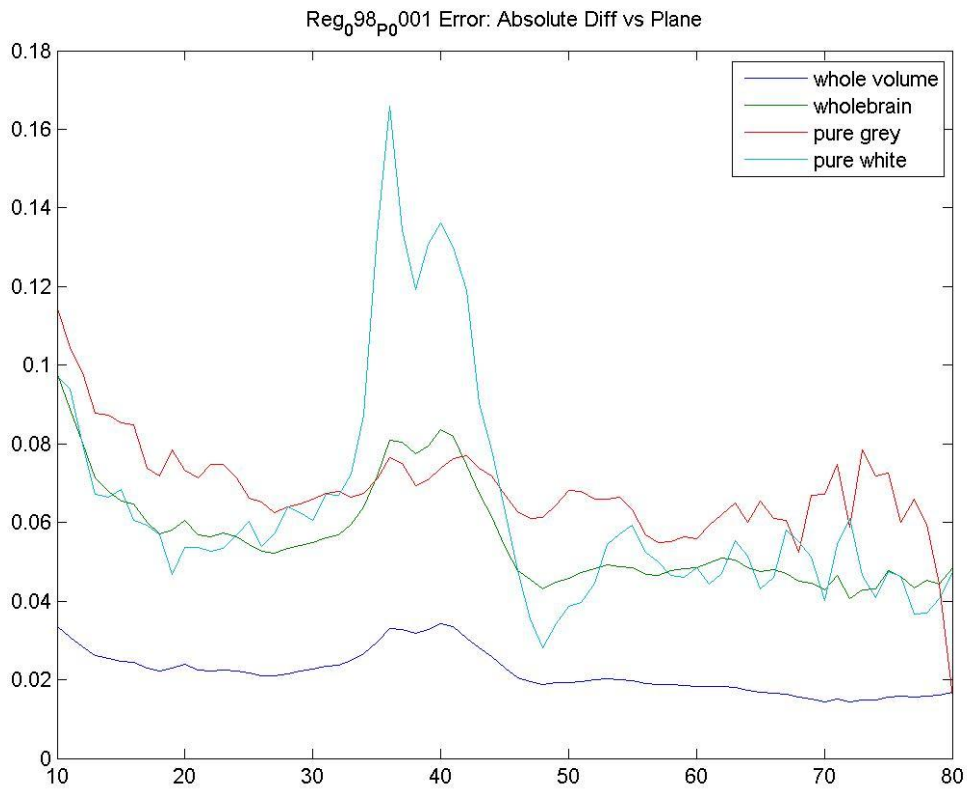
Example #3. Siemens ECAT Accel (098_P_0002). Example with relatively poor image quality. Asymmetry seen between left and right side, and large errors between planes 30 and 50. But is this a function of poor scan quality, or a Hoffman phantom with extra space between plexiglass planes?



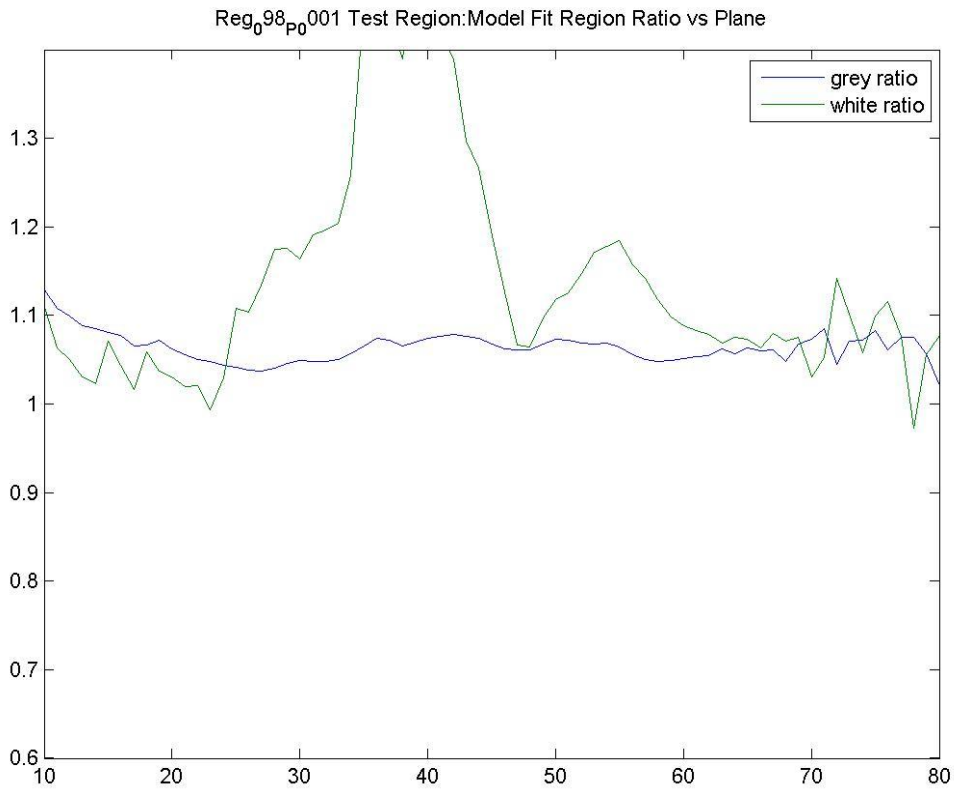
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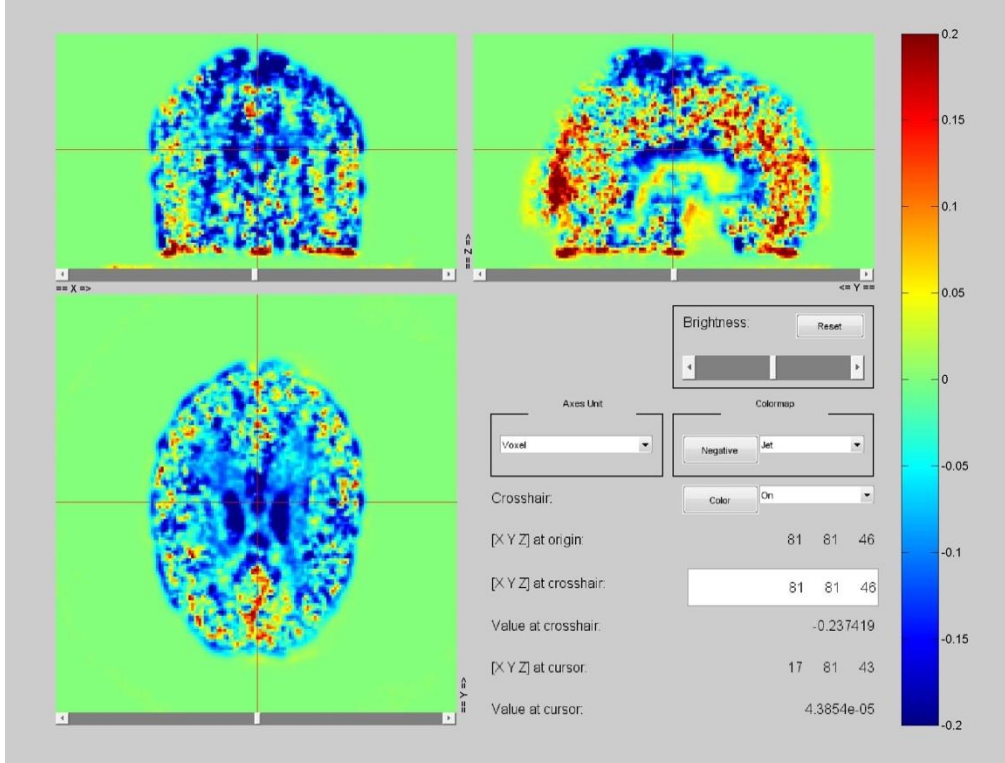


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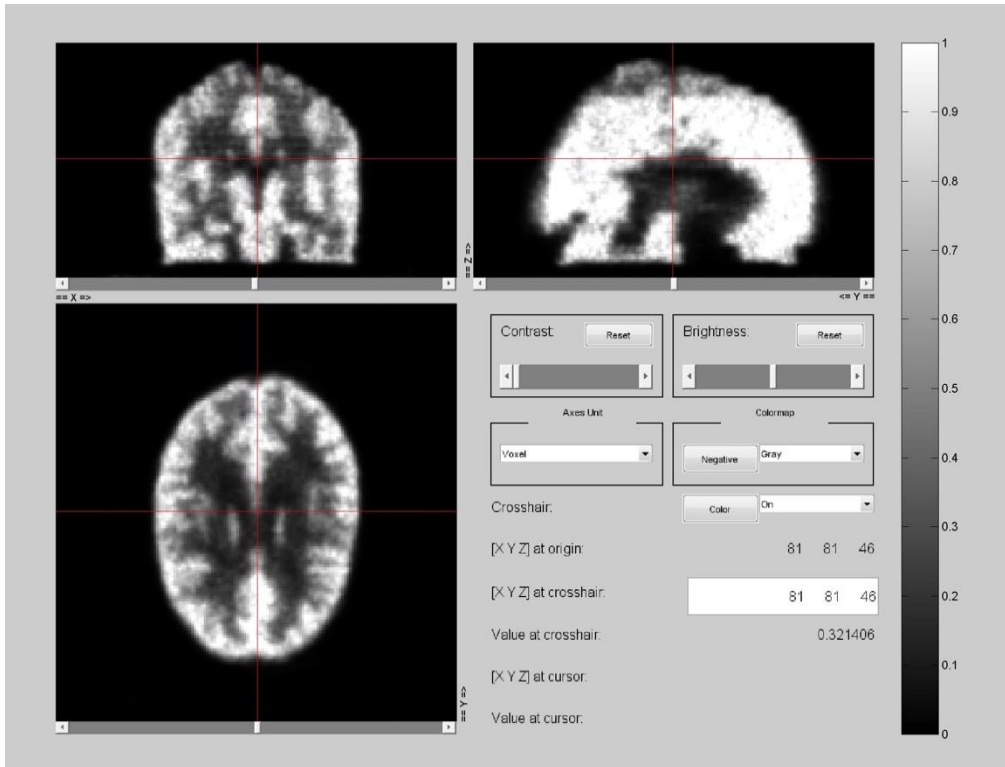
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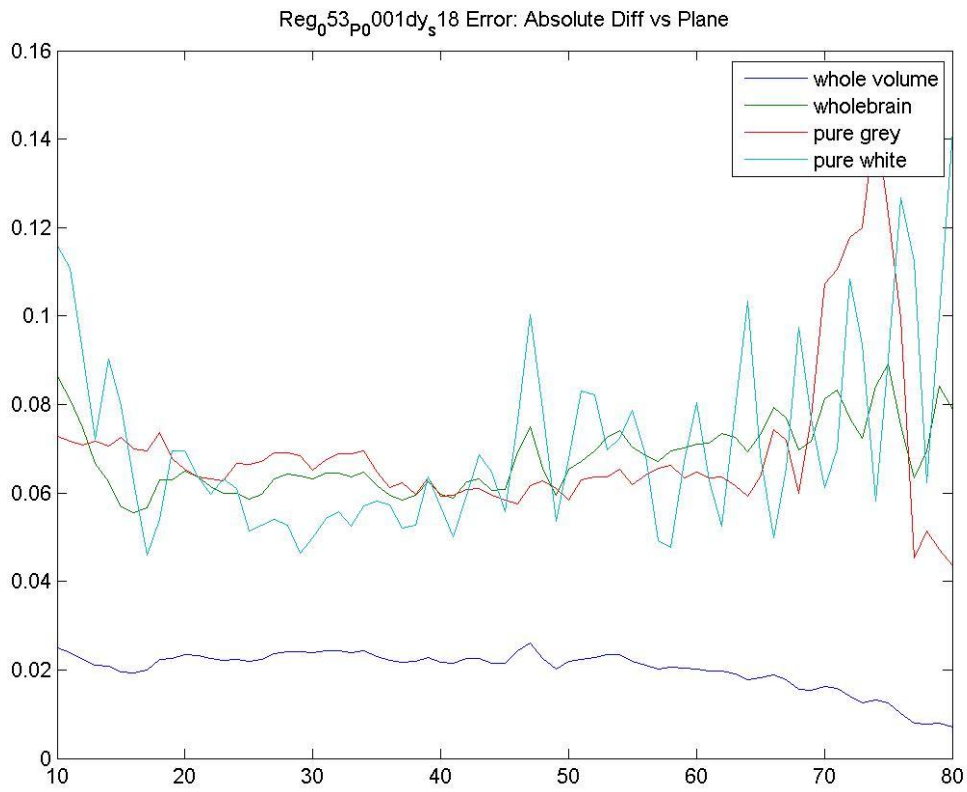
Example #4. HRRT Example (128_P_0001). Poor performance at bottom of volume most likely due to scatter correction problems. Otherwise, the scan quality is reasonably good. Difference image for most of the brain is negative (blue regions) probably due to global image intensity normalization been driven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



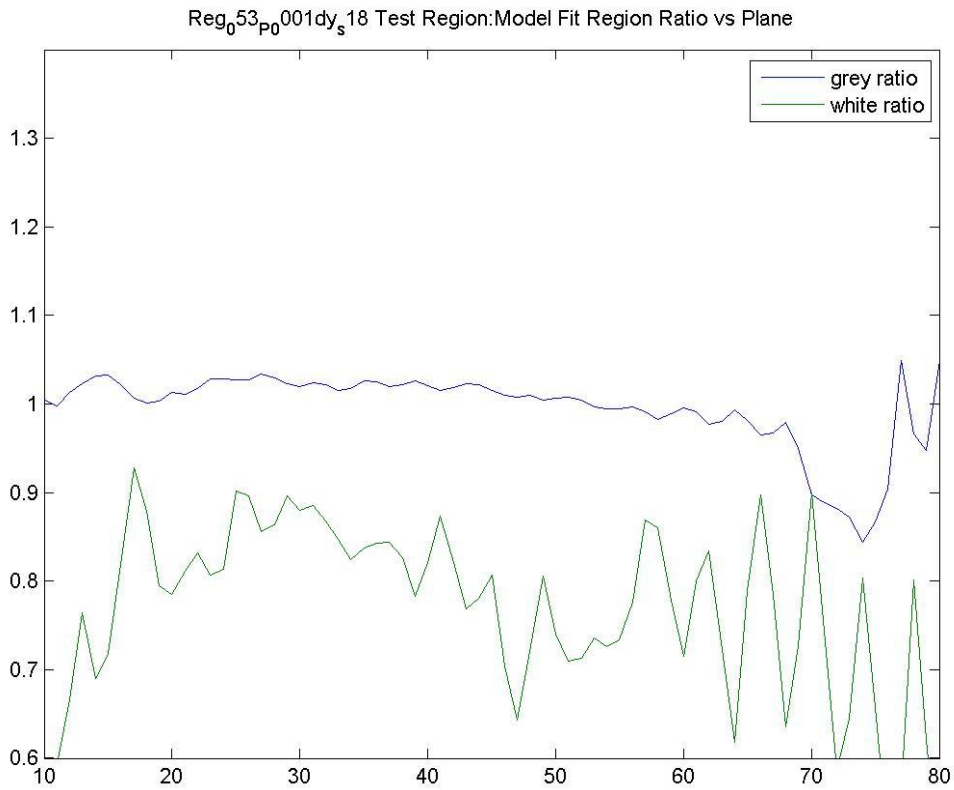
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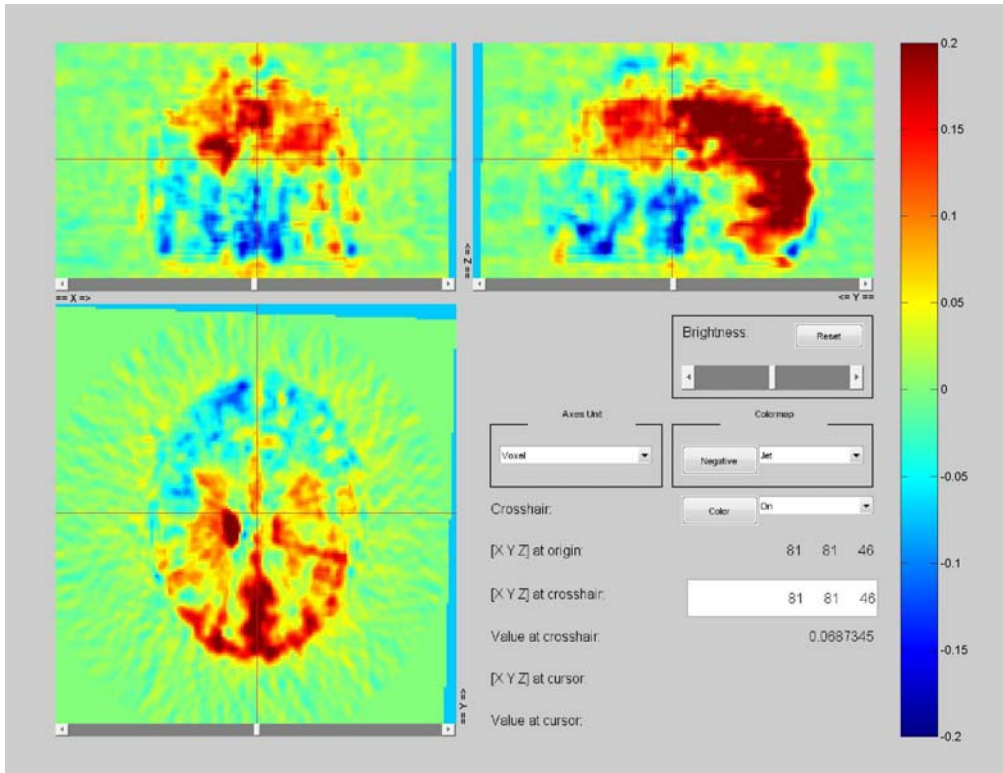


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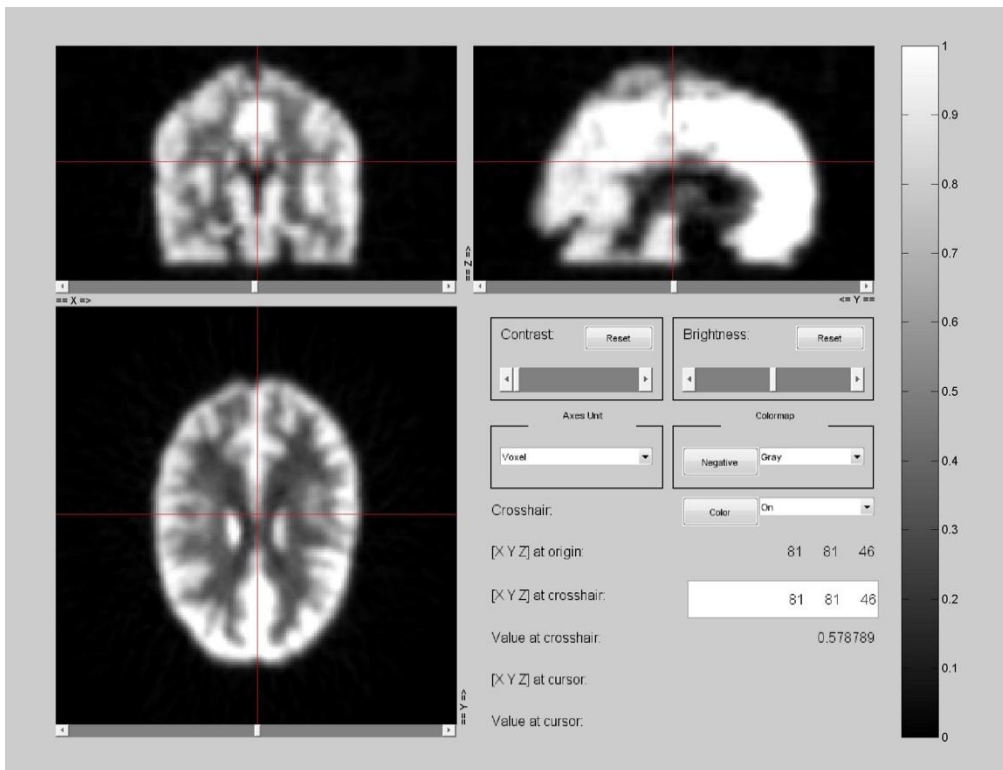
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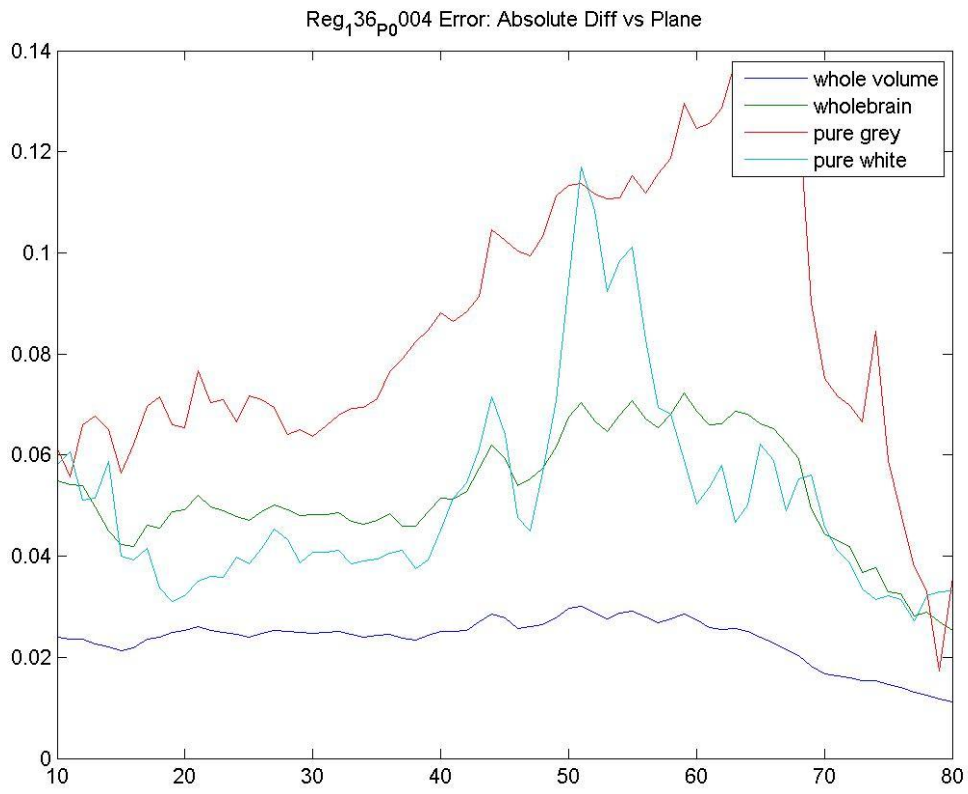
Example #5. (136_P_0004) – GE Discovery ST. Poor Quality – likely fail. Very large errors in the frontal lobe regions. White matter values compared to reference very high.



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Appendix I: Kinetic Modeling and Comparison to SUVR

This section is intended as a reference to explain (a) the difference between late timeframe SUVR measurement and the DVR measure calculated through full kinetic modeling, (b) reasons that amyloid burden values can differ between these two approaches, (c) cautions regarding potential sources of error introduced in SUVR measurement that are addressed through kinetic modeling, (d) logistical considerations in acquiring full dynamic images, and (e) recommendations for measurement approaches.

The contributors to amyloid PET signal

The signal intensity measured in a particular image voxel (three dimensional pixel) of a PET image reflects the amount of radiotracer present in that location at the time of measurement. To translate the signal intensity of an amyloid PET tracer into a meaningful measure of amyloid binding, it is necessary to separate out the contributions of tracer present in the blood, tracer bound to the target (the measurement of interest), tracer bound non-specifically (to entities other than target, for example white matter) and unbound tracer in tissue. The amount of tracer in each of these is dependent upon blood flow rate, membrane permeability impacting the rate of tracer diffusion into tissue, the presence of target (e.g. amyloid) in tissue, and the rate at which the tracer is cleared from the body (“clearance rate”).

Signal intensity in first few minutes reflects perfusion

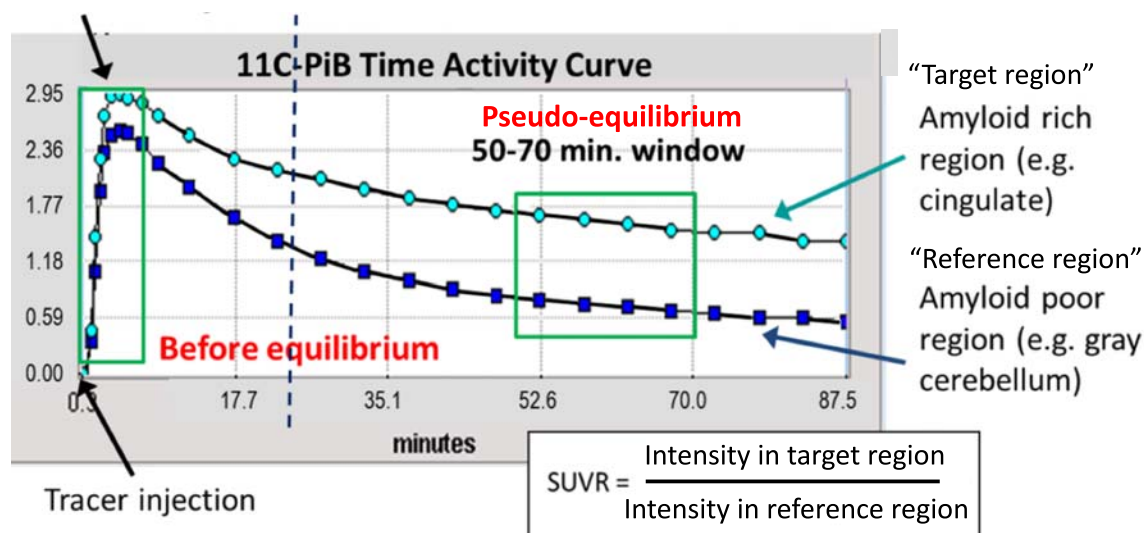


Figure 1.

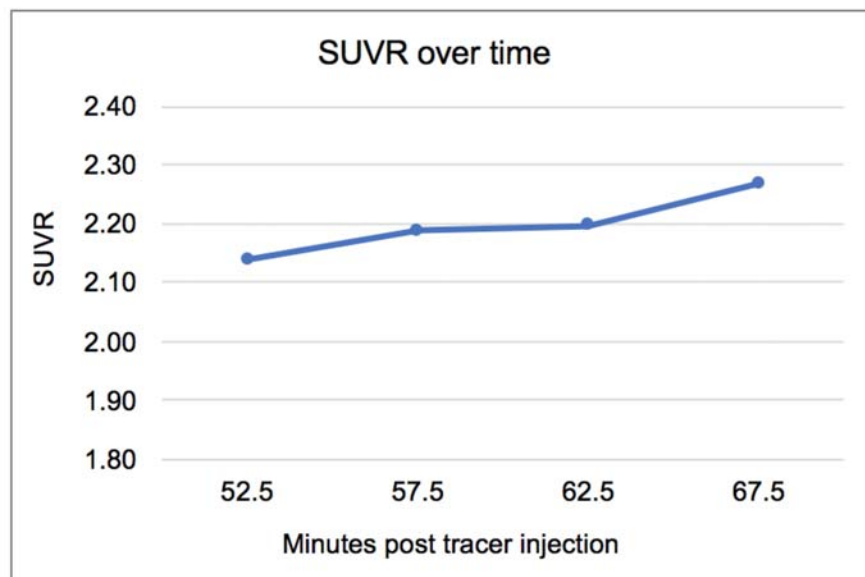
Time activity curves.

Stages of tracer uptake and clearance

Figure 1 shows the signal intensity measured for the original amyloid tracer 11C-PIB in two different regions of the brain from the time of tracer injection to 90 minutes post-injection. The signal intensity curve for any given region over the time from tracer injection to a time following achievement of relative equilibrium is called a Time Activity Curve (TAC). In the initial minutes, the signal intensity reflects the rate at which the

282 tracer is being taken up into tissue (perfusion multiplied by first pass extraction), which is driven by the
283 combination of blood flow rate and membrane permeability. Studies of amyloid tracers including 11C-PIB
284 and Amyvid (florbetapir) have demonstrated a strong correlation between the early frame image and that
285 of a blood flow image for the same subject (Forsberg 2012, Gjedde 2013, Hsiao 2012, Rostomian 2011).
286 Following the first few minutes, the tracer begins to clear from the tissue, clearing less rapidly from
287 amyloid-containing tissue to which the tracer binds. The rate of clearance into the bloodstream and out of
288 the body is determined by several factors including kidney function and medication effects. After a tracer-
289 specific period of time (40 to 45 minutes for 11C-PIB), the rate of tracer influx to tissue is in approximate
290 equilibrium with its efflux back to the bloodstream.

291
292 Using the TAC values from Figure 1, the SUVR over time is shown in Figure 2. It can be noted that this SUVR
293 is not a stable value over time, for reasons discussed below. For a visualization of SUVR over time using the
294 amyloid tracer flutemetamol see also Figure 6 of Nelissen et al (2009).



296
297 Figure 2. SUVR over time based upon the TAC values in Figure 1.

298 299 Kinetic modeling

300 Several different models have been developed that use simultaneous differential equations to solve for the
301 “flux” into and out of compartments, and ultimately the amount of tracer bound to target (in this case,
302 amyloid). The gold standard approach uses arterial blood measurements to obtain the actual tracer
303 concentration in blood. This method has some disadvantages due to patient and staff burden and variability
304 in the blood measurements (Lopresti 2005, Tolboom 2009). Alternate modeling approaches make use of
305 regional measurement of carotid artery radioactivity (Lopresti 2005) or eliminate the need for blood
306 sampling by making use of reference measurements in tissue that does not contain the binding target. For
307 amyloid tracers, this is often the cerebellar cortex, which is generally devoid of amyloid except in latest
308 stages of Alzheimer’s disease (ref) and certain familial forms of AD (Sepulveda-Falla 2011). The validity of
309 the reference region approach as an approximation for blood based modeling must be tested for each new

310 tracer, as it has been for 11-PIB (Price 2005), Amyvid (florbetapir, Wong 2010), Vizamyl (flutemetamol,
311 Nelissen 2009), and Neuroseq (florbetaben, Becker 2013). All kinetic models make use of the entire time
312 course of tracer measurement (TAC) from time of injection to a point at which a “pseudo-equilibrium” has
313 been reached. All of these models have the advantage of segregating the contribution of blood flow and
314 clearance from that of bound tracer. In the process, they provide a measure of “R1”, i.e perfusion relative
315 to reference perfusion. Given the correlation between blood flow and cerebral glucose metabolism that
316 exists in many cases, this provides an additional “FDG like” image reflecting neuronal function. The
317 creation of a full TAC using an early time window and late time window has also been demonstrated
318 (Bullich 2017). The measure of target burden (in this case amyloid) derived from a kinetic model is called
319 the Distribution Volume Ratio (DVR or $V_{\text{tissue}}/V_{\text{nondisplaceable}}$), equal to non-displaceable Binding Potential
320 (BPnd) + 1. Published studies that used kinetic modeling may state the DVR value or may alternatively state
321 the BPnd value when stating amyloid burden.

322 **Standardized Uptake Value Ratio**

323 Despite the advantages provided by full kinetic modeling in accounting for contributions from blood flow,
324 binding, and clearance, there are practical drawbacks. It is difficult for patients, particularly those with
325 disease, to lie still in the scanner for the hour plus it may take to acquire a dynamic scan. Acquiring dynamic
326 scans presents additional burden on staff, and starting the scan at time of injection may require two
327 technicians to be present. Historically, not all scanners have supported the acquisition modes or memory
328 capacity required to acquire the number of discrete timeframes necessary to capture a full TAC, although
329 most newer scanners have this capability. Using the scanner for a full hour or more also precludes its use
330 for other patients during that entire time.

331
332 For these reasons, the SUVR is often used as an approximation for DVR. This measurement uses only a “late
333 timeframe” segment during which the tracer is in equilibrium. In true equilibrium, and assuming that blood
334 flow rates are the same in target and reference tissue, the ratio of the two tissues provides a relative
335 measure of the signal contribution due to amyloid binding. In reality, equilibrium is “pseudo”, in that tissue
336 continues to lose activity. However, numerous studies have demonstrated that the simpler SUVR approach
337 can provide discrimination between normal, MCI, and AD groups and, with adequate numbers of subjects,
338 measure group level increases or decreases (Biogen ref) over time.

339 **Bias in SUVR measurements**

340 The fact that true equilibrium is never reached can create an upward bias in SUVR value relative to DVR
341 (Slifstein et al, 2007, Carson et al, 1993, Frokjaer et al, 2007, van Berckel et al, 2013). To illustrate this
342 conceptually, from the TACs in Figure 1, it can be seen that the “receptor poor” reference region TAC
343 asymptotes, or flattens, more rapidly than the “receptor rich” TAC. This is because tracer binding slows
344 tracer flux back into the bloodstream. Even in late timeframes, neither curve is flat, which would be the
345 case if equilibrium were reached and net flux were zero. However, the receptor poor curve approaches a
346 “flatter” stage first, as the concentration difference between tissue and plasma is lower. The difference
347 between the rate of change in the receptor rich TAC (the SUVR numerator) and the reference TAC (the
348 SUVR denominator) creates an artificially high value. A mathematical expression of this is provided in
349 Slifstein et al (2007), which the reader is encouraged to review for further detail along with other
350 references cited. In brief, as described mathematically in Slifstein, a change in concentration in a given
351 region is depicted by $[k_1 * C_{\text{plasma}}] \text{ minus } [k_2 * C_{\text{tissue}}]$, where k_1 is the transport coefficient from plasma to
352 tissue, C_{plasma} is the concentration in plasma, k_2 is the transport coefficient from tissue to plasma, and C_{tissue}
353 is the concentration in tissue. At equilibrium, these would sum to zero consistent with a lack of net
354
355

356 concentration change. The expression $C_{\text{tissue}}/C_{\text{reference}}$, which is the SUVR, would equal the DVR (where $DVR = V_{\text{tissue}}/V_{\text{ND}}$ and ND refers to nondisplaceable binding in reference region). However, only “pseudo-equilibrium” is reached and instead, $C_{\text{tissue}}/C_{\text{reference}} = [V_{\text{tissue}} * (k_1 C_{\text{plasma}} + |dC_{\text{tissue}}/ct|)] / [V_{\text{tissue}} * (k_1 C_{\text{plasma}} + |dC_{\text{reference}}/ct|)]$. The rate of change in tissue $|dC_{\text{tissue}}/ct|$ in the numerator of this expression is greater than the rate of change $|dC_{\text{reference}}/ct|$ for the reference tissue (which “flattened” earlier) in the expression denominator. This erroneously increases the value of the $C_{\text{tissue}}/C_{\text{reference}}$, the SUVR.

363 SUVR bias is often on the order of 10% (Lopresti 2005) but can reach 20% or greater depending upon the value of k_1 (van Berckel et al, 2013). Bias increases from the point at which the approach toward pseudo-equilibrium begins (e.g. 30 to 35 minutes for 11C-PIB) and continues to increase (until approximately 70 minutes for 11C-PIB, van Berckel et al, 2013) before plateauing. If blood flow and clearance rates do not change from scan to scan, this bias would cancel out for longitudinal measurement. However, longitudinal error in measuring a change in SUVR can occur if the k_1 value changes from one scan to another. Changes in k_1 are influenced by blood flow and first pass extraction. Blood flow in particular can be impacted by medications including candidate therapeutics for AD. In a simulation modeled by van Berckel et al, error decreases with later timeframes, but for a decrease in k_1 from 0.32 to 0.26 the error introduced at 60 minutes would be approximately -4%, significant in the context of amyloid accumulation rates.

374 Longitudinal error can also occur if the ratio (R1) of the rate of tracer delivery to the target (“amyloid rich”) region to the rate of tracer delivery to the reference region changes from one scan to another. Such a change could be produced by (a) blood flow rate changes (e.g. decreases) in certain cortical regions relative to flow rate in a cerebellar reference region, or (b) changes in regional membrane permeability influencing tracer extraction efficiency. Using a longitudinal follow up period of 30 +/- 5 months, Van Berckel et al found that R1 values were stable over time in normal controls and MCI patients, but were reduced by approximately 20% in AD patients. This is consistent with decreases in blood flow that have been observed with AD progression in regions consistent with those in which glucose hypometabolism becomes pronounced. Changes in regional blood flow rate and local membrane permeability can also be caused by therapeutic agents. A 20% reduction in R1 value was estimated to create a 2% longitudinal increase in SUVR at 60 minutes post tracer injection (van Berckel). A study that used the early (first 20 minutes) and late frames (50 to 70 minutes) of florbetapir images acquired in ADNI subjects to estimate the contribution of blood flow unaccounted for in SUVR measures, also found that potential longitudinal errors on the order of 2% to 5% could occur in late MCI/AD patients due to changes in blood flow (Cselenyi et al, 2015). In the van Berckel example (Figure 1 of the reference publication), it can be seen that the error is more pronounced in the 60 to 90 minute SUVR than the 40 to 60 minute SUVR. While part of this may be due to the bias phenomenon, it has also been observed that 60 to 90 minute PIB SUVR measurements involve substantially more technical variability than earlier measurement, likely arising from lower tracer signal with noise inflated through decay correction, and greater subject motion as time in scanner proceeds.

394 **Bias in kinetic models (and SUVRs) that use a reference region**

395 It should be noted that bias also occurs in kinetic models, depending upon the model (and potentially the tracer) used, for a different reason than that discussed above for SUVRs. All reference tissue models, whether DVR or SUVR assume that:

- 398 1. the level of non-specific binding is the same in target and reference regions
- 399 2. the ratio K_1/k_2 is the same for target and reference regions.

400 If either of these assumptions is violated, then the reference tissue model will not produce a true reflection
401 of binding to target. Whether or not the model can still be used on a practical basis depends upon study
402 objectives. Assumption 1 could be violated in the case of off-target binding, which is not homogeneous, and
403 assumption 2 could be violated in the case of blood brain barrier (BBB) breakdown.

404
405 In a comparison of several modeling methods applied to the same 11C-PIB scans, Lopresti et al (2005)
406 compared DVRs generated using the Logan graphical model with arterial blood sampling over 90 minutes
407 (“gold standard”) to DVRs generated using methods including arterial sampling and a 60 minute interval,
408 Logan reference region models with cerebellar cortex as reference, the Simplified Reference Tissue Model
409 (SRTM), and SUVRs measured from 40 to 60 minutes and 40 to 90 minutes with cerebellar cortex as
410 reference. Logan reference tissue models showed a negative bias averaging -11% for high DVR subjects,
411 while the SRTM model showed a mean 5% bias but with broader variance than all other models for low
412 DVR subjects, and a mean -5% bias for high DVR subjects. For comparison, the mean bias for SUVR models,
413 high DVR subjects was 6% (60 minutes) to 9% (90 minutes). Van Berckel et al (2013) showed that DVRs
414 generated using the Logan reference region method were 6% lower than those generated using the model
415 Receptor Parametric Mapping (RPM2), while SUVRs were biased upward. Kinetic model bias has been
416 attributed to a suspected difference between tracer clearance rate in the cerebellar cortex reference tissue
417 vs. plasma (Lopresti 2005), or to differences in model susceptibility to reference region noise (van Berckel
418 2013). These factors can be mitigated in part through optimized model selection.

419 420 **Logistical considerations for dynamic modeling**

421 Acquisition of discrete timeframe data for dynamic modeling requires several short duration frames
422 occurring immediately following tracer injection, followed by longer timeframes later on. The scanner must
423 be capable of acquiring multi-frame data and must have adequate memory storage to support what will
424 likely be more than 20 frames in a single session (this issue has decreased with newer scanners). The site
425 must also either have scanner equipment that provides for a button enabling start of scan along with tracer
426 injection, or a second staff person available to initiate scanner data acquisition at time of injection. There
427 are further considerations with the length of the IV line depending upon the tracer (due to affinity for
428 tubing walls for some tracers), and the position of the subject within the scanner. As additional
429 considerations, scanner utilization time and patient burden are increased. A dual “early” (first minutes post
430 injection) and “later” (pseudo equilibrium) data acquisition approach has been demonstrated that allowed
431 extrapolation of a full TAC for kinetic modeling while also allowing the subject to have a “break” (Bullich
432 2017). However, the potential benefit of allowing a site to fit an extra scan within that “break” period is
433 offset by the potential occurrence of a delay in continuing the scan, and associated introduction of
434 technical variability. To assess blood flow changes, alternate modalities such as arterial spin labeling (ASL)
435 MRI have been proposed; however, these require validation for use in this context and do not capture
436 clearance changes.

437
438 It should be noted that kinetic modeling does not overcome error introduced by subject motion,
439 misalignment between emission and transmission scan, or other technical sources of noise. Since the risk of
440 subject movement increases with longer times in the scanner, these variables can actually outweigh the
441 benefits unless provisions are made to align each timeframe prior to attenuation correction.

442 443 **Conclusions**

444 Longitudinal changes in SUVR arising from systematic changes in blood flow ratios and clearance rates
445 mentioned in this section are not accounted for in the coefficient of variation in the profile Claim, which

446 captures non-systematic variability. The impact of systematic changes is highly dependent upon the study
447 population and therapeutic agent. When evaluating patient populations where the disease process may
448 impact blood flow or clearance rate, or where a therapeutic intervention could impact these factors, it is
449 strongly recommended to conduct at least an initial study using full dynamic modeling in order to
450 determine whether the SUVR approach is an acceptable substitute. Despite the logistical challenges of
451 conducting full dynamic imaging, there are certain sites that routinely acquire data of this type. The benefit
452 of characterizing potential erroneous signal changes due to changes in blood flow or clearance merits
453 inclusion of such studies prior to broadening a longitudinal amyloid measurement trial through use of
454 SUVR.