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

Version with PUBLIC COMMENTS and TECHNICAL CONFORMANCE QUESTIONNAIRE COMMENTS considered

~~02May2018~~14Apr2022

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# Table of Contents



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Table of Contents



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# Change Log

This table is a best-effort of the authors to summarize significant changes to the Profile.

| Date | Sections Affected | Summary of Change |
|---|---|---|
| 2022.04.09 | All | Finalization for Technical Confirmation decision based upon feedback and decisions associated with Technical Conformance questionnaire responses.<br>Checklists added per updated Profile template.<br>Formatting to align with updates to QIBA Profile guidelines. |
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# Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved.

| **Issues** |
|---|
| None in this version. |
| |

# ~~Open~~Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

| **Issues** |
|---|
| **Modifications to address public comments**<br>Modifications have been incorporated to address public comment and issues that were outstanding, including the Claim(s). |
| **Conformance Methodology**<br>The methodology to perform conformance testing of the image analysis workstation is included; this relies upon using a Digital Reference Object (DRO), which was funded as a NIBIB groundwork project. The description of the DRO and its use have been modified to address questions and findings in the testing of this procedure. |
| **Conformance Testing**<br>Describes measurement procedures 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 SUVRs, and 3) linearity with a slope of one is a reasonable assumption. |
| **Modifications to address technical conformance questionnaire feedback**<br>Modifications have been incorporated to address responses from the Technical Conformance questionnaire that indicated a lack of feasibility and/or alternate preferred ways to approach. |

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

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| |
|---|
| Modifications to address public comments<br><br>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<br><br>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<br><br>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 SUVRs, and 3) linearity with a slope of one is a reasonable assumption. |

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1. Executive Summary

# 1. Executive Summary

## 1.1 1.1 Overview

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker.

Profile development is an evolutionary, phased process; this Profile is in the Technical Conformance stage in preparation for being Technically Confirmed. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document's context:

http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages.

The **Claim** (Section 2) describes the biomarker performance.
The **Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim.
The **Conformance** section provides **Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.
**References** are provided in section 5.
**Appendices** (Section 6) are provided that include additional information for performing Activities as well as Checklists that can be completed to evaluate Profile conformance.

In general, QIBA Profiles provide DESCRIPTIVE text sections as background and recommended considerations, and **SPECIFICATIONS** (tables) that include prescriptive (required to meet claim) items in clear boxes and potential or future items in gray boxes.

This QIBA Profile **"18F-labeled PET tracers targeting Amyloid as an Imaging Biomarker"** documents specifications and requirements to provide comparability and consistency for the use of PET imaging using 18F labeled tracers that bind to fibrillar amyloid in the brain. Quantitative measurement of amyloid, a hallmark pathology of Alzheimer's disease, has become increasingly used in clinical trials for patient inclusion, evaluation of disease progression, and assessment of treatment effects. The current version of the Profile focuses on a longitudinal Claim, where the primary purpose is to assess change in amyloid load due to disease or following an intervention. In this case, precision is most important as long as bias remains constant over time. Characterization of measurement bias will be important for a cross-sectional Claim wherein the amyloid tracer is used primarily to select amyloid positive subjects.

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

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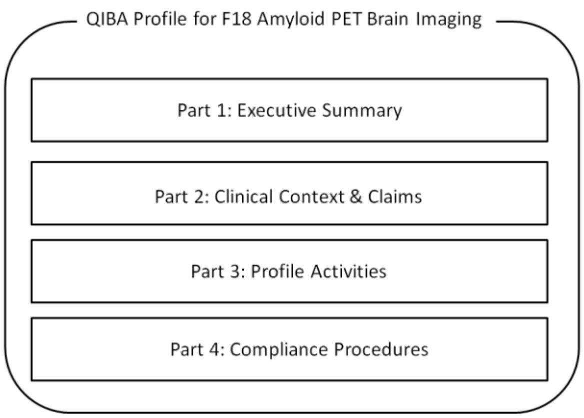
~~The guidance in this Profile can be applied for clinical trial use as well as individual patient management.~~

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

The Profile is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints. The guidance in this Profile can be applied for clinical trial use as well as individual patient management.

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

This Profile, developed through the efforts of the amyloid Profile writing group in the QIBA Nuclear Medicine Technical Subcommittee, shares some content with the QIBA FDG-PET Profile, and includes additional material focused on the devices and processes used to acquire and analyze amyloid tracer PET data. QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found

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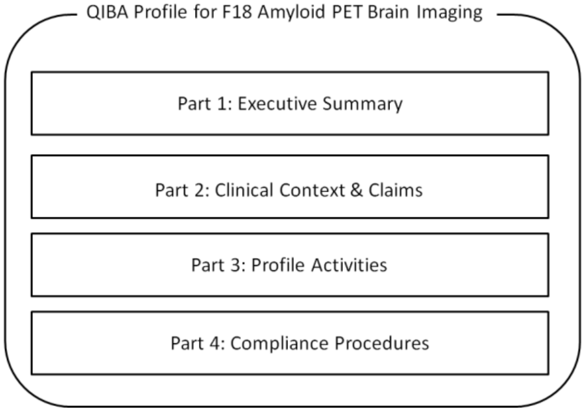
at qibawiki.rsna.org. Thise Profile is organized as follows:



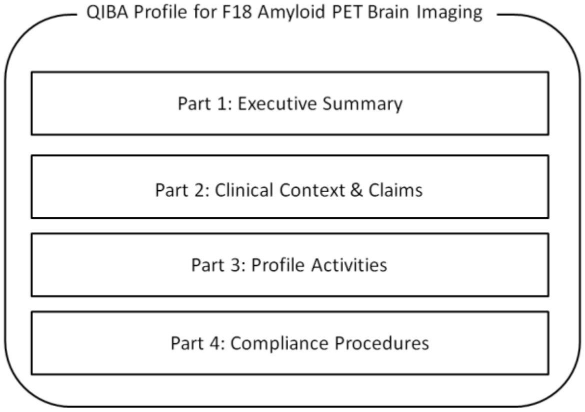




Figure 1: ~~Figure 1:~~ Illustration of the Profile components

The Profile Part 3 is derived from multiple sources, including material contained in the work performed by the Alzheimer's Disease Neuroimaging Initiative (ADNI).

## 1.2 Summary of Use in Clinical Trials

~~The current version of the Profile focuses on a longitudinal Claim, where the primary purpose is to assess change in amyloid load due to disease or following an intervention. In this case, precision is most important as long as bias remains constant over time. Characterization~~

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~~of measurement bias will be important for a cross-sectional Claim wherein the amyloid tracer is used primarily to select amyloid positive subjects.~~

## ~~1.2 1.2 Summary for Clinical Trial Use~~

Thise QIBA Amyloid-PET Profile defines the technical and behavioral performance levels and quality control specifications for brain amyloid tracer PET scans used in single- and multi-center clinical trials of neurologic disease, particularly Alzheimer's disease. Examples of clinical application are detailed below in the Claims section 2.3.

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

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

## 1.3 ~~1.3~~ Intended Audiences

The intended audiences of this document include:

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

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

# 2. ~~2.~~ Clinical Context and Claims

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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 3.3.3.1.2 ~~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. The important role of longitudinal quantitation of amyloid has been highlighted with the recent FDA approval of anti-amyloid immunotherapies such as Aduhelm (aducanumab), and other immunotherapies in the regulatory approval pipeline.

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:

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**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 <=1.94%.**

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

## 2.2 Considerations for claim

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## ~~2.1 2.1. Claim~~

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## ~~1.1 If Profile criteria are met, then:~~

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## 1.1 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 <=1.94%.

## 1.1

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

## 1.1

## 2.2 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 3.6.3.2.23.4.3.2.2.

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

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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 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

## ~~2.3 2.3. Clinical Trial Utilization~~

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

The wCV stated in the technical performance Claim can be used to derive confidence intervals for individual subject changes in amyloid burden. However, because amyloid accumulation rates reported in the literature average from 1 percent to a few percent per year, SUVR confidence intervals derived from the wCV may not be relevant to the assessment of individual change over the duration of a typical clinical trial. In this case, the wCV value can be used to guide the number of subjects to include in clinical trials



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targeting measurement of longitudinal change in amyloid SUVR. A few examples of practical uses of the Claim are described below, and further guidance is found in the "Statistical Planning for a Clinical Trial Guidance document" posted on the QIBA website, in development as a full manuscript.

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

1.

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

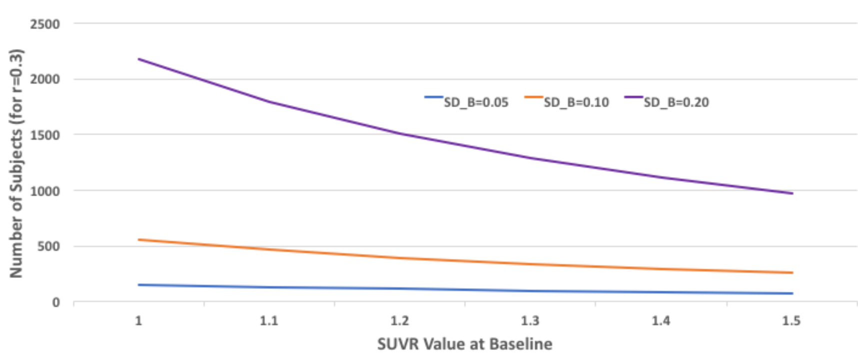


**Figure 2a.** Example of powering a clinical trial to measure rate of amyloid accumulation, r=0.3.

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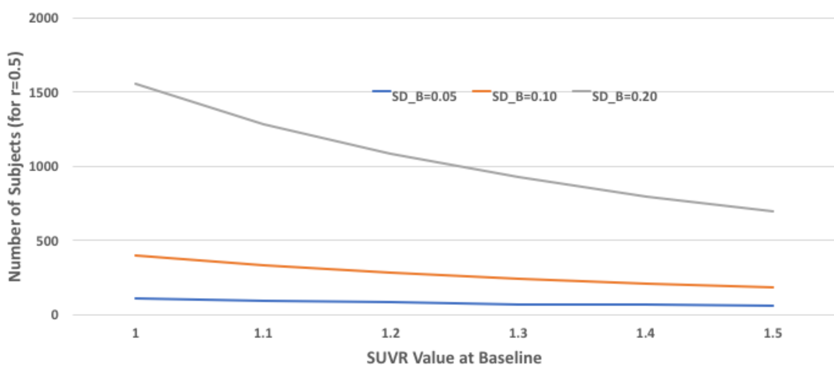


**Figure 2b.** Example of powering a clinical trial to measure rate of amyloid accumulation, r=0.5.

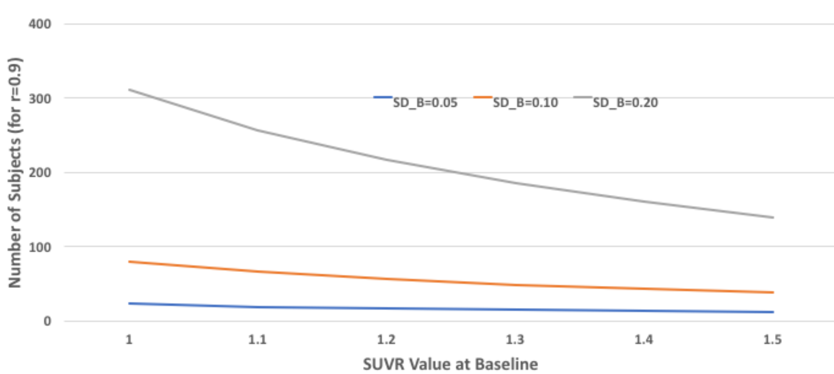


**Figure 2c.** Example of powering a clinical trial to measure rate of amyloid accumulation, r=0.9.

~~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

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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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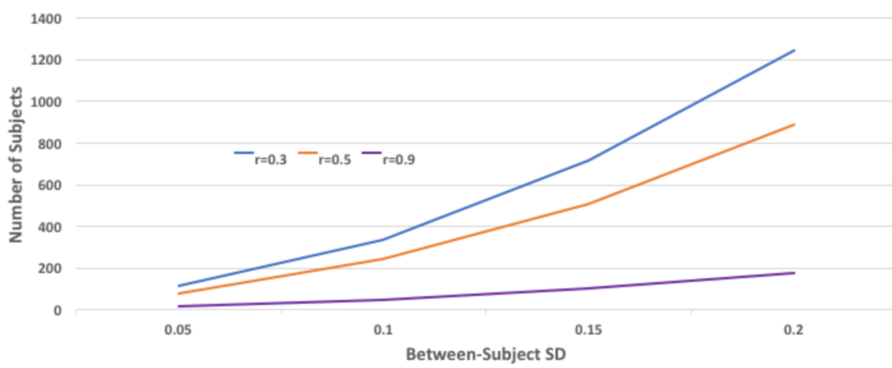


**Figure 3.** Example of powering a clinical trial to measure a reduction in the rate of amyloid accumulation

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

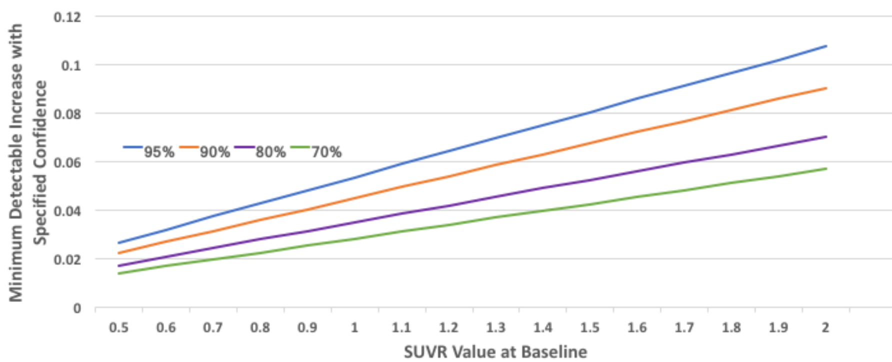


**Figure 4.** Example of minimum detectable increase for individual subject.

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4. **Confidence interval for an individual's true change.** For an individual's SUVR measurements of Y1 at baseline and Y2 at follow-up, the 95% confidence interval for the true change associated with the wCV of Claim 1 is given by the equation: (Y2-Y1) ± 1.96 × √([Y1 ×0.0194]^2 + [Y2 ×0.0194]^2).

# 3. Profile Activities

~~3.~~ ~~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.~~

## 3.1 ~~Patients may be selected or referred for amyloid-PET imaging though a variety of mechanisms.~~ Amyloid PET actors and activities

The Profile is documented in terms of "Actors" performing "Activities". Equipment, software, staff or sites may claim conformance to this Profile as one or more of the "Actors" in the following table.

Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced Section.

**Table: Actors and Required Activities**

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PAT Uniform Phantom Analysis

| Actor | Activity | Section |
|---|---|---|
| PET Tracer | Subject handling | 3.3 |
| Acquisition Device (Scanner, ancillary equipment) | Equipment qualification | 3.8, 4.2 |
| | Periodic QC | 3.8, 4.2 |
| PET Technologist | Subject handling | 3.3 |
| | Image data acquisition | 3.2 |
| | Image data reconstruction | 3.3 |
| Radiologist or Nuclear Medicine Physician | Image analysis | 3.6 |
| | Image interpretation | 3.7 |
| | Staff qualification (Quality Control) | 3.8 |
| Image analyst or other qualified person | Image analysis | 3.6 |
| | Image interpretation | 3.7 |
| Medical physicist | Equipment qualification | 3.8, 4.2 |
| | Periodic QC | 3.8, 4.2 |
| Reconstruction Software | Image data reconstruction | 3.5 |
| Image Analysis Tool | Image analysis | 3.6 |
| Site (Imaging Facility Coordinator) | Site conformance | 3.8 |

The imaging steps corresponding to Figure 1 are:

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

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

Images may be obtained at a single time point or multiple time points over months or years, for example at a minimum of two time points before and after therapeutic intervention for a response assessment. The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a "shall" in this Profile is a protocol deviation. Although

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deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable, and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

## 3.2 Amyloid PET activity process flow

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The sequencing of the Activities specified in this Profile are shown in Figure 5 below.

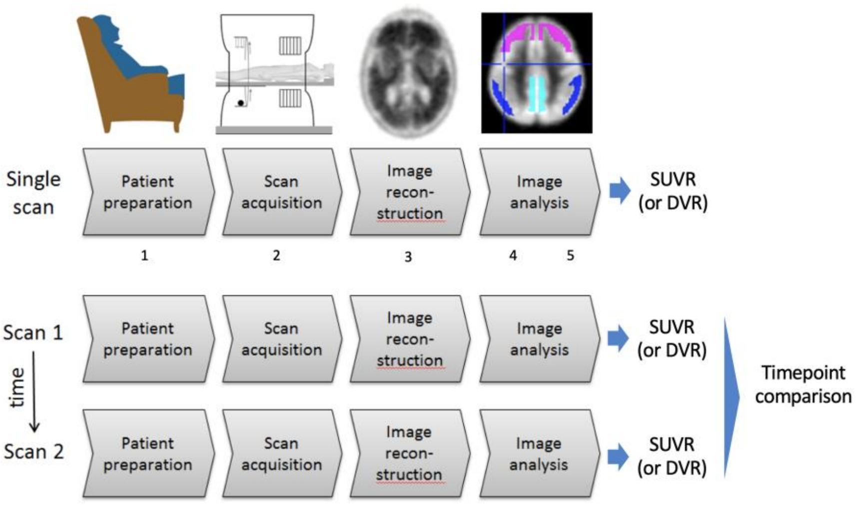


**Figure 5:** The method for computing and interpreting brain amyloid burden using PET may be viewed as a series of steps using either one scan (corresponding to a fit for use of a future 'Cross-sectional' Claim) or two or more scan sequences or time points (addressed by the current Profile's 'Longitudinal' Claim). SUVR = Standardized Uptake Value Ratio; DVR = Distribution Volume Ratio.

The imaging steps corresponding to Figure 5 are:

1) Patients or subjects are prepared for scanning. The amyloid tracer is administered. Patient waits for bio-distribution and uptake of amyloid tracer.
2) Emission and transmission data are acquired (typically the PET scan and CT scan if a PET-CT scanner).
3) Data correction terms are estimated and the attenuation and scatter corrected images are reconstructed.
4) Images are assessed for quality control and may separately be reviewed visually for qualitative interpretation (outside of the scope of this Profile).
5) Quantitative (and/or semi-quantitative) measurements are performed.

Prior to the patient preparation steps, patients may be selected or referred for amyloid-PET imaging though a variety of mechanisms. Performance of the activities in Figure 5 results in a numeric value

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representing amyloid burden. This value is then interpreted per the thresholds and/or other criteria determined per the study (this differs from visual interpretation of the scan). The primary focus of this Profile is the Standardized Uptake Value Ratio (SUVR), the ratio of tissue concentration for a designated brain region(s) compared to the activity from a reference region. Appendix I provides information regarding use of kinetic modeling to obtain a Distribution Value Ratio (DVR) measure rather than SUVR. The Profile also provides information regarding the conversion of SUVR units to the Centiloid measure (Klunk et al, 2015, section 3.4.3.4) which has been developed to reconcile values across amyloid PET tracers and measurement methods.

Note that a visual read of the images and the quantitative measurement and analysis (the topic of this Profile) may occur in either order or at the same time, depending upon the context of the review (clinical research versus clinical practice) with reference to the specifications described in each tracer's package insert. Currently, the quantitative use of amyloid-PET tracers is not approved by any regulatory authorities in clinical practice in the U.S. However, quantitation is available as part of various scanner and workstation software packages and is used extensively in clinical trials.

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

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

| ~~Section~~ | ~~Title~~ | ~~Performed by~~ |
|---|---|---|
| ~~3.1~~ | ~~Subject Handling~~ | ~~Personnel, (including Technologists and Schedulers) at an Image Acquisition Facility~~ |
| ~~3.2~~ | ~~Image Data Acquisition~~ | ~~Technologist, at an Image Acquisition Facility using an Acquisition Device~~ |
| ~~3.3~~ | ~~Image Data Reconstruction~~ | ~~Technologist, at an Image Acquisition Facility using Reconstruction Software~~ |
| ~~3.4~~ | ~~Image Analysis~~ | ~~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~~ |

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

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## ~~3.1~~3.3 ~~3.1.~~ Subject Handling

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

### ~~*3.1.1*~~*3.3.1* ~~*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 3.3.2~~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~~3.3.1.1 ~~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~~3.3.1.2 ~~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~~3.3.1.3 ~~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.

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### ~~3.1.2~~3.3.2 ~~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~~3.3.2.1 ~~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~~3.3.2.2 ~~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~~3.3.2.3 ~~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 recommend~~t~~ations) 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

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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~~3.3.3 ~~3.1.3.~~ *Imaging-related Substance Preparation and Administration*

#### ~~3.1.3.1~~3.3.3.1 ~~3.1.3.1.~~ Radiotracer Preparation and Administration

##### ~~3.1.3.1.1~~3.3.3.1.1 ~~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~~3.3.3.1.2 ~~3.1.3.1.2~~ Radiotracer Activity Calculation and/or Schedule

The amyloid ~~seeking~~ binding radiotracer activity administered will depend upon the specific tracer utilized (See Table below, which includes tracers approved by the FDA to date). 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.

**Tracer reference table**

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

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**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Administered amyloid r~~R~~adio-tracer Activity | Imaging Technologist, Physician, Nurse, or other qualified Health Professional | The qualified Health Professional shall:<br>1. Assay the pre-injection radiotracer activity (i.e. radioactivity) and record time of assay ~~and time of measurement,~~<br>2. Inject the quantity of radiotracer as prescribed in the protocol and r~~R~~ecord the time that radiotracer was injected into the subject~~,~~<br>~~3.~~ Assay the residual activity in the syringe (and readily available tubing and components) after injection and record the time of measurement~~.~~<br>~~4.~~3. ~~Inject the quantity of radiotracer as prescribed in the protocol.~~<br><br>These values shall be entered into the scanner during the PET/CT acquisition.<br><br>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.<br><br>All data described herein on activity administration shall be documented. |
| | | All data should be entered into the common data format mechanism (Appendix E). |

#### ~~3.1.3.1.3~~3.3.3.1.3 ~~3.1.3.1.3~~ Radiotracer Administration Route

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

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



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

SPECIFICATIONS

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Amyloid radiotracer ~~a~~Administration | Technologist or Physician | Technologist or Physician shall administer the amyloid radiotracer intravenously through an indwelling catheter (24 gauge or larger), preferably into a large vein (e.g., antecubital vein). Intravenous ports should not be used ~~,~~ unless no other venous access is available.<br><br>A three-way valve system should be attached to the intravenous cannula so as to allow at least a 10 cc normal (0.9% NaCl) saline flush following radiotracer injection. |
| Suspected infiltration or extraneous leakage | Technologist and/or Physician ~~or Physicist~~ | Technologist shall:<br><br>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.<br><br>2. Image the infiltration site. |
| | | Record the event and expected amount of amyloid tracer into the common data format mechanism (Appendix E). |

## ~~3.2~~3.4 ~~3.2.~~ Image Data Acquisition

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

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

For clinical trials with quantitative imaging requirements, a subject should have all scans performed on only one scanner unless quantitative equivalence with a replacement scanner can be clearly demonstrated. However, it should be noted that there are currently no accepted criteria for

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demonstrating quantitative equivalence between scanners. It is anticipated that future version of this Profile will provide such criteria.

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

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

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

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

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

### *~~3.2.1~~3.4.1 ~~3.2.1~~ Imaging Procedure*

~~3.2.1.1~~ 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.

#### ~~3.2.1.2~~3.4.1.1 ~~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.

Tracer acquisition parameter example table (Refer to manufacturer label for actual use in case of changes)

| **Parameter** | **Florbetapir (Amyvid) [1]** | **Flutemetamol (Vizamyl) [2]** | **Florbetaben (Neuraceq) [3]** |
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| | | | |
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| 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, NAV-4694, 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.

**SPECIFICATIONS**

| 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 3.4.1.1~~3.2.1.1~~).<br>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 (as closely as possible and not more than ± 5 minutes). |

The following sections describe the imaging procedure.

### ~~3.2.1.3~~3.4.1.2 ~~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. Motion can be

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measured in terms of linear movement in the x, y, and z directions and rotational movement around those axes. Figure 6 illustrates the effects of subject head motion between the emission scan and transmission scan upon measured regional values. These were determined by systematically translating and rotating the mu maps for the same scan and then reconstructing the image each time (QIBA grant funded project). Similar errors resulted from the simulation of subject head motion within the emission scan through systematic translation and rotation of the reconstructed scan relative to region of interest placement.

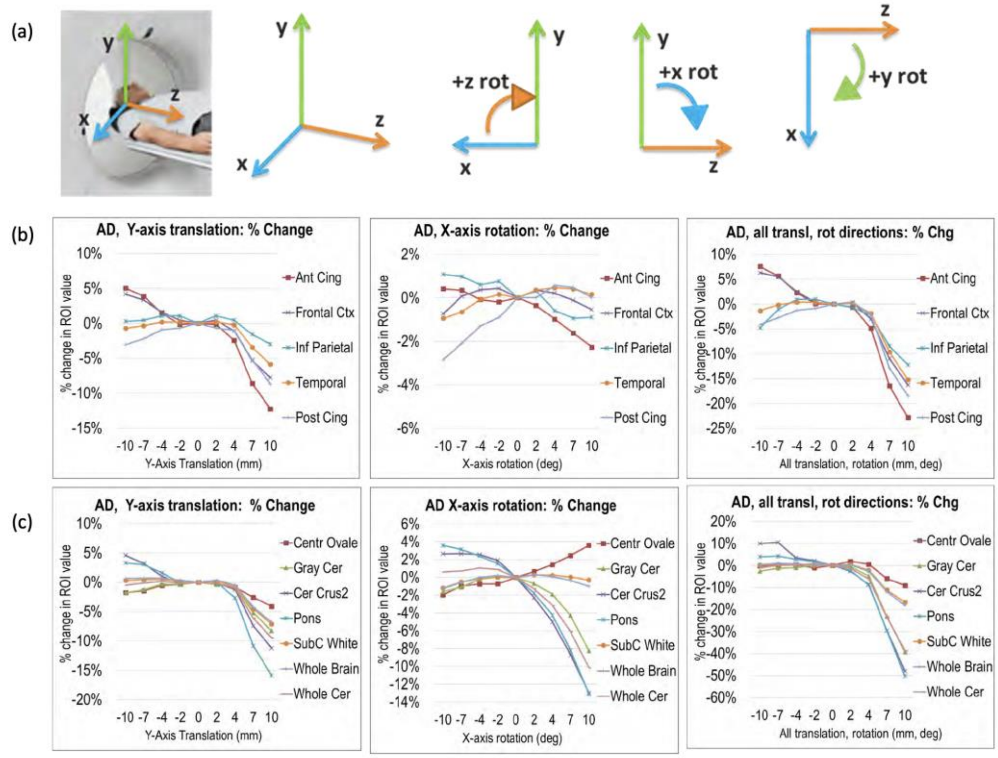


**Figure 6**. The effects of linear, rotational, and combined linear and rotational head movement between the transmission scan and emission scan upon several target regions and reference regions: (a) x, y, and z directions, (b) percent change in target region of interest measures, (c) percent change in reference region measures. The SUVR error incorporates the ratio of the percent change in the target region(s) / the percent change in the reference region.

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 3.5~~3.3.2.2.1~~.

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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 region ~~serves~~ may be used as a reference region for subsequent quantification.

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

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

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

## SPECIFICATIONS

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Subject Positioning | Technologist | The Technologist shall position the subject according to the ~~specific~~ protocol specifications consistently for all scans, with brain fully in field of view, ideally centered with bottom of cerebellum at least 2.5 cm away from edge of axial FOV unless otherwise specified by protocol. |
| Subject Positioning | Technologist | The Technologist shall ensure the comfort of the subject in the head holder prior to initiating the scan, to minimize the likelihood of movement. |
| Subject positioning | Technologist | The Technologist shall instruct the subject to hold as still as possible during the scan. |
| Subject Positioning | Technologist | The Technologist shall document the head position of the subject in the scanner FOV so that this can be replicated for subsequent scans. |
| Positioning Non-compliance | Technologist | The Technologist shall document issues regarding subject non-compliance with positioning. |
| | | The Technologist shall document issues regarding subject non-compliance with breathing and positioning using the common data format mechanism (Appendix E). |

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PAT Uniform Phantom Analysis

| ~~Parameter~~ | ~~Entity/Actor~~ | ~~Specification~~ |
|---|---|---|
| Motion non-compliance | Technologist | The Technologist shall document issues regarding subject non-compliance with not remaining still.<br>The Technologist shall document issues regarding subject non-compliance (not remaining still) motion using the common data format mechanism (Appendix E). |

#### ~~3.2.1.4~~3.4.1.3 ~~3.2.1.3~~ Scanning Coverage and Direction

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

**SPECIFICATIONS**

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

#### 3.4.1.4 ~~3.2.1.4~~ Scanner Acquisition Mode Parameters

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

##### 3.4.1.4.1 PET Acquisition

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

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site-specific acquisition parameters should be determined upon calibration with the appropriate phantom (see below).

**SPECIFICATIONS**

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

##### 3.4.1.4.2 CT Acquisition

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

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

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## SPECIFICATIONS

| 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. |

| 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.<br>The protocol shall be recorded and documented. |
| CT Technique: Dose Exposure | Technologist | The Technologist shall ensure that CT dose exposure is the lowest radiation dose necessary to achieve the diagnostic objective. |

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

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# ~~3.3~~3.5 ~~3.3.~~ Imaging Data Reconstruction and Post-Processing

## ~~3.3.1~~3.5.1 ~~3.3.1~~ *Imag~~inge~~ Data Reconstruction*

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

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

**SPECIFICATIONS**

| 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~~2.5 mm in the z direction (older scanners such as GE Advance may require up to 4.5 mm but are not as recommended). |

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| 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. |
| | | 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 at this stage. |
| 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. |

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

### 3.5.2 ~~3.3.2~~ Image Data Post-processing

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Processed image data are images that have been transformed in some manner in order to prepare them for additional operations enabling measurement of amyloid burden. Some post-processing operations are typically performed by the PET technologist immediately following the scan. Additional steps may be

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performed by a core imaging lab, or by an analysis software package accessed by the radiologist or nuclear medicine physician.

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

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

#### ~~3.3.2.1~~3.5.2.1 Ensure image orientation

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

SPECIFICATIONS

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

#### ~~3.3.2.2~~3.5.2.2 Create Static Image

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

##### ~~3.3.2.2.1~~3.5.2.2.1 Intra-scan inter-timeframe assessment and alignment

For a scan comprised of multiple timeframes, it is important to ensure that the frames are spatially aligned so that the same brain tissue is located in the same coordinates for measurement across the frames. It is preferable that this alignment be performed prior to attenuation correction (that is, as part of the steps in the previous Section 3.3.2.2) in order to prevent embedded error due to misalignment between emission and transmission scan. However, at present, because of limitations in the tools provided with

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typical scanner workstations, inter-timeframe alignment is typically not performed during image reconstruction and attenuation correction. Rather, visual checks are typically applied and excessive motion may or may not be flagged. If automated, precise tools become available in scanner workstations in the future, the inter-frame alignment and static image formation described in this section may become part of the image reconstruction process. Even when inter-timeframe alignment is performed prior to attenuation correction or at the imaging site, it is important that the discrete binned frames prior to inter-frame alignment, the transmission scan, and the alignment parameters applied, be made available for quality control in later processing and analysis steps.

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

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

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

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SPECIFICATIONS

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

##### ~~3.3.2.2.2~~3.5.2.2.2 Combine discrete timeframes

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

SPECIFICATIONS

| 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. |

### ~~3.3.2~~3.5.3 ~~3.3.3~~ *Imaging Data Storage and Transfer*

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



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

***Post-processed image data*** are images that have been transformed after reconstruction in some manner. This is typically a stack of DICOM slices/files constituting a PET image volume that can still be analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS system, etc.

For archiving at the local site or imaging core lab (if relevant), the most important data are the original images, i.e. the image raw data. In the unlikely event that the scanner raw data (which should be archived by the local site) is required for later reprocessing; this should be made clear in the protocol.

SPECIFICATIONS

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

## ~~3.4~~3.6 ~~3.4.~~ Image Analysis

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

### ***~~3.4.1~~3.6.1 ~~3.4.1~~ Input Data***

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

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### ~~3.4.2~~3.6.2 ~~3.4.2~~ Image Quality Control and Preparation

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

#### 3.6.2.1 ~~3.4.2.1~~ Correction for Partial Volume Effects (PVE)

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Partial Volume Effects Correction (PVEc) is not recommended as a "by default" step in this Profile due to the fact that the process itself can introduce a great deal of variability, countering the tolerance goals of the Profile. However, we discuss this step here, as it may be included in certain study protocols particularly if methodology is systematically employed that does not increase variability.

As background on this topic, due to the limits of PET scanner resolution, the signal measured at the borders of white and gray tissue, or tissue and cerebrospinal fluid (CSF) can contain contributions from both types of tissue within the boundaries of the same voxel. In particular, some amyloid PET tracers have high levels of nonspecific white matter uptake, producing high signal intensity that "spills into" neighboring gray tissue measures. In addition, neurodegenerative patients may exhibit substantial, progressive atrophy, increasing spill-in from CSF that can dilute increases or accentuate decreases originating from the atrophic tissue elements.

Several different mathematical algorithms and approaches have been developed to correct or compensate for PVE and tissue atrophy. However, these approaches are not necessarily sensible in the setting of amyloid imaging and quantification. Simply applying correction for the loss of cerebral gray matter results in upscaling of image signal intensity, and is most appropriate when the tissue origin of the signal is lost, resulting in the atrophy (such as loss of synaptic neuropil in [18F]2-fluoro-D-2-deoxyglucose (FDG) cerebral glucose metabolism imaging). In the case of amyloid deposition in neurodegenerative dementia, however, the deposits are not contained with normal cerebral gray matter elements. Amyloid plaques are extracellular accumulations and are unlikely to degenerate as gray matter atrophies due to losses of synapses and neurons ensues. Thus, applying gray matter atrophy-correction PVEc may inappropriately "upscale" the amyloid signal from atrophic cortical regions. Usually PVEc approaches result in a new image, typically containing only gray matter, and has been shown to increase the apparent amyloid in AD patients by as much as 30% to 56%. The most sensible approach to PVEc in amyloid images is to apply correction for spillover from subcortical white matter into the gray matter regions, which is likely to become increasingly problematic as the cortical gray matter becomes atrophic.

Appropriate use of PVEc can potentially help to increase sensitivity to longitudinal change, and to reduce error associated with changes in atrophy or white matter uptake. However, PVEc methods can also introduce variability, and results are highly sensitive to subjective selections of the parameters used in calculating the correction. Effects upon measurement of longitudinal change have varied from no effect to an increase in measured change. The tradeoff between benefit vs. these considerations must be considered and the decision as to whether or not to use may be study dependent. The point in the process at which PVEc is applied may vary, for example either applied to spatially normalized images or to native images, prior to or after the creation of a SUVR image.

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#### 3.6.2.2 ~~3.4.2.2~~ Image Smoothing

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

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

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Image smoothing | Image analyst | When combining scans from different scanners and/or reconstruction software that produce different image resolutions, filtering will be applied per protocol to produce comparable signal for the same amount of radioactivity. |

### ~~3.4.3~~3.6.3 ~~3.4.3~~ *Methods to Be Used*

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

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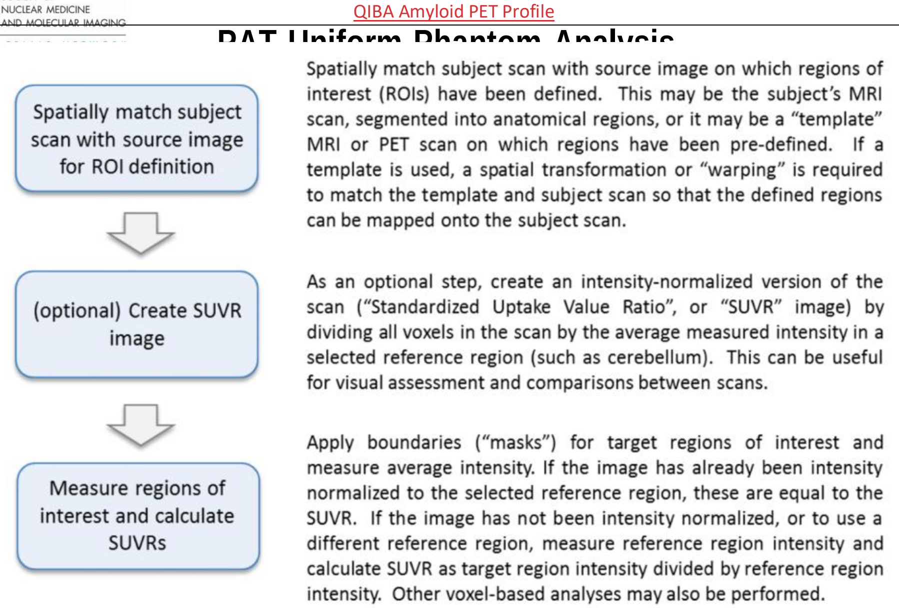


**Figure 47.** Typical steps in image processing and measurement for SUVR calculation

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

#### 3.6.3.1 ~~3.4.3.1~~ Spatially Match Subject and Template

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

##### ~~3.4.3.1~~3.6.3.1.1 ~~3.4.3.1.1~~ "Fuse" MRI and PET images

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

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

**SPECIFICATIONS**

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

##### ~~3.4.3.2~~3.6.3.1.2 ~~3.4.3.1.2~~ Longitudinal PET co-registration

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

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

It is noted here that some studies (unpublished, multiple groups) have shown that a superior longitudinal alignment of sequential PET scans can be achieved when co-registering the series of PET scans together rather than separately co-registering each PET to the MRI. However, it is also noted that in cases of substantial longitudinal atrophy or ventricular expansion, care must be taken in ensuring that the VOIs applied to each scan account for the actual gray tissue present in the brain.

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

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**SPECIFICATIONS**

| 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. |

##### ~~3.4.3.3~~3.6.3.1.3 ~~3.4.3.1.3~~ Spatial Mapping of Subject Image and Template Image

The following approaches can be applied for spatial mapping:

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

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

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

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

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.

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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.

**SPECIFICATIONS**

| 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. |

#### 3.6.3.2 ~~3.4.3.2~~ VOI Placement: Target / Reference

##### ~~3.4.3.4~~3.6.3.2.1 ~~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 to~~–~~ 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.

**SPECIFICATIONS**

| **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. |

##### ~~3.4.3.5~~3.6.3.2.2 ~~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~~ because 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.

***Cerebellar cortex:*** The cerebellar cortex (gray matter) has been a reference region of choice in numerous studies of amyloid since it typically does not accumulate fibrillar amyloid and because its gray tissue kinetics are assumed be reasonably matched to those of gray tissue target regions. Because of its low signal and lack of binding, the cerebellar cortex provides the most sensitive reference for measuring cross sectional differences. However, due to its low signal level, small swings in value will create large swings in calculated SUVR. Further, the physical location of the cerebellum toward the edge of the scanner transaxial field of view makes it susceptible to edge noise, scatter, and tissue exclusion (particularly in scanners with a shorter axial field of view). In head rotation and in emission-transmission scan misalignment, the posterior edge of the cerebellar cortex can be particularly impacted. In addition, slight shifts in position can cause a blending of white and gray tissue that will impact the reference

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measurement. Further, the cerebellum is located in transaxial slices that are not in proximity to several typical target VOIs, and signal in those slices may not change in the same way due to technical factors. In longitudinal studies~~, for~~ of ~~one radiotracer~~florbetaben, the cerebellar cortex has been demonstrated to show stability over time (Villemagne, AAIC 2015) while for others variability with regard to measured change has been shown, decreasing statistical power. Even in cross-sectional measurements, technical noise embedded in the cerebellum (or any reference region) may cause a subject whose amyloid burden is at the threshold of positivity to "tip" in one direction or another. If the reference regions does include the cerebellum, it is recommended to omit the superior portions of the cerebellum to avoid radiotracer contamination form surrounding structures such as the occipital cortex or the fusiform gyrus and to omit the lowest slices that exhibit greatest variability. These strategies have been employed in various studies (Shcherbinin et al, 2016; Barrtet et al, 2016; Pontecorvo et al, 2017; Hahn et al, 2017). Alternate reference region comparisons are also recommended to ensure that noise has not driven the SUVR result.

***Whole cerebellum:*** Use of whole cerebellum has been specified as a reference of choice with some PET tracers (such as florbetapir), and can reduce variability arising from shifts that include more white matter (Joshi, JNM 2015), since white matter is already included. However, the same issues with spatial location, edge noise, and lower average signal still apply.

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***Pons:*** As an alternative reference, the pons has been applied in multiple studies, and found to have a slightly lower variability. Its advantages include higher signal due to white matter inclusion, and more central location in the brain at a slightly further distance from the edge of the scanner transaxial field of view. Some studies using florbetapir, flutemetamol and 11C-PIB have found that the pons exhibited lower longitudinal variability than a cerebellar reference region (Thurfjell et al, 2014; Shokouhi et al, 2016; Edison et al, 2012). However, the narrow cylindrical size and shape of the pons make it vulnerable to subject motion, and it, too, can be affected by technical variability.

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***Subcortical white matter:*** Subcortical white matter provides another alternate reference region, with the advantages of higher signal, larger measurement volume, transaxial alignment with target regions of interest. Studies have demonstrated benefit in lower variability using subcortical white matter, and thus greater statistical power in measuring longitudinal change, relative to other reference regions (Chen et al, 2015; Brendel et al, 2015; Schwarz et al, 2016; Blautzik et al, 2017). One consideration in the use of a white matter reference is that the kinetic properties of white matter differ from those of the gray tissue target regions, with unclear impact upon measurement validity. There is not yet a published full dynamic modeling study of white matter as a reference. White matter axonal integrity may decline with AD progression and age, potentially increasing advantageous cross~~-~~sectional differences between AD and Normal, and introducing possible variability over time. However, findings support the ability to detect increases in amyloid positive populations as expected and seen with gray tissue reference regions, yet with lower variability (ideally this would be compared to full kinetic modeling results to demonstrate accuracy). When white matter is used, careful definition based upon the MRI, with erosion from neighboring gray tissue, is recommended.

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***Composites:*** Combinations of whole cerebellum, pons, and subcortical white matter, or cerebellar white matter and pons, or "amyloid poor" gray regions other than cerebellum have also been applied with reductions in longitudinal variability (for florbetapir) resulting in increased statistical power (Tryputsen et al, 2015; Landau et al, 2015). It is finally noted that regions comprised of both gray and white matter, whether whole cerebellum or composite regions, may include divergent changes over time. These may be a suitable match for probabilistic target regions that include both gray and white matter ~~,~~ or given white matter spillover into gray tissue. However, for "pure" gray target regions, their longitudinal use may

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introduce some non-amyloid related variability. All of this must 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.

**SPECIFICATIONS**

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

##### ~~3.4.3.6~~3.6.3.2.3 ~~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.

SPECIFICATIONS

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

#### 3.4.3.73.6.3.3 3.4.3.2.4 Generate SUVR Image Determine SUVR

##### 3.6.3.3.1 Generate SUVR image

There are two ways to generate SUVR values. In one case, the SUVR image can be generated, and then each target region measurement constitutes a SUVR value, as there is no need to divide by the reference region, which is 1. In the other case, SUVR values are generated by measuring values in target regions and dividing each by the value measured in the reference region. Once To generate a SUVR image, once a reference region has been applied to the scan (i.e. the boundaries aligned with the scan), and either before target region measurement, or afterward, athe SUVR image (or DVR in the case of a fully dynamic scan) can optionally be generated by dividing each voxel value by the reference region mean.

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

##### 3.4.3.3 Create SUVR

##### 3.4.3.83.6.3.3.2 3.4.3.3.1 Measure Regional Values

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

##### 3.4.3.93.6.3.3.3 3.4.3.3.2 CalculateCalculate SUVR

The If a SUVR image is not being used, then the SUVR is calculated by dividing the VOI value by the reference region value (which will be 1.0 if measured on a SUVR image). If a parametric image was generated using full dynamic scanning, or if a kinetic model is being applied to a multi-timeframe dynamic image, a DVR value is generated instead.

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### 3.4.3.103.6.3.4 3.4.3.3.3 Relating SUVR values to other studies: the Centiloid

Different protocols involve different tracers, target regions, and reference regions, and all of these contribute to how the SUVR can be interpreted with regard to amyloid burden. A value of 1.2, for example, can be amyloid positive using one tracer and/or set of regions for analysis, but amyloid negative using a different tracer and/or regions. In order to reconcile findings across data acquisition, processing, and analysis protocols, the concept of the Centiloid was developed (Klunk et al, 2015). The Centiloid is not intended to dictate the method for acquiring and processing data, but rather to provide a way to equate results obtained with a broad variety of protocol parameters. The basis for the Centiloid is a "gold standard" set of results derived from young healthy controls and elderly AD patients. These results have been generated using the radiotracer 11C-PiB and a defined set of target region, reference region, and image processing and analysis steps. A linear progression of values from 0 (no amyloid) to 100 (mean for amyloid positive sporadic AD patients) has been established using 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).

### *3.4.43.6.4 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.

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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~~3.7 ~~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.

SPECIFICATIONS

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

## ~~3.6~~3.8 ~~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~~3.8.1 ~~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~~3.8.1.1 ~~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

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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.

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Accreditation / Qualification | Imaging ~~Site & Image Acquisition Device~~Facility Coordinator | 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~~3.8.2 ~~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.

**SPECIFICATIONS**

| 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. |

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| Parameter | Entity/Actor | Specification |
|---|---|---|
| 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~~3.8.3 ~~3.6.3 Amyloid-~~PET ~~Acquisition~~ Scanner

#### 3.8.3.1 PET scanner models

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 also ~~already~~ be ~~included in this Profile~~used if the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the claims.

~~The scanners should~~Scanners used in a study 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.

PET scanner technology continues to evolve and in general for a study, and where possible it is advisable to minimize variability in scanner resolution and performance across sites. Newer scanners with greater resolution and lower noise offer the opportunity to resolve signal in smaller structures and to minimize spill-in to cortical regions from surrounding tissue. It is advisable to use scanners that are well supported by the manufacturer, and likely to be in use for the duration of a clinical trial.

#### 3.8.3.2 Use of same scanner for longitudinal scans

To achieve its longitudinal claim, this Profile requires that all scans for a given subject be imaged on the same device over the entire course of a study. In theory, it may be feasible to use a replacement scanner

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if quantitative equivalence with the replacement scanner can be clearly demonstrated. However, there are currently no accepted criteria for demonstrating quantitative equivalence between scanners. Future versions of this Profile may provide such criteria. It is imperative that the trial sponsor be notified of a scanner substitution if a scanner change occurs.

It is also advisable that the same scanner software be used for all longitudinal scans for a subject. In the event that software upgrades are required, the quality control measures discussed in section 3.8.4 should be performed before and after to assure that SUVR or other quantitative endpoints will be consistent.

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.It is imperative, however, that the trial sponsor be notified of scanner substitution if it occurs.

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Scanner hardware | Imaging Facility Coordinator | The same scanner will be used for all longitudinal scans acquired for the same subject. |
| Scanner operating software | Imaging Facility Coordinator | The same scanner software will be used for all longitudinal scans acquired for the same subject (or requalified if update is necessary). |
| 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. |

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#### 3.6.3.1 3.6.3.1 Ancillary Equipment

##### 3.6.3.1.1 3.6.3.1.1 Radionuclide Calibrator

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

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

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

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

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

##### 3.6.3.1.2 Scales and stadiometers

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

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PAT Uniform Phantom Analysis

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

#### 3.6.3.1.2 3.6.3.1.4 Clocks and timing devices

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

| 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.<br>Synchronization of all clocks used in the conduct of the amyloid-PET study shall be checked weekly and after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur) |
| Scanner and site clocks | Specific Device | Provide time synchronization as per the IHE Consistent Time Integration Profile. |
| Dose calibrator clock | Dose Calibrator | Electronic record of output from a dose calibrator shall be synchronized with other time keeping devices. |

### *3.6.43.8.4 3.6.4 Phantom Imaging PET Scanner Quality Control*

#### 3.8.4.1 Requirements for quality control

In order to meet profile claims, it is important that the PET scanner meets certain performance specifications. PET scanners must undergo routine quality assurance and quality control processes



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(including preventive maintenance schedules) appropriate for clinical applications, as have been well established by professional and/or regulatory agencies. In order to assure adequate quantitative accuracy and precision of imaging results, several quality assurance measures require particular attention and explicit testing. These are discussed in the sections below and include: uniformity, calibration, resolution, and contrast. A baseline assessment of these scanner imaging properties is required before any subjects are scanned in the trial, after any major hardware of software modifications that could affect these properties, and at least annually in an extended study.

During clinical trials, any changes to scanner equipment, either hardware or software, should be immediately reported to the trial sponsor and/or imaging CRO and may result in the need for re-qualification prior to imaging additional trial subjects.

#### 3.8.4.2 Phantoms for quality control

##### 3.8.4.2.1 Phantom requirements

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Some of the required tests, such as uniformity, can be performed with a uniform cylinder and appropriate measurement software. Other tests, such as contrast or spatial resolution, require phantoms and/or software methods beyond simple uniform cylinder measurements. The type of phantom(s) that can be used to test each specification are indicated for each case below. Phantoms should be adequate to model and characterize effects of attenuation correction and scatter correction.

##### 3.8.4.2.2 Anthropomorphic phantoms

An anthropomorphic phantom with a spatial distribution similar to cortical gray/white matter, such as the Hoffman Phantom, is recommended when available for testing some of the specifications. Such a phantom is useful to simulate the human brain, amyloid uptake patterns, and the amyloid SUVR measurand. Tests (described in sections below) for which such a phantom can be used include verifying:

- contrast
- resolution
- uniformity
- scanner normalization via in-plane and axial comparisons to an analytical gold standard for that phantom over the complete field of view to be used by the amyloid measurement.

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Contrast ratios of amyloid tracer uptake vary between normal and abnormal subjects, and also between different amyloid tracers. However, it is recommended that the phantom be filled such that the activity concentration in the highest uptake regions be similar to the expected white matter uptake in subjects with amyloid deposition. For the Hoffman phantom, it is recommended that the activity at the start of the scan be 0.5-0.6 mCi (18.5-22.2 MBq) to obtain approximately a 15 kBq/ml activity in the gray matter regions of the phantom. For data acquisition, the Hoffman phantom should be centered in the FOV of the PET scanner and data acquired for 20 minutes. Moreover, image reconstruction methods and settings should equal those specified in the study. The post-processing and data analysis should be as similar as possible to those used with patient data. See Appendices G and H for best practices guidance for this phantom.

A caveat in using the Hoffman phantom is that due to its complexity, filling artifacts (air bubbles, uneven mixing) can arise, leading to erroneous conclusions regarding uniformity.

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## PAT Uniform Phantom Analysis

To support use of phantoms such as the Hoffman, options that might be considered on a per-protocol basis include but are not limited to:

1. Each site uses a single phantom for the duration of the trial but not necessarily the same model of phantom used at other sites.
2. All sites use phantoms of the same model for the duration of the trial.
3. All sites use phantoms built to precise specifications for the duration of the trial.
4. All sites share a single phantom for the duration of the trial.

##### 3.8.4.2.3 Alternate phantoms

Phantoms such as the Hoffman are relatively expensive and therefore many or most imaging sites do not own one. Sharing a phantom may not be feasible for a clinical trial, or for clinical application that does not involve a centrally managed trial. Alternative phantom approaches are therefore listed for each of the test requirements. In addition, software developed by Lodge et al (2009) and available to SNMMI members at www.SNMMI.org/PAT allows systematic measurement of the following scanner characteristics: using a uniform cylinder:

- contrast
- resolution
- uniformity
- scanner normalization

An example report produced by the software is included as Appendix J.

Alternative phantoms having variable intensity regions may also be used for testing.

##### 3.8.4.2.4 Other considerations

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

#### 3.8.4.3 Routine quality control schedule

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Routine QA/QC Checks | Technologist | At a minimum, QA/QC procedures shall be performed daily, quarterly, and annually according to vendor recommendations.<br>Daily QC procedures shall be performed prior to any subject scan. |

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PAT Uniform Phantom Analysis

#### 3.6.4.1 3.6.4.1 Uniformity and Calibration

#### 3.8.4.4

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Verification of scanner normalization with a uniform phantom is a minimum requirement for all scanners used in clinical trials including those that only have qualitative endpoints.

**In addition to head motion, variation in the uniformity of the PET scanner can have one of the greatest adverse effects upon longitudinal amyloid measurement variability.** A Hoffman or equivalent phantom may be used in place of a uniform phantom to verify scanner normalization via in-plane and axial comparisons to an analytical gold standard for that phantom over the complete field of view to be used by the amyloid measurement. For trials with quantitative PET measurements, this assessment should also include a comparison against a radionuclide calibrator to ensure quantitative accuracy; that is, a comparison of the absolute activity measured versus the measured amount injected should be performed. An essential requirement for extracting quantitative data from images is that there be known calibration accuracy and precision and/or cross calibration of the PET system against the (locally) used radionuclide calibrator (within 10%). The QC procedures should utilize the same acquisition/reconstruction protocol, software and settings that are used for the subject scans.

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This comparison is particularly important after software or hardware upgrades. If the trial requires absolute quantification in baseline images or absolute changes in longitudinal studies, it should be considered to include an image quality and/or contrast recovery QC assessment as part of the routine QC procedures and/or scanner validation process. Clinical trials using only relative changes in longitudinal studies may not require contrast recovery assessments provided there is appropriate consideration for the minimum size of target lesions based on the partial volume effect.

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

To illustrate this, Figure 8 shows a volumetric MRI brain positioned within the axial field of view of two different scanners. Within the brain, an example target region and reference region are delineated. The deviations of the actual slice-by-slice decay- and scatter-corrected values measured using a uniform cylindrical phantom relative to the average value are plotted. These graphs were generated using software (Lodge et al, 2009) available to members of SNMMI at www.SNMMI.org/PAT. The scanner on the left has uniformity within 1.55% of the mean axial value, whereas the scanner on the right deviates by more than 5%. Worse cases exist in the field, and the standard allowed tolerance is 10%. This tolerance is problematic for longitudinal amyloid measurement and can introduce error that would invalidate the longitudinal Claim of this profile. In the case on the right, if the head is positioned differently from one scan to the next, an automatic measurement error will be introduced into the SUVR due to the difference in slice sensitivities. For example, target region and/or reference region values may change by several percent simply because they are now aligned with a slice(s) whose sensitivity deviates from that of the previous slice(s) with which the regions were aligned. If the reference region and target region are in the same axial slices, the difference will cancel out. However, the cerebellum or pons, often used as reference regions, do not occupy the same slices as most target regions and therefore error does not cancel out. In practice, the head is typically at an angle within the scanner, but the same principles apply.

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## PAT Uniform Phantom Analysis

~~**Uniformity** – In-plane and axial uniformity of the purpose-specific phantom should be within 1% throughout the scanner field of view to be used in the calculation of the amyloid PET measurand. Note that the historical axial uniformity tolerance of 10% has the implication that if a subject is imaged in one axial location for one scan, and in a different axial location (e.g. a few cm different) for the next scan, then the slices used to calculate each reference or target region value may change DIFFERENTLY. This can introduce error of a few percent to many percent into the longitudinal SUVR change. Selection of reference region and target region in the same axial slices can help to mitigate this potential source of noise, as the differences cancel out.~~

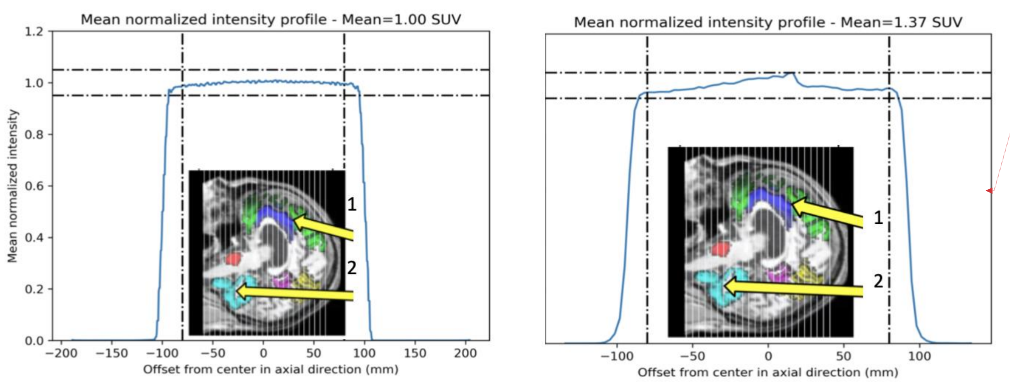


**Figure 8.** Uniformity measurement across the axial field of view, and impact on SUVR measurement. The scanner at left has a maximum deviation from the mean value of -1.55%, whereas the scanner on the right deviates by 5.05%. **Typical standards allow deviations of up to 10%, which can introduce significant error into longitudinal measurement.**

In addition, in both of the examples shown in Figure 7, **it can be seen that toward the edges of the axial field of view (FOV), measurement sensitivity becomes much more variable. This is particularly problematic in scanners with short FOVs** such as the Siemens ECAT HR+. The flltering that is typically applied to compensate for sensitivity loss at the edges actually serves to amplify noise. If the reference tissue is at the edge of the scanner field of view additional error may be introduced that causes large swings in measured SUVR. Longitudinal errors of up to 33% have been measured in data from ADNI 1, for example, when using cerebellar cortex as the reference region.

Selection of reference region and target region in the same axial slices can help to mitigate this potential source of noise, as the differences cancel out. Alternatively or in addition, positioning the subject's head in exactly the same location from scan to scan can help to minimize error as long as the scanner slice-by-slice sensitivity has not changed (which may or may not be the case). Despite these mitigations, it is still important to assure that scanner uniformity (other than at the very edge, where typically infeasible), is within a tolerance that is +/- 3% in this Profile.

Note that uniformity should also be consistent in-plane, i.e. in x and y directions. An example of poor in-plane uniformity is shown in Appendix H, Example 5, visibly obvious using a Hoffman phantom.

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## SPECIFICATIONS

| Parameter | Entity/Actor | Specification |
|---|---|---|
| ~~Phantom tests: Frequency of uniformity measurements~~ | ~~Imaging Site~~ | ~~Shall perform at baseline, quarterly and after scanner upgrades, maintenance or repairs, and new setups.~~ |
| Uniformity QC | Technologist | At baseline and at least quarterly and following software upgrades, maintenance or repairs, and new setups, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom:~~.~~<br>1. Visual check that no streak artifacts or axial plane non-uniformities are present.<br>~~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.~~<br>2. 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.<br>~~3.~~ Alternatively, if the Hoffman phantom or equivalent is available, in-plane and axial uniformity can also be visually assessed as shown in Appendix H. |
| ~~Phantom tests: transaxial uniformity measurement~~ | ~~Imaging Site~~ | ~~Shall measure the transaxial (within-plane) uniformity as specified in NEMA NU2 1994; uniformity should be ≤ 10 % for each qualified axial slice (see below).~~ |
| ~~Phantom tests: axial~~U ~~u~~niformity measurement | ~~Imaging Site~~Technologist or Medical Physicist | Axial uniformity shall be measured at least monthly 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. The phantom image is to be corrected for attenuation, scatter, and decay. Mean axial concentrations in ROIs in the central 80% of planes shall be within ±3% of the overall average for each qualified axial slice within sufficient distance from the axial edge of the field of view (2-4 cm as available). A method and software such as the PAT Uniformity software available from SNMMI may be used for measurement. ~~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~~ |

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| | | ~~each ROI. Axial planes whose COV is < 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.)~~<br>Uniformity across planes against a gold standard reference can also be measured using a Hoffman phantom as described in Appendix H. |
| | | Harmonized image reconstruction protocols are available. (i.e., known recovery coefficients versus size for a given test object such as the modified NEMA NU-2 Image Quality phantom. |

### ~~3.6.4.2~~3.8.4.5 ~~3.6.4.2~~ Resolution

The spatial resolution of a scanner refers to its ability to distinguish between two different point sources in a reconstructed image, typically referred to as the full-width at half-maximum (FWHM) of a point spread function (PSF). ~~The assessment of adequate resolution should include both a qualitative evaluation (using clinical or anthropomorphic phantom images) and quantitative assessment (using phantom-defined criteria).~~ PET scanner hardware, reconstruction methods and reconstruction parameter selections can result in dramatically different spatial resolutions in the reconstructed images. Because partial volume effects (especially between gray and white matter regions) can bias many amyloid PET measurands, it is essential to calibrate the spatial resolution of each scanner using the acquisition and reconstruction protocol planned for patient imaging. For group analyses involving scans acquired from different scanners, a post-reconstruction smoothing operation can then be applied for calculation of a measurand at a uniform spatial resolution across scanners. Reducing variability translates into increased statistical power given a certain sample size. For a single within-subject evaluation where cross-scanner reconciliation is not relevant, ensuring adequate resolution can still translate to clinical impact regarding the ability to distinguish amyloid signal and to detect change. The Claim of this Profile is for a single scan and therefore smoothing, while recommended for group analyses, is not stated as a required activity.

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

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| PET scanner Resolution | Nuclear Medicine Physician or Image Analyst | Shall perform and document, on at least an annual basis or during an initial site qualification process,~~,~~ ~~and document~~ a qualitative resolution QC test by using the manufacturer's settings and ~~demonstrating~~ verifying resolution of normal gross anatomic features within either ~~clinical images of the brain~~a clinical image or representative brain phantom. |

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PAT Uniform Phantom Analysis

| Parameter | Entity/Actor | Specification |
|---|---|---|
| PET scanner 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. The FWHM resolution of the scanner should be <= 8.0 mm with a preferable target of 4 to 5 mm.<br>Measurements methods may include the following:<br>(1) 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. See appendix H for details.<br>(2) 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. Use the software available to SNMMI members at www.SNMMI.org/PAT.<br>(3) Use a published method as in Gong et al, [Phys Med Biol. 2016 Mar 7; 61(5): N193–N202], or Quality assurance for PET and PET/CT systems. — Vienna: International Atomic Energy Agency, 2009, ISBN 978–92–0–103609–4, or alternative reference. |

3.6.4.3

### 3.8.4.6 3.6.4.3 Noise

#### 3.6.4.4 SPECIFICATIONS

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

### 3.6.4.53.8.4.7 3.6.4.4 Amyloid-PET Specific Phantom Measurements Contrast

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

1. Each site uses a single phantom for the duration of the trial but not necessarily the same model of phantom used at other sites.
2. All sites use phantoms of the same model for the duration of the trial.
3. All sites use phantoms built to precise specifications for the duration of the trial.
4. All sites share a single phantom for the duration of the trial.

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

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

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Phantom test: contrast measurement | Medical physicist | At baseline and at least quarterly and following software upgrades, maintenance or repairs, and new setups, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom: |
| Phantom test: contrast measurement | Medical physicist | Using a phantom that contains different regions having uptake ratios between 2:1 and 4:1, measure the high to low ratio and ensure that the ratio is within the spec.<br>If using ACR PET phantom, see the American Association of Physicists in Medicine (AAPM) Task Group 126 (TG-126) 2019 report on PET/CT Acceptance Testing and Quality Assurance.<br>If using Hoffman phantom, see Appendix H for more details on use of the Hoffman phantom, which has a 4:1 gray to white contrast ratio. |

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## PAT Uniform Phantom Analysis

- Spatial resolution – PET scanner hardware, reconstruction methods and reconstruction parameter selections can result in dramatically different spatial resolutions in the reconstructed images. Because partial volume effects (especially between gray and white matter regions) can bias many amyloid PET measurands, it is essential to calibrate the spatial resolution of each scanner using the acquisition and reconstruction protocol planned for patient imaging. A post-reconstruction smoothing operation can then be applied for calculation of a measurand at a uniform spatial resolution between scanners.

1.1.1.1 Uniformity – In-plane and axial uniformity of the purpose-specific phantom should be within 1% throughout the scanner field of view to be used in the calculation of the amyloid PET measurand. Note that the historical axial uniformity tolerance of 10% has the implication that if a subject is imaged in one axial location for one scan, and in a different axial location (e.g. a few cm different) for the next scan, then the slices used to calculate each reference or target region value may change DIFFERENTLY. This can introduce error of a few percent to many percent into the longitudinal SUVR change. Selection of reference region and target region in the same axial slices can help to mitigate this potential source of noise, as the differences cancel out.

- Absence of reconstruction artifacts – Reconstructed purpose-specific phantom data should be visually free of reconstruction artifacts, such as streaks due to failing detectors or axial plane non-uniformities due to errors in normalization.

- Qualitative and quantitative accuracy – Measurands using ratios, such as the SUVR must demonstrate accuracy with 10% of an analytical or otherwise known gold standard.

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

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PAT Uniform Phantom Analysis

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

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

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

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PAT Uniform Phantom Analysis

| 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. |

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#### PAT Uniform Phantom Analysis

#### 3.8.4.8 Accuracy

For trials with quantitative PET measurements, assessment of scanner uniformity should also include a comparison against a radionuclide calibrator to ensure quantitative accuracy; that is, a comparison of the absolute activity measured versus the measured amount injected should be performed. A cross calibration of the PET system against the (locally) used radionuclide calibrator should be within 10%. The QC procedures should utilize the same acquisition/reconstruction protocol, software and settings that are used for the subject scans. This comparison is particularly important after software or hardware upgrades. If the trial requires absolute quantification in baseline images or absolute changes in longitudinal studies, it should be considered to include an image quality and/or contrast recovery QC assessment as part of the routine QC procedures and/or scanner validation process.

Clinical trials using only relative changes in longitudinal studies, such as for the claim in this Profile, may not require contrast recovery assessments provided there is appropriate consideration for the minimum size of target lesions based on the partial volume effect.

| Parameter | Entity/Actor | Specification |
| --- | --- | --- |
| Phantom test: SUVR accuracy | Medical physicist | The quantitative accuracy of the scanner shall be within +-10% of the cross-referenced radionuclide calibrator (when properly calibrated).<br>Accuracy may be tested using the SNMMI PAT Uniformity software and a uniform cylinder. Alternatively, using a Hoffman phantom PET image or an alternate phantom measurement method that provides similar contrast intensities, perform the intended post-processing and image analysis to confirm SUVR accuracy. See Appendix H for more details on the Hoffman phantom, and Appendix F for DRO. |

#### 3.6.4.6 3.6.4.5 Phantom imaging data analysis

Purpose-specific phantom options that might be considered on a per-protocol basis include, but are not limited to:

- Each site uses a single phantom for the duration of the trial but not necessarily the same model of phantom used at other sites.
- All sites use phantoms of the same model for the duration of the trial.
- All sites use phantoms built to precise specifications for the duration of the trial.
- All sites share a single phantom for the duration of the trial.

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PAT Uniform Phantom Analysis

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

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

### *3.8.5 Ancillary Equipment*

#### 3.8.5.1 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.

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Radionuclide Calibrator Constancy | Technologist | Shall evaluate daily (or after any radionuclide calibrator event) using a NIST-traceable (or equivalent) simulated 18F, Cs-137, or Co-57 radionuclide calibrator standard and confirmed that measured activity differs by no greater than ±2.5 % from the expected value. |
| Radionuclide Calibrator Accuracy | Technologist | Shall evaluate annually (or after any radionuclide calibrator event) with a NIST-traceable (or equivalent) simulated F-18 radionuclide calibrator standard (preferred although use of other long-lived NIST standards are acceptable). Shall confirm that net measured activities differ no greater than ±2.5% from expected value. |
| Radionuclide Calibrator Linearity | Technologist or Radiation safety officer or Medical Physicist | Shall evaluate quarterly (or after any radionuclide calibrator event) using either 18F or Tc-99m and should be within ±2.5 % of the true value over an operating range of 37-1110 MBq (1 to 30 mCi) and the true value is determined by a linear fit |

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| | | (to the log data) over the same operating range. Concentric sleeve method is acceptable. |
| PET Radiation Dose | Technologist | Shall record the radiation dose from the administered activity and accompanying information in a DICOM Radiopharmaceutical Administration Radiation Dose Structured Report. |

#### 3.8.5.2 Scales and stadiometers

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

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Scales | Technologist / Physicist / Approved personnel | Shall evaluate annually or after any repair by qualified personnel. |

#### 3.8.5.3 Clocks and timing devices

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

**SPECIFICATIONS**

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Scanner and site clocks | Technologist / Physicist / 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.<br>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) |

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PAT Uniform Phantom Analysis

| Parameter | Entity/Actor | Specification |
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| | | |
| Scanner and site clocks | Specific Device | Provide time synchronization as per the IHE Consistent Time Integration Profile. |
| Dose calibrator clock | Dose Calibrator | Electronic record of output from a dose calibrator shall be synchronized with other time keeping devices. |

### ~~3.6.5~~3.8.6 ~~3.6.5~~ *Quality Control of Amyloid-PET studies*

#### ~~3.6.5.1~~3.8.6.1 ~~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~~3.8.6.2 ~~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.

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# 5.4. 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.

## 5.14.1 4.1. Performance Assessment: Image Acquisition Site

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

- Appropriate imaging equipment and quality control processes,
- Appropriate ancillary equipment and access to radiotracer and contrast material,
- Experienced Technologists (CT and PET trained) for the subject handling and imaging procedure,
- Appropriately trained Radiologists/Nuclear Medicine Physicians for image analysis and diagnostic interpretation,
- Appropriately trained image analysts, with oversight by a Radiologist or Nuclear Medicine Physician,
- Medical Physics support to ensure appropriate scanner and equipment calibration, and to address issues relating to quantification such as attenuation maps or movement
- Processes that assure imaging QIBA Profile-conformant image generation in appropriate time window

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

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PAT Uniform Phantom Analysis

SPECIFICATIONS

| Parameter | Entity/Actor | Specification |
|---|---|---|
| PET Scanner | ~~Acquisition Facility~~Site | 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.~~Follow manufacturer's recommendations. |
| 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 | Technologist | Calibrated to 18F using NIST traceable source or equivalent either by site or calibrator manufacturer. |

## ~~5.2~~4.2 ~~4.2.~~ Performance Assessment: PET Acquisition Device

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

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

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

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

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

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

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

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

The concept endorsed here is that the needed meta-data is identified. Through revisions of this Profile, the DICOM standard, and technology the meta-data is inserted into the analysis stream (Figure 5~~3~~) in a more direct manner and technology and accepted standards evolve.

**SPECIFICATIONS**

| 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. |

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PAT Uniform Phantom Analysis

| Parameter | Entity/Actor | Specification |
|---|---|---|
| PET QA status | Acquisition Device | Date/time and status of system-wide QA checks should be captured separately. |
| Radionuclide calibrator calibration | Acquisition Device | Calibration factor for an F-18 NIST -traceable (or equivalent) source with identifying information shall be tracked in the DICOM header with Date/Time. |
| PET Scanner calibration | Acquisition Device | Shall be able to be calibrated according to the specifications in section 3.8.4~~Shall be able to be calibrated according to the following specifications:~~<br>~~• Using an ACR type uniform cylinder containing F-18 in water (ideally the same used for dose calibrator cross-calibration)~~<br>~~• Using a long scan time of 60 min or more (to minimize noise), and an ACR type ROI analysis~~<br>~~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).~~<br>~~Slice-to-slice variability shall be no more than ± 5%. (not including end slices, as per ACRPET Core Lab).~~ |
| Weight | Acquisition Device | Shall be able to record patient weight in lbs or kg as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Weight field (0010,1030) in the DICOM image header, as per DICOM standard. |
| | | Patient weight shall be specifiable with 4 significant digits.<br>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. |
| BMI | Acquisition Device | Depending upon the study requirements, BMI shall be specified. |
| Height | Acquisition Device | Shall be able to record patient height in feet/inches or cm/m as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard. |
| | | Patient height shall be specifiable with 3 significant digits.<br>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. |

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

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PAT Uniform Phantom Analysis

| Parameter | Entity/Actor | Specification |
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| 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).<br>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.<br>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 ~~Acquisition Device~~ | Shall be able to support Profile Protocol (Section 3) PET and CT order(s) of acquisition.<br>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.<br>Shall be configurable to store (or receive) acquisition parameters as pre-defined protocols (in a proprietary or standard format), to allow re-use of such stored protocols to meet multi-center specifications and to achieve repeatable performance across time points for the same subject. |
| CT Acquisition Parameters | Acquisition Device | Shall record all key acquisition parameters in the CT image header, using standard DICOM fields. Includes but not limited to: Actual Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation Time, Exposure and Slice Width in the DICOM image header. |

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| Parameter | Entity/Actor | Specification |
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| 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.<br>Voxels shall be square, although are not required to be isotropic in the Z (head-foot) axis.<br>Not required to be the same as the reconstructed PET voxel size. |
| Subject Positioning | Acquisition Device | Shall be able to record the subject position in the Patient Orientation Code Sequence field (0054,0410) (whether prone or supine) and Patient Gantry Relationship Code field Sequence (0054,0414) (whether head or feet first). |
| Scanning Direction | Acquisition Device | Shall be able to record the scanning direction (craniocaudal vs. caudocranial) into an appropriate DICOM field. |
| Documentation of Exam Specification | Acquisition Device | Shall be able to record and define the x-y axis FOV acquired in Field of View Dimensions (0018,1149) and reconstructed in Reconstruction Diameter (0018,1100). |
| | | Shall be able to define the extent of anatomic coverage based on distance from defined landmark site (e.g., vertex, EAM). (both the landmark location (anatomically) and the distance scanned from landmark) would require DICOM tags). |

| Parameter | Entity/Actor | Specification |
|---|---|---|
| | | Shall be able to be reportable for future scanning sessions.<br>The Acquisition Device shall record the z-axis FOV which represents the actual distance of scan anatomic coverage (cm). |
| Differential Acquisition Time | Acquisition Device | Shall be able to acquire and record non uniform scan times dependent upon areas of clinical concern. Recording can be done through the use of Actual Frame Duration (0018,1242) and Frame Reference Time (0054, 1300). |
| 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 | 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.<br>PET images shall be transferred and stored without any form of lossy compression. |
| DICOM Editing | Acquisition Device | Shall be able to edit all fields relevant for SUV calculation before image distribution from scanner.<br>Shall provide appropriate warnings if overriding of the current values is initiated. |

### 5.34.3 4.3. Performance Assessment: Reconstruction Software

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

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

Data can be reconstructed including all corrections needed for quantification as well as without scatter and attenuation correction. Analytical or iterative reconstruction methods should be applied. If the system is capable of providing resolution recovery and/or time of flight, then the decision to 'turn on' or 'turn off'

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this /these capabilities should be made prospectively, as dictated by the specific protocol, and should be consistent for a given subject across multiple time points.

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

## SPECIFICATIONS

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Metadata | Reconstruction Software | Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Reconstruction section. |
| Data 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.<br>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).<br>Pixels shall be square, although voxels are not required to be isotropic in the z (head-foot) axis. |

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| 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).<br>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. |

## 4.4 Performance Assessment: Image Analysis Workstation

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

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

**SPECIFICATIONS**

| 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:<br>• slope ($\widehat{A}_1$) between 0.95 and 1.05 |

| Parameter | Entity/Actor | Specification |
|---|---|---|
| | | • R-squared ($R^2$) >0.90<br>See Appendix F. |

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

**SPECIFICATIONS**

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

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

**SPECIFICATIONS**

| 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 |

| Parameter | Entity/Actor | Specification |
|---|---|---|
| Intra-scan, inter-frame alignment | Image Post-processing workstation | Shall allow selection of an anchor frame to which other frames are aligned |
| Intra-scan, inter-frame alignment | Image Post-processing workstation | Shall measure and display the translational and rotational parameters necessary to align each frame to the reference frame. |
| Static image creation | Image Post-processing workstation | Shall allow exclusion of one or more frames from the static image that is created through frame averaging or summation |
| Static image creation | Image Post-processing workstation | Shall be able to sum and/or average the selected timeframes to create a static image for analysis |
| Smoothing | Image Post-processing 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) |

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.

## SPECIFICATIONS

| 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 | Image Analysis workstation | Shall provide either the means for defining target and reference region of interest boundaries to be applied to |

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| Parameter | Entity/Actor | Specification |
|---|---|---|
| region definition | | the subject scan, or for importing pre-defined region of interest boundaries (or masks) that may have been generated using other software (such as generated through segmentation of subject's MRI or pre-defined based upon an image template and atlas). |
| SUVR image creation | Image Analysis workstation | Shall be able to create an SUVR image by dividing each voxel by the average value within a selected reference region, if this option is implemented. |
| Region placement | Image Analysis workstation | Shall be able to apply (place for measurement) pre-specified regions of interest onto the PET scan in an anatomically accurate manner. |
| 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. |

## ~~5.5~~4.5 ~~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.

# PAT Uniform Phantom Analysis

## SPECIFICATIONS

| 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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### Two-year period

1. Brendel M, Högenauer M, Delker A, Sauerbeck J, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Improved longitudinal [(18)F]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction. Neuroimage. 2015 Mar;108:450-9. doi: 10.1016/j.neuroimage.2014.11.055.
2. Chen K, Roontiva A, Thiyyagura P, Lee W, Liu X, Ayutyanont N, Protas H, Luo JL, Bauer R, Reschke C, Bandy D, Koeppe RA, Fleisher AS, Caselli RJ, Landau S, Jagust WJ, Weiner MW, Reiman EM; Alzheimer's Disease Neuroimaging Initiative. Improved power for characterizing longitudinal amyloid-β PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region. J Nucl Med. 2015 Apr;56(4):560-6.

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

## Amyloid Imaging Methodology Papers

1. Barret O, Alagille D, Sanabria S, Comley RA, Weimer RM, Borroni E, Mintun M, Seneca N, Papin C, Morley T, Marek K, Seibyl JP, Tamagnan GD, Jennings D. Kinetic Modeling of the Tau PET Tracer 18F-AV-1451 in Human Healthy Volunteers and Alzheimer's Disease Subjects. J Nucl Med. 2016 Dec 1.
2. Blautzik J, Brendel M, Sauerbeck J, Kotz S, Scheiwein F, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Reference region selection and the association between the rate of amyloid accumulation over time and the baseline amyloid burden. Eur J Nucl Med Mol Imaging. 2017 Aug;44(8):1364-1374.
3. Brendel M, Högenauer M, Delker A, Sauerbeck J, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Improved longitudinal [(18)F]-AV45 amyloid PET by white matter


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PAT Uniform Phantom Analysis

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# Amyloid PET: Kinetic Modeling (in Appendix I)

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## Package Inserts

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Note that U.S. prescribing information is listed below for approved tracers. However, this profile is not limited to the U.S. and prescribing information for the relevant country should be consulted for studies outside of the U.S.

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# 6. Appendices

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## ~~7.1~~6.1 Appendix A: Acknowledgements and Attributions

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

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## 6.2 Appendix B: Background Information for Claim

## ~~7.21.1 Appendix B: Background Information for Claim~~

## ~~1.1~~

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

**Test-Retest studies:** Test-retest amyloid PET studies were identified for the tracers florbetapir (Joshi et al, 2012, scans within 4 weeks) and flutemetamol (Vandenberghe et al, 2010, scans 7 to 13 days apart). Other available studies with images acquired during this time period were excluded for reasons including: a) use of 11C-PIB and a 60 to 90 minute timeframe at the end of a full dynamic scanning session where greater technical variability is observed; this can be due to subject motion and also to low signal whereby decay correction amplifies the noise contribution; and b) intentional varying of administered radioactivity during the study to test the impact of that parameter. The study by Joshi et al acquired florbetapir PET images in 10 AD patients and 10 healthy controls (HC) over a time window of 50 to 70 minutes post injection, and used whole cerebellum as the reference region. Mean Repeatability Coefficient (RC) and 95% confidence 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 wCV were 1.94% and 1.20% respectively. The study by Vandenberghe et al acquired flutemetamol PET images in 5 AD patients over a time period of 85 to 115 minutes post injection, and used cerebellar cortex as the reference region. Mean Repeatability Coefficient (RC) was 3.18% with a 95% CI of 1.99% to 7.81%. The value for wCV was 1.15%. The greatest ("worst") value of 1.94% from these studies was applied to the Claim. F As noted in the Claim Considerations, the number of short term test-retest studies was a limitation, and for this reason and for practical context, this value was also compared to the wCVs calculated for the longer term studies described below.

**Longer term longitudinal variability:** Several studies have examined the effects of applying different reference regions or other parameters to amyloid SUVR data acquired over one or two years. Two studies were identified that measured amyloid SUVR in florbetapir PET scans acquired in subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) at baseline and after 2 years. This period is representative of a clinical trial duration. The table below shows the RC means and 95% CI for these studies, using different reference regions. The mean RC in four of the five cases ranged from 3.45% to 4.45%, within the range of 3.18% to 5.38% of the short term test-retest studies described above (Joshi,

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Vandenberghe). In the Brendel analyses, SUVRs measured using the same subjects but two different reference regions resulted in an RC% of 9.37% that was more than 2x larger when using a whole (full) cerebellum reference as that using white matter as a reference. This was also double the RC% measured by Chen using a different subset of ADNI scans across three different reference regions: pons, cerebellar cortex, and subcortical white matter. These comparisons suggest the following: 1) even over a longitudinal period of 2 years, it is feasible to achieve the wCV identified through the short term test retest studies above; and 2) choice of reference region coupled with analysis methods can materially impact the RC% and 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% |

CN = cognitively normal

# ~~7.3~~6.3 Appendix C: Conventions and Definitions

## *~~7.3.1~~6.3.1 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.

## *~~7.3.2~~6.3.2 Definitions*

| | |
|---|---|
| 3D | Three-dimensional |
| 11C | Carbon-11, an isotope of carbon |
| 18F | Flourine-18, an isotope of fluorine |
| AB | Amyloid-B |
| AC | Attenuation Correction. Attenuation is an effect that occurs when photons emitted by the radiotracer inside the body are absorbed by intervening tissue. The result is that structures deep in the body are reconstructed as having falsely low (or even negative) tracer uptake. Contemporary PET/CT scanners estimate attenuation using integrated x-ray CT equipment. While attenuation-corrected images are generally faithful representations of radiotracer distribution, the correction process is itself susceptible to significant artifacts. |
| Accreditation | Approval by an independent body or group for broad clinical usage (requires ongoing QA/QC) e.g. ACR, IAC, TJC. |
| AD | Alzheimer's Disease |
| ALARA | As Low As Reasonably Achievable |
| BBB | Blood Brain Barrier |

| | |
|---|---|
| $BP_{ND}$ | Binding Potential. $BP_{ND}$ is the ratio of the density of available receptors to the affinity of the tracer for the receptor, corrected for the free fraction of ligand in the non-displaceable compartment. |
| CLIA | Clinical Laboratory Improvement Amendments: Accreditation system for establishing quality standards for laboratory testing. |
| Co-57 | Cobalt-57, an isotope of cobalt |
| Conformance | Meeting the list of requirements described in this document, which are necessary to meet the measurement claims for this QIBA Profile. |
| CRF | Case Report Form (CRF) is a paper or electronic questionnaire specifically used in clinical trial research. The CRF is used by the sponsor of the clinical trial (or designated CRO etc.) to collect data from each participating site. All data on each patient participating in a clinical trial are held and/or documented in the CRF, including adverse events. |
| CRO | Contract Research Organization. A commercial or not-for-profit organization designated to perform a centralized and standardized collection, analysis, and/or review of the data generated during a clinical trial. Additional activities which may be performed by an imaging core lab include training and qualification of imaging centers for the specific imaging required in a clinical trial, development of imaging acquisition manuals, development of independent imaging review charters, centralized collection and archiving of images received from study sites, performing pre-specified quality control checks/tests on incoming images and development and implementation of quality assurance processes and procedures to ensure that images submitted are in accord with imaging time points specified in the study protocol and consistent with the quality required to allow the protocol-specified analysis /assessments |
| Cs-137 | Cesium-137, an isotope of Cesium |
| CSF | Cerebrospinal fluid |
| CT | X-ray computed tomography (CT) is a medical imaging technique that utilizes X-rays to produce tomographic images of the relative x-ray absorption, which is closely linked to tissue density. |
| CTDI | Computed tomography dose index |
| DICOM | Digital Imaging and Communications in Medicine (DICOM) is a set of standards for medical images and related information. It defines formats for medical images that can be exchanged in a manner that preserves the data and quality necessary for clinical use. |
| DLP | Dose length product |
| Dose | Can refer to either radiation dose or as a jargon term for 'total radioactivity'. For example, 10 mCi of 18F-FDG is often referred to as a 10 mCi dose. |
| DRO | Digital Reference Object |
| DVR | Distribution Volume Ratio |
| FDG | Fluorodeoxyglucose |
| FWHM | Full width at half maximum |

| | |
|---|---|
| HIPAA | Health Insurance Portability and Accountability Act |
| IAC | The Intersocietal Accreditation Commission (IAC) provides accreditation programs for Vascular Testing, Echocardiography, Nuclear/PET, MRI, CT/Dental, Carotid Stenting and Vein Center. |
| IAEA | International Atomic Energy Agency |
| IOD | Information Object Definition |
| kBq | Kilobecquerel |
| kVp | Peak kilovoltage |
| LBM | Lean Body Mass is calculated by subtracting body fat weight from total body weight. The Lean body mass (LBM) has been described as an index superior to total body weight for prescribing proper levels of medications and for assessing metabolic disorders. |
| mAs | Milliampere-seconds |
| MBq | Megabequerel. An SI-derived unit of radioactivity defined as 1.0 × 10^6 decays per second. |
| MCI | Mild Cognitive Impairment |
| mCi | millicuries. A non-SI unit of radioactivity, defined as 1 mCi = 3.7 × 10^7 decays per second. Clinical FDG-PET studies inject (typically) 5 to 15 mCi of 18F-FDG. |
| mpi | minutes post injection |
| MRI | Magnetic Resonance Imaging |
| NA | North America |
| NTP | Network Time Protocol |
| PACS | Picture archiving and communication system |
| PiB | Pittsburgh compound B, a radioactive analog of thioflavin T. |
| PET | Positron emission tomography (PET) is a tomographic imaging technique that produces an image of the in vivo distribution of a radiotracer, typically FDG. |
| PET/CT | Positron emission tomography / computed tomography (PET/CT) is a medical imaging system that combines in a single gantry system both Positron Emission Tomography (PET) and an x-ray Computed Tomography (CT) scanners, so that images acquired from both devices can be taken nearly-simultaneously. |
| PSF | Point Spread Function |
| PVEc | Partial Volume Effects Correction |
| QA | Quality Assurance. Proactive definition of the process or procedures for task performance. The maintenance of a desired level of quality in a service or product, esp. by means of attention to every stage of the process of delivery or production. |
| QC | Quality Control. Specific tests performed to ensure target requirements of a QA program are met. Typically, this is done by testing a sample of the output against the specification. |

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

Organizations

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

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| | |
|---|---|
| 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. |

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| | |
|---|---|
| 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. |

# 7.56.4 Appendix D: Model-specific Instructions and Parameters

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

## *7.5.16.4.1 D.1. Image Acquisition Parameters*

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

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

Sites using models listed here are encouraged to consider using these parameters for both simplicity and consistency. Sites using models not listed here may be able to devise their own acquisition parameters that result in data meeting the requirements of Section 3.6.4 and conform to the considerations in Section 4. In some cases, parameter sets may be available as an electronic file for direct implementation on the imaging platform.PET image acquisition parameters have been optimized through large multi-site studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), and many clinical trials have adopted these data acquisition protocols. For each phase of ADNI, the protocols for each of the scanners included in the study (a range of Siemens, GE, and Philips models) have been made available on-line, including both acquisition and reconstruction parameters.

## *7.5.26.4.2 D.2. Quality Assurance Procedures*

Examples of recommend quality assurance procedures are shown for specific GE, Philips, and Siemens PET/CT scanners in the tables below. However, since equipment models continually evolve, it is important to reference the manufacturer's specifications for the particular models of equipment in use for data acquisition.

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

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

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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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## ~~7.6~~6.5 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 SUVRs. 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 5~~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

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d. Site of injection (and assessment of infiltration)
e. Net injected activity (calculated including decay correction)
f. Uptake time



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## 6.6 Appendix F: Testing PET Measurement Systems with the UW-PET QIBA Amyloid Digital Reference Object (DRO)

### ~~7.6.1 Appendix F: Testing PET Display and Analysis Systems with the UW-PET QIBA Amyloid Digital Reference Object (DRO) Series~~

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### 6.6.1 DRO Description

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

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

As mentioned above, the UW-PET QIBA PET Amyloid DRO series is based on a single segmented MRI scan of a patient. The MRI scan digitally had the skull and skin removed, and then was segmented into GM, WM, and CSF, which allows for different values of PET activity to be simulated in these regions. Six different versions of the same "subject" (having the same brain morphology) have been created, each with a different ratio of cortical gray tissue value to white tissue value. These simulate progressive levels of tracer uptake (in this case, amyloid accumulation) in cortex. The cerebellar cortex is maintained at a constant value, simulating gray tissue devoid of tracer target and uptake. The range of values (ratios between cortical tissue and white tissue) was selected to cover negative and positive SUVR values that could be encountered using a range of tracers including florbetapir and flutemetamol.

These simulated images have been modulated with digital noise to simulate the somewhat lower resolution and increased technical noise that would be expected in a PET image. For each ratio of gray to white matter, five different "noise instances" have been created in which random digital noise was applied to the image. These instances are intended to capture additional technical variability that would be encountered in clinical PET images. However, for each of the six ratio versions, the noise variation should not impact the mean SUVR value measured in the tissue.

**The simulated PET scans that comprise the DRO series are deidentified, and any subject or birth date information present in the image headers do not represent an actual individual.** The file names for each instance are identified by their ratio of gray to white matter.

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A deidentified T1 weighted MRI scan is made available for use in image processing pipelines that use an MRI for region of interest segmentation and/or spatial warping. As in typical clinical studies, the PET images should be coregistered to the MRI scan and any other processing steps applied as part of the

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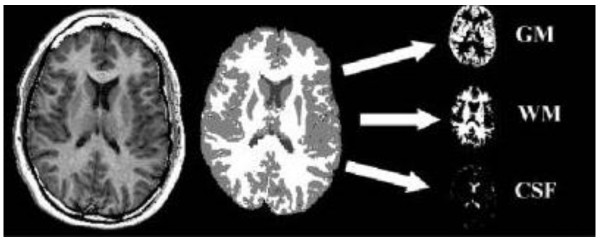
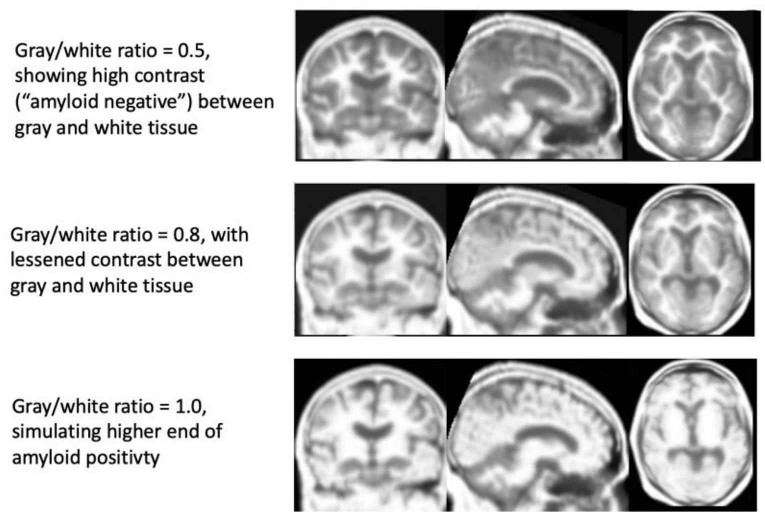
measurement pipeline. The simulated PET images may also be processed and measured using PET-only pipelines.




~~Illustration of how the DRO series was created.~~

Figure 10 below shows three of the DRO gray/white ratios, prior to inclusion of random noise. In this case, the image was spatially warped to a common template.




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

### *6.6.2 Linearity*

The linearity of the IAW will be assessed by testing a range of different subjects, as defined by varying SUVR values. The table below gives more detail about the simulated subjects and their respective SUVR values. Note that due to the simulation of PET-like resolution and noise in the images, the actual ratios measured will likely not be identical to the designed ratio shown in the table below. Similarly, depending upon the region definition boundaries applied for target regions and reference region, the measured SUVRs may vary. However, for a given processing and measurement pipeline or software platform, the relationship between the measured values and the ratios shown in the table should be linear. The slope of the relationship will be important in application of the claim.

| Simulated SUVRs by reference region | | | SUV settings in DRO | | | | Ratios | |
|---|---|---|---|---|---|---|---|---|
| Ref. Whole Cbl | Ref. Cbl Cortex | Ref. White | Cerebellar cortex | Cortical gray tissue | White** | CSF | Gray / White | White / Gray |
| 0.88 | 1.00 | 0.50 | 0.5 | 0.50 | 1.0 | 0.25 | 0.50 | 2.00 |
| 1.06 | 1.20 | 0.60 | 0.5 | 0.60 | 1.0 | 0.25 | 0.60 | 1.67 |
| 1.23 | 1.40 | 0.70 | 0.5 | 0.70 | 1.0 | 0.25 | 0.70 | 1.43 |
| 1.41 | 1.60 | 0.80 | 0.5 | 0.80 | 1.0 | 0.25 | 0.80 | 1.25 |
| 1.59 | 1.80 | 0.90 | 0.5 | 0.90 | 1.0 | 0.25 | 0.90 | 1.11 |
| 1.76 | 2.00 | 1.00 | 0.5 | 1.00 | 1.0 | 0.25 | 1.00 | 1.00 |

The activity in the CSF region will be set to 0.

Cbl = cerebellum

Hippocampus, amygdala, thalamus, putamen, globus pallidus regions are same value as cortical gray

Subcortical white, white cerebellum, and pons all have same value

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

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

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

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#### *6.6.3 Reproducibility*

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

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

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

#### ~~The DRO Series~~

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

#### 6.6.3.1 IAW Conformance Procedure

~~a.~~1. Download the UW-PET QIBA PET Amyloid DRO series from QIDW <give link when ready>.

~~b.~~2. Analyze the 30 volumes using the same procedure, target regions and reference regions as will be used with patient data.

For each target region for a fixed reference region, the information to form the graph below should be calculated, and will be called a given target's results, e.g. (Frontal Target/Whole Cerebellum Reference Region). Note that the appropriate value range for "truth" depends upon the reference region selected. The slope of the line does not need to be, and is not expected to be, 1 because of the degraded resolution, added noise, and the variation introduced by region of interest boundary definition. However, that slope should be

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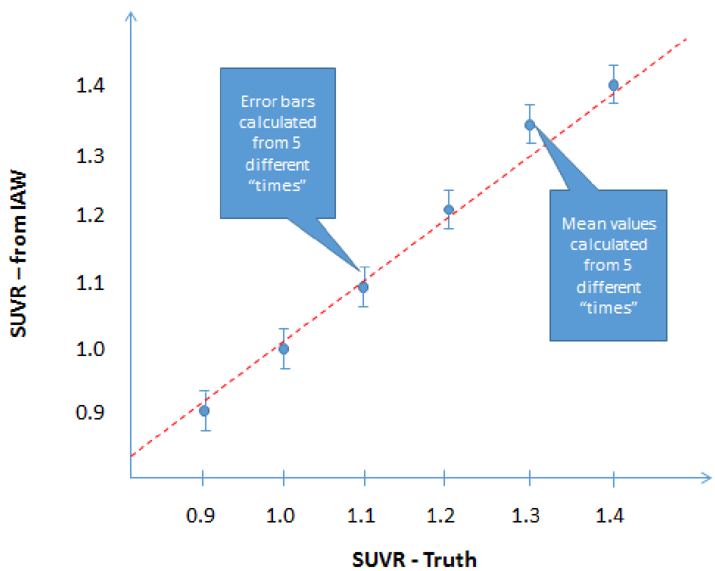
documented and taken into account when calculating study power based upon expected performance. Results:

## 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**

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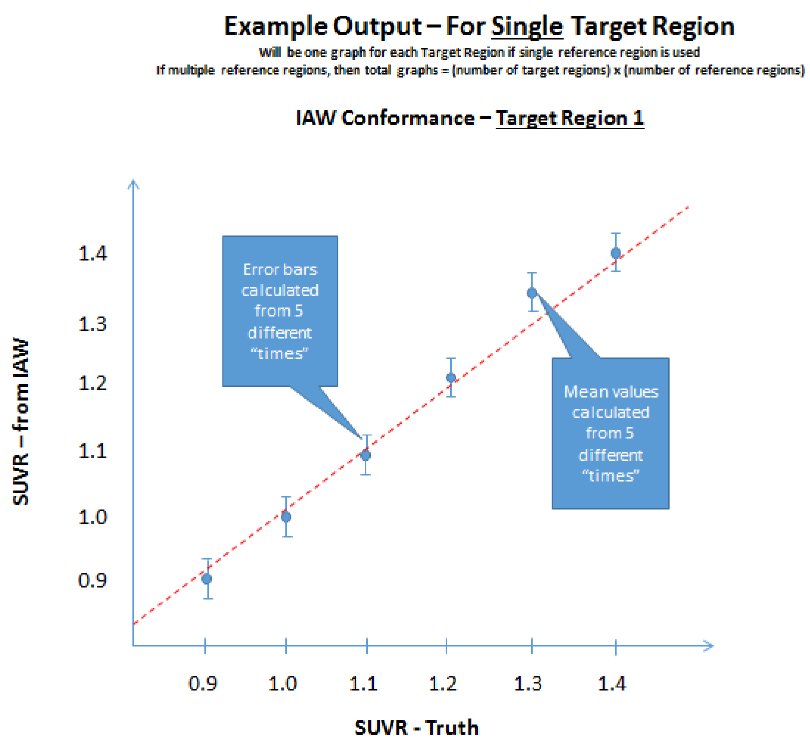
4. If multiple reference regions will be used, generate the same information as in point 3 above using this new reference region. The final number of target results or graphs will be (number of target regions) x (number of reference regions).




5. The following statistical analysis should be performed on each target result.
   a. Fit an ordinary least squares (OLS) regression of the $Y_i$'s on $X_i$'s (where Y's are the SUV measurements from the IAW, and X's are the true SUV measurements). A quadratic term is first included in the model: $Y= \beta_o+\beta_1X+\beta_2X^2$ .
      - The estimate of $\beta_0$, $\beta_1$ and $\beta_2$, *along with their 95% Confidence Intervals (CIs),* shall be reported as part of the assessment record (see last point below).
   b. Re-fit a linear model: $Y= A_o+A_1X$ (red dotted line on graph above).
      - The estimate of $A_0$ and $A_1$, *along with their 95% CIs,* shall be reported as part of the assessment record (see last point below).
      - R-squared ($R^2$) shall be >0.90 for the IAW to be compliant for the given target and reference regions.
   c. For each of the 6 true SUVR values, calculate the mean (blue points in graph above) of the 5 measurements and the wSD (blue error bars in graph above) using the following equations where the summations are from J=1 to J=5:

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

d. $\bar{Y}_i = \sum(Y_{ij})/J$ and

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

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

d.

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

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. **Because this is a small sample set, the value of 2.6% may not be met.** The value increases with a reasonable reduction in the required confidence interval for a sample set of this size. It is also noted that if the pons is used as a reference region for these calculations, the variability in the DRO is likely to be higher. Therefore, for the purposes of conformance, it may be useful to apply whole cerebellum, cerebellar cortex, or white matter as the reference rather than pons.)

- 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.

6.

| Ref Region | Visual Placement Check | Target Region | Visual Placement Check | $\beta_0$ | $\beta_1$ | $\beta_2$ | $A_0$ | $A_1$ | $R^2$ | $R^2 >$ 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 | $7.6 \times 10^{-3}$ | 2.1 | Pass |
| 1 | Pass | 2 | Pass | 0.05 | 0.9 | 0.02 | 0.07 | 0.95 | 0.91 | Pass | $1.05 \times 10^{-2}$ | 2.9 | Fail |
| 1 | Pass | 3 | Fail | - | - | - | - | - | - | - | - | - | - |

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| Ref Region | Visual Placement Check | Target Region | Visual Placement Check | $\beta_0$ | $\beta_1$ | $\beta_2$ | $A_0$ | $A_1$ | $R^2$ | $R^2 >$ 0.90 | wCV | %RC | %RC $\leq$ 2.6% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | $7.6 \times 10^{-3}$ | 2.1 | Pass |
| 3 | Pass | 2 | Pass | 0.04 | 0.95 | 0.04 | 0.03 | 0.92 | 0.93 | Pass | $8.0 \times 10^{-3}$ | 2.2 | Pass |
| … | … | … | … | … | … | … | … | … | … | … | … | … | … |

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

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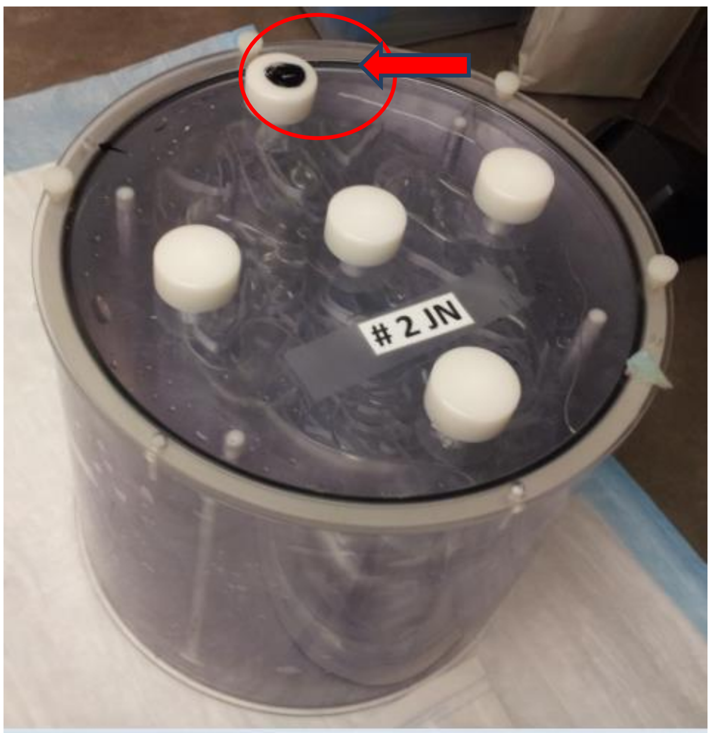
## ~~7.7~~6.7 Appendix G: Best Practice Guidance for the Hoffman Brain Phantom

- 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.

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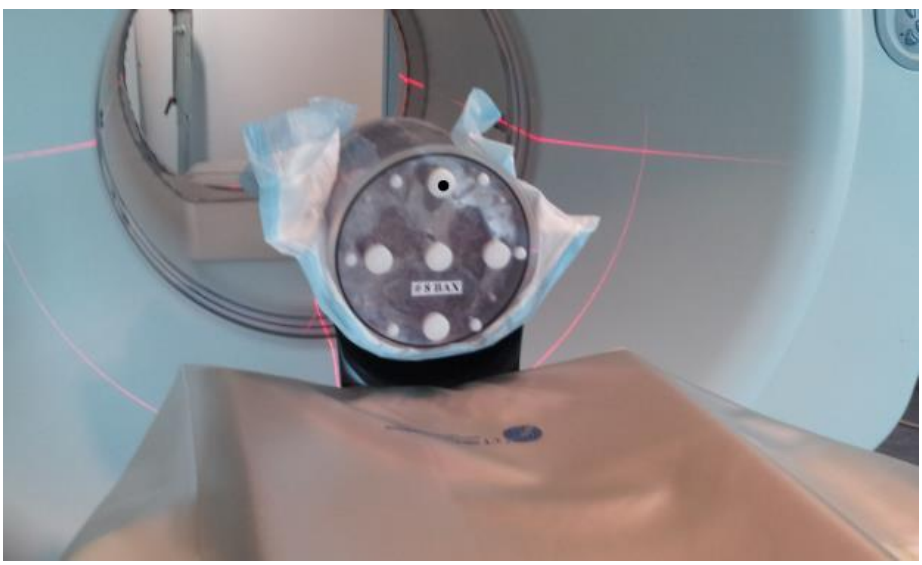
- Measure the residual in both needles and syringe. We suggest you place these in a surgical glove before placing in the dose calibrator to prevent contamination of the dose calibrator.
- Once injected, replace the cap and roll back and forth vigorously for about 5min. Occasionally, pick up and tip up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

Generally, this process takes about 10-20min.



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

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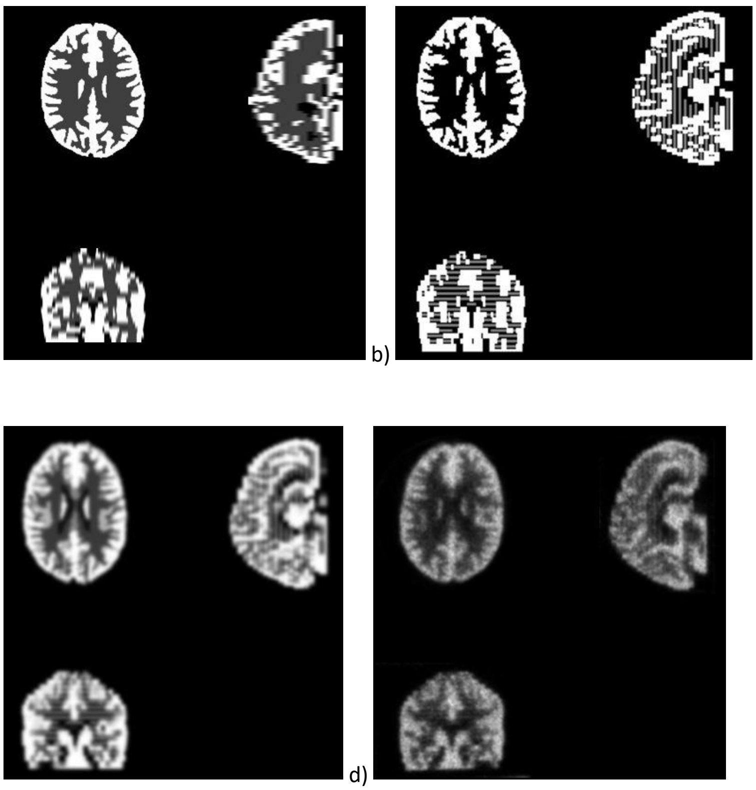
# ~~7.8~~6.8 Appendix H: Detailed Example of Hoffman Phantom Data Analysis

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.



a) b)

b) d)

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.

## ~~7.8.1~~6.8.1 *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

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matter. Areas of CSF are left completely void. Each layer is therefore composed of a "sandwich" in this order: GG|W|GG|W|GG. The most caudal slice and most cranial slice consist of just 4 gray layers (GG|GG).

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

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

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

### ~~7.8.2~~6.8.2 Methods and Metrics

#### ~~7.9~~6.8.2.1 Method Overview

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

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

#### ~~7.10~~6.8.2.2 Relevant Data Files

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

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Reference Files

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

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

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

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

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

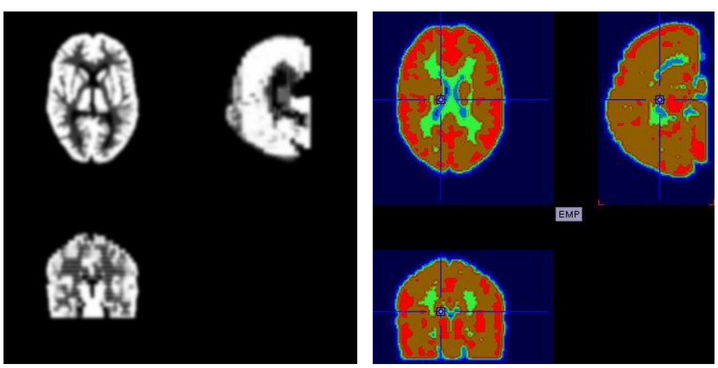

Figure 2. Six-region Volume of Interest mask. The smoothed digital reference (left), and the volume of interest mask volume created in PMOD using multi-thresholding segmention (right). The VOI mask is used

## PAT Uniform Phantom Analysis

to define areas representing primarily pure gray (shown in red) and pure white matter (shown in green). These regions are used for image intensity normalization and various image quality metrics.

Input files

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

Intermediate Files

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

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

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

Output Files

Volumes

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

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

Text

**RegSourceXXXfit.txt** – summary output file

JPG -

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

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

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

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



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### ~~7.10.1~~6.8.3 Method Details: Processing Steps

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

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

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

This step sums the dynamic PET data to obtain an averaged PET source file, and then registers the averaged PET to the Hoffman reference image. It is assumed that there is no motion between image time frames, so a motion correction step is not necessary like it would be for a patient study. As a reference image, the version of the Hoffman reference smoothed with a 5 mm isotropic Gaussian filter is used (**ctiHoffman5.0_5.0.nii**). This represents the resolution of an image that would be expected from the highest resolution PET scanners. In PMOD's registration module, Normalized Mutual Information and the "scale" option are selected to allow an affine match that will compensate for slightly different phantom actual sizes. No other pre-smoothing is used during the registration. The batch process saves the averaged and the registered dataset as two separate files. This step can be run on one or many different PET files. PMOD is not set up yet to record the reorientation matrix (I have requested this), so we do not have a full track of all operations.

3) 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, FWHMxy and FWHMz.* An unconstrained nonlinear estimation approach is use to find the Gaussian smoothing kernels that produce a smoothed version of the digital reference phantom best matching the normalized source volume. (using Matlab's "fminsearch" function). We investigated various image difference measures: absolute difference, squared difference, correlation, and brain-masked differences, and the simple absolute difference appeared to work well. The code is written so that any of these options can be selected, but the default is the absolute difference.

2) Calculation of Quality Metrics from the Normalized Source Image and Difference Image

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## PAT Uniform Phantom Analysis

The difference between the normalized source image and the digital reference smoothed to fit the source image is the main basis for the comparison. Additionally, some measures can also be computed from the normalized source image alone. Basic ideas to consider in this analysis include:

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

Quality Metrics

a) Global Volume Metrics
   i) **Comparison of fit smoothing parameters to published data from ADNI / Bob Koeppe's group**. This value should be consistent for a given scanner type. Differences in Z-smoothing compared to ADNI results are expected due primarily to Z-scaling during the affine registration process. Based on empirical observation, there most likely is a problem if the fit smoothing parameters differ by more than 1 mm FWHM.
   ii) **Average Global Absolute Difference – total image volume** : ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
   iii) **Average Global Absolute Difference in the brain region only**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
   iv) **Gray:White mater ratio in the source image**. Ideally, this should be 4.0. For scanners of lower resolution we would expect the value to be less.
   v) Ratio of Gray:White in the Source image compared to smoothed reference. Ideally, this should be 1.0. Would expect at most a 10% variation.
   vi) **Ratio of White matter intensity standard deviation in the Source imaging compared to the smoothed reference**: This measure gives an indication of image noise. By comparing to the reference volume, variation with the white matter region due to the partial volume effect should cancel out.
   vii) **Ratio of Gray matter intensity standard deviation in the Source imaging compared to the smoothed reference**. : This measure gives an indication of image noise. By comparing to the reference volume, variation with the white matter region due to the partial volume effect should cancel out.

b) Slice-by-slice Metrics (computed between planes 10-80, which represent the plane with brain data in the Hoffman reference volume)
   i) **Average Slice Absolute Difference – total slice**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
   ii) **Average Slice Absolute Difference** – brain region only: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
   iii) **Average Slice Absolute Difference – gray matter only (VOI region #6)**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.

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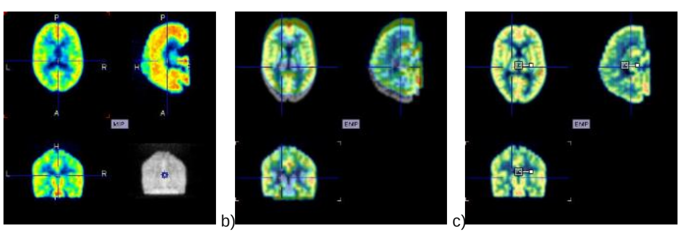
iv) **Average Slice Absolute Difference – white matter only (VOI region #4)**: ideally, this should be less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
v) Ratio of mean gray intensity in VOI region #6 for Source compared to smoothed reference: ideally, this should be 1.0
vi) Ratio of mean white intensity in VOI region #6 for Source compared to smoothed reference. Ideally, this should be 1.0.
vii) **Profile Coefficient of Variation for Gray slice mean gray intensity.** This metric can be used as a sentinel for unacceptable variations in axial sensitivities.

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



a) b) c)

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).

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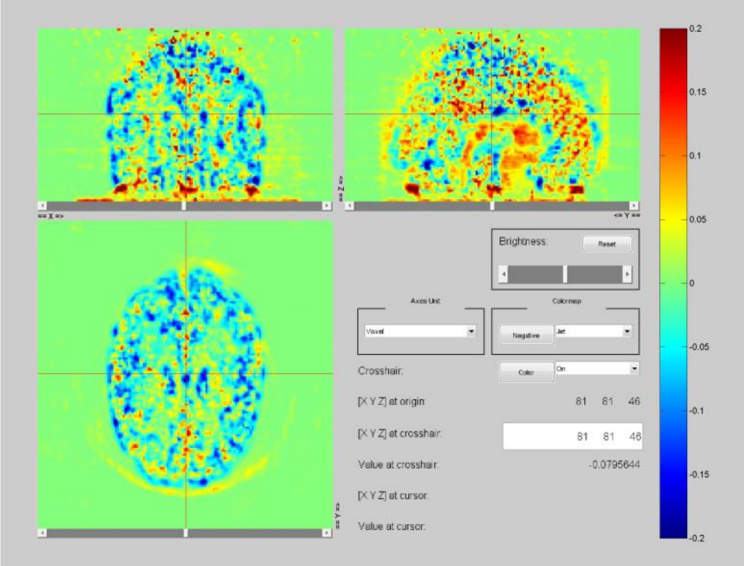
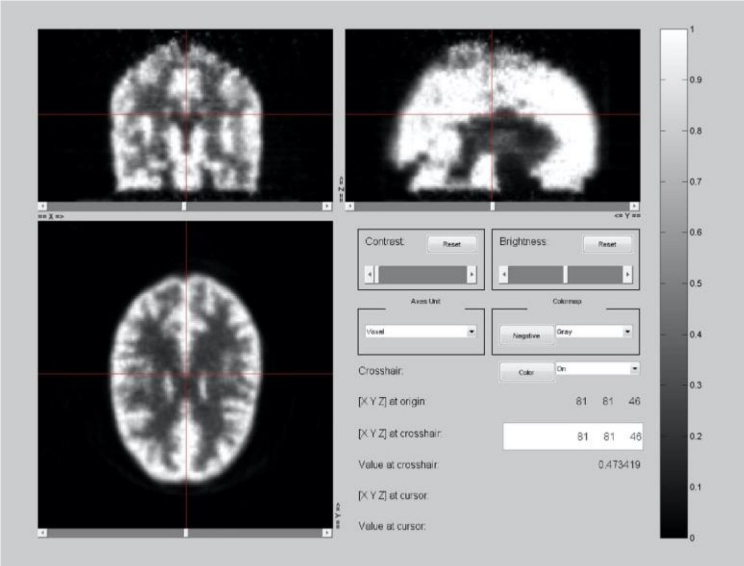
## PAT Uniform Phantom Analysis

Example Results using the ADNI Hoffman Qualification Data

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

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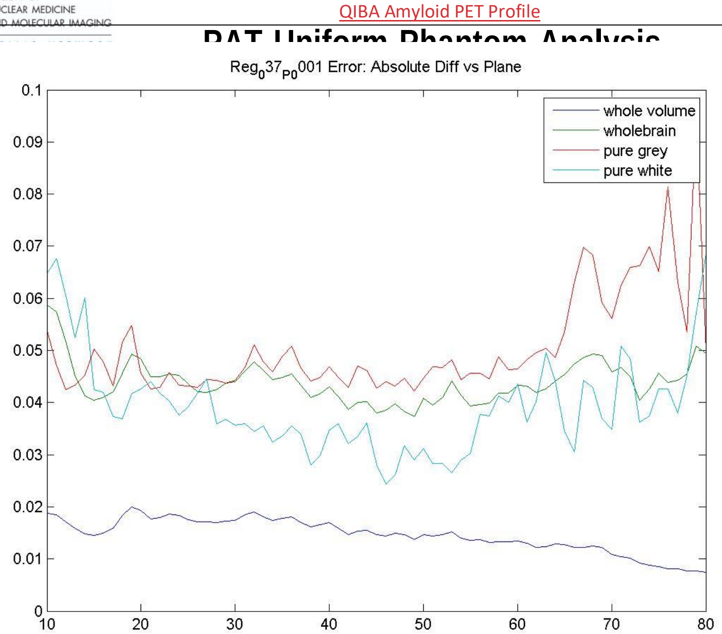


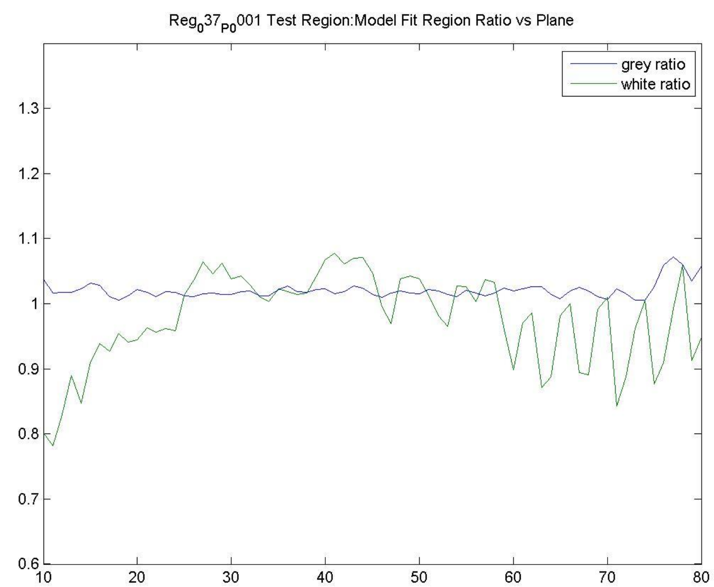


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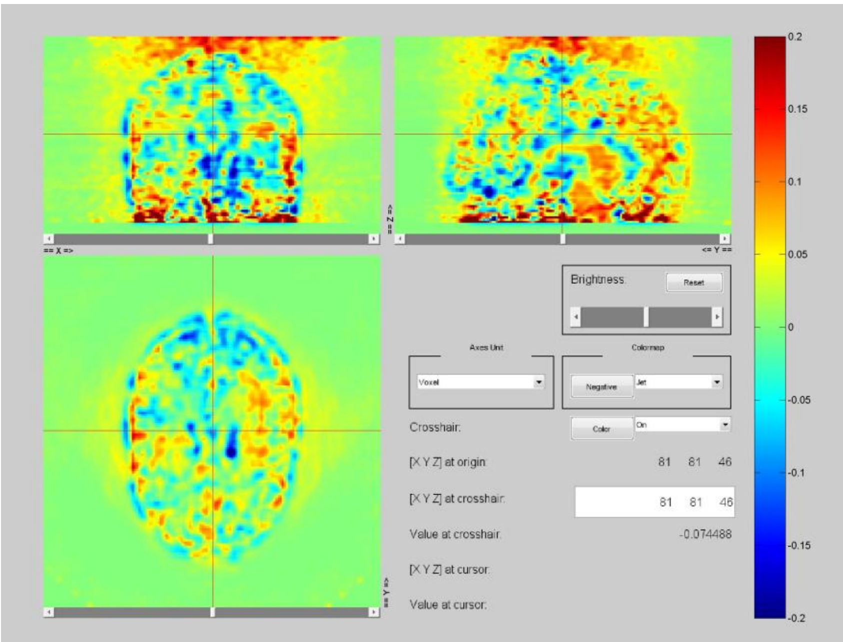
PAT Uniform Phantom Analysis

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

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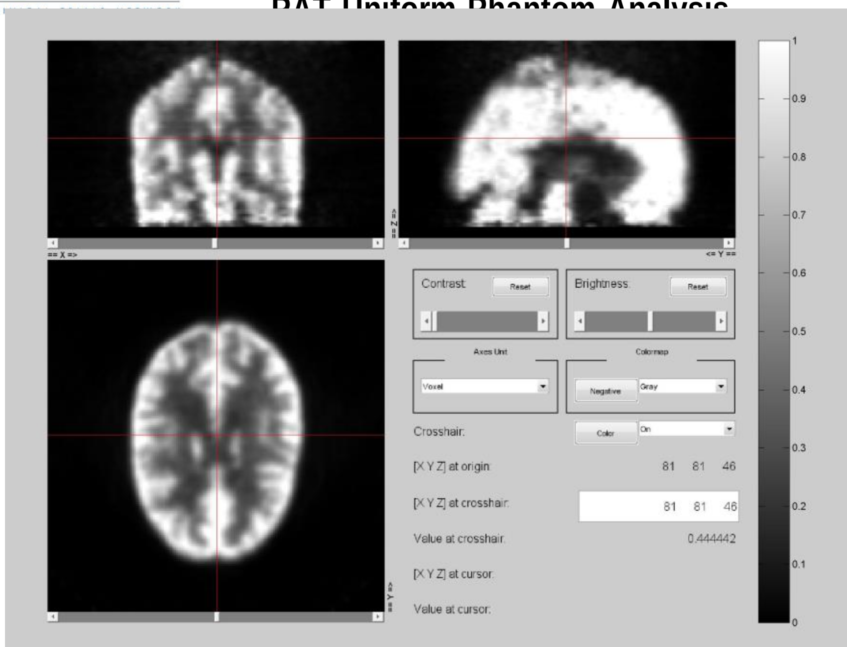


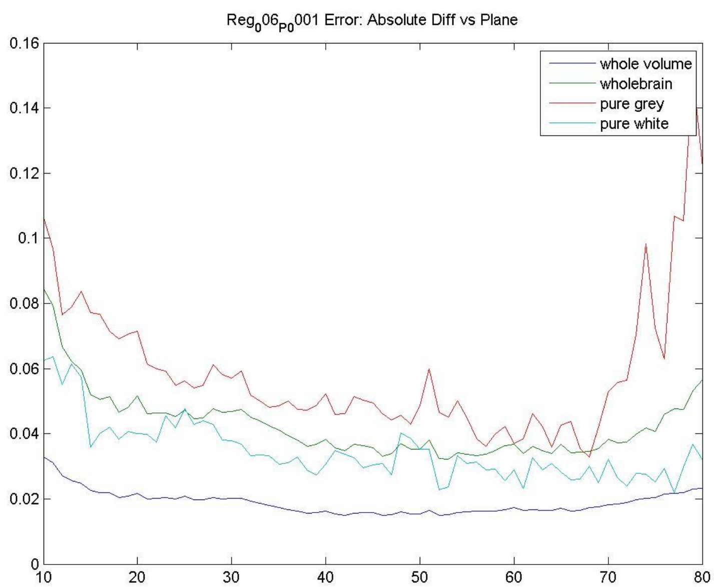


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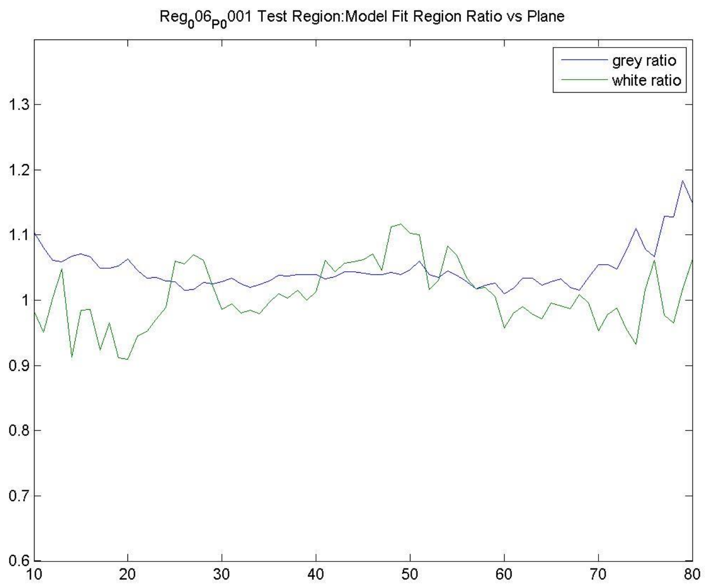


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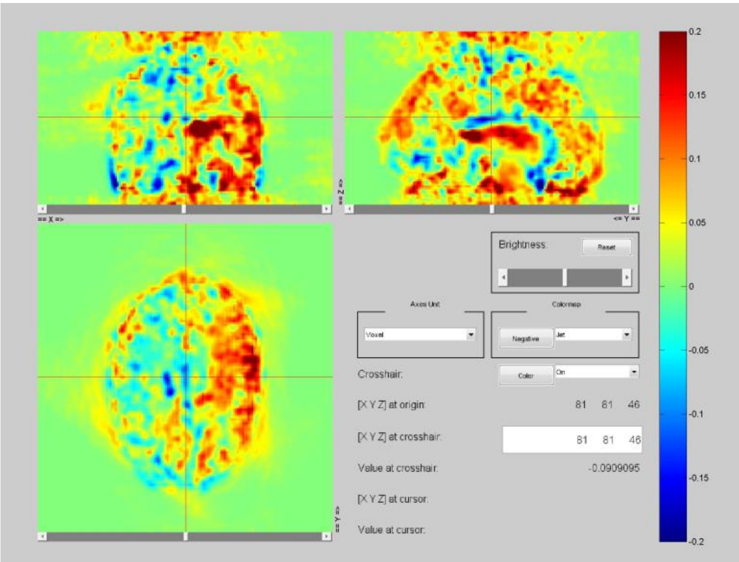
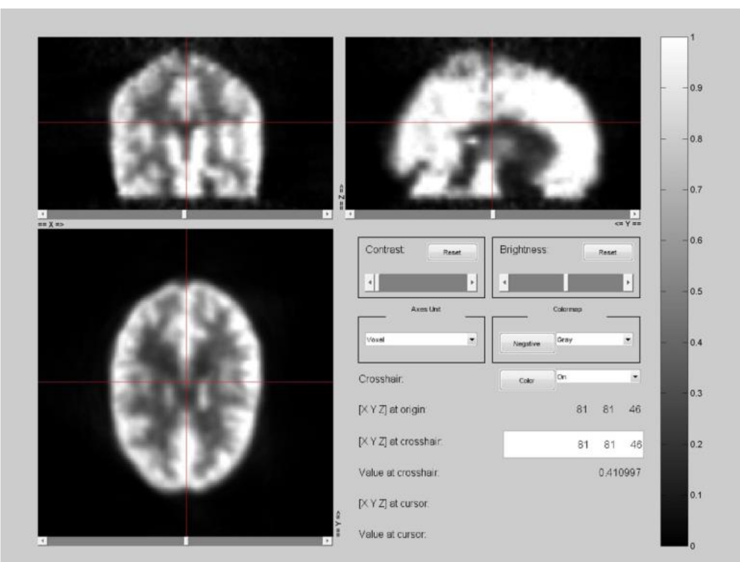
## PAT Uniform Phantom Analysis

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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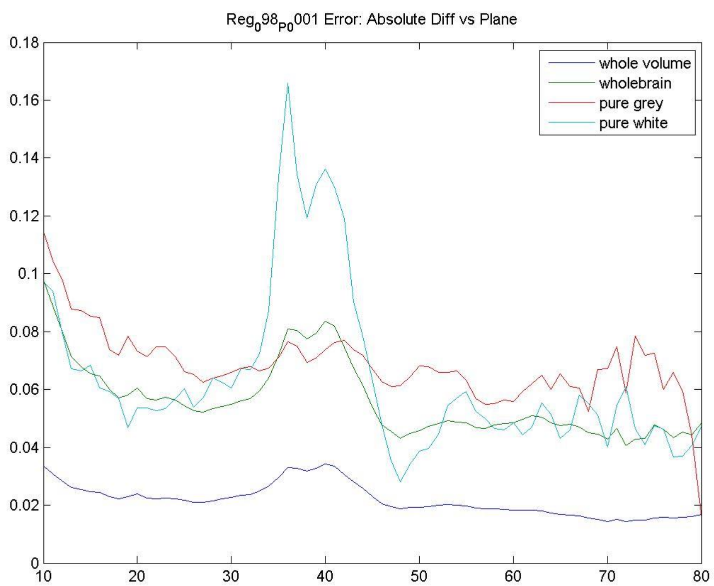


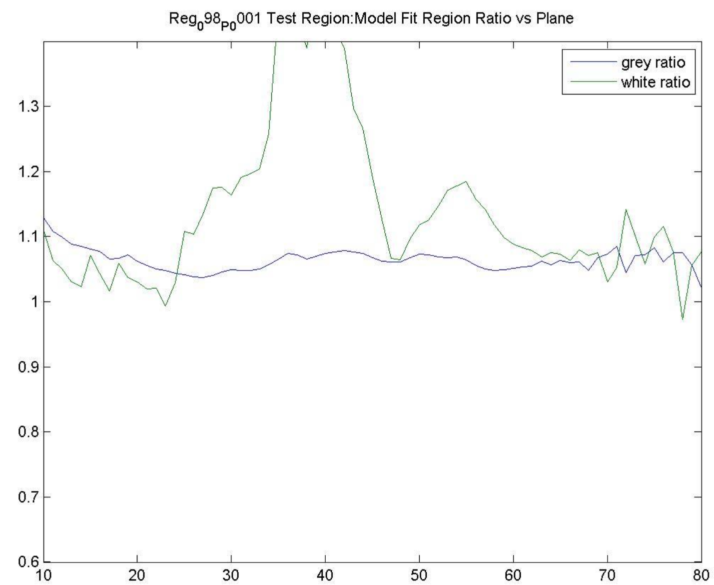


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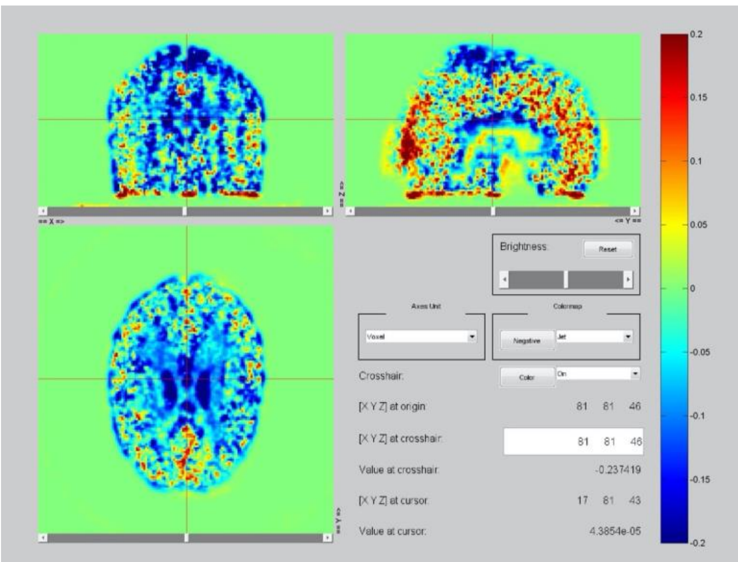
## PAT Uniform Phantom Analysis

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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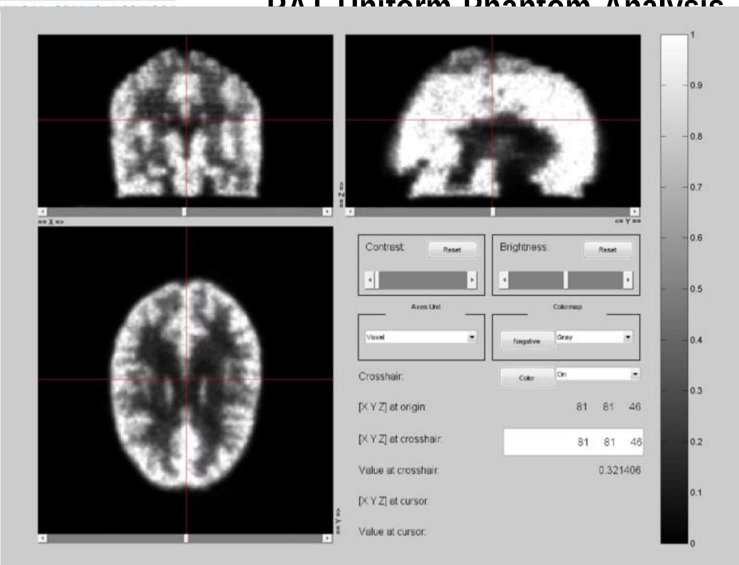


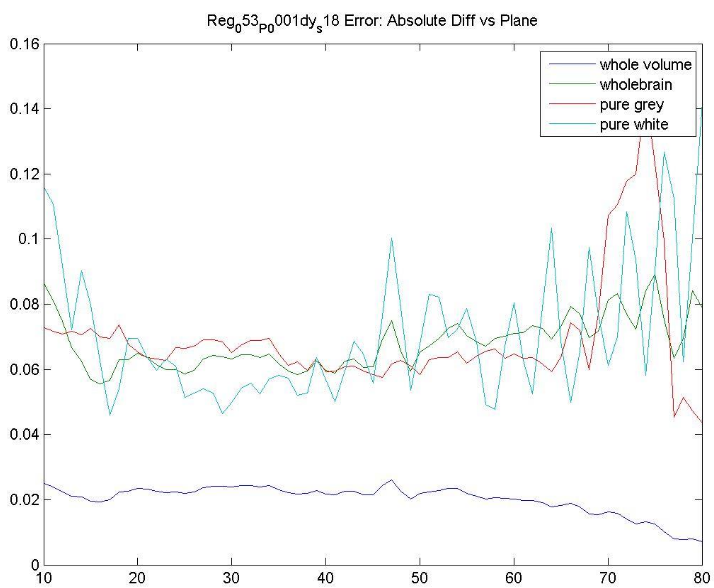


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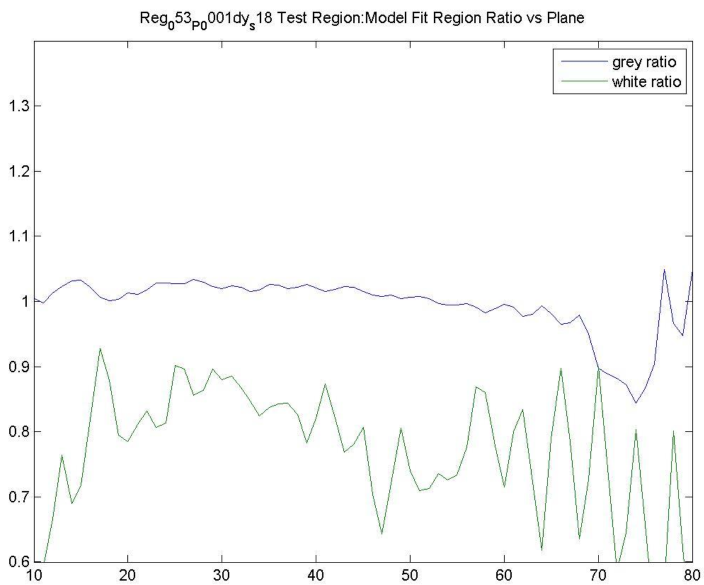


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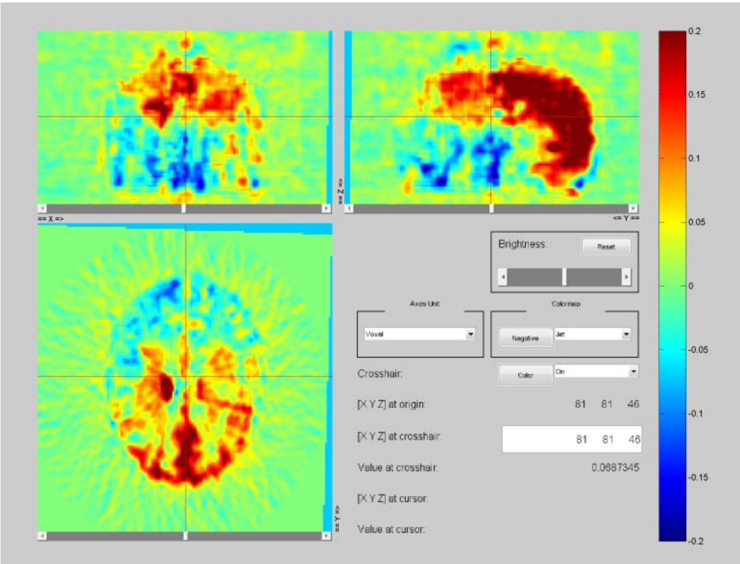
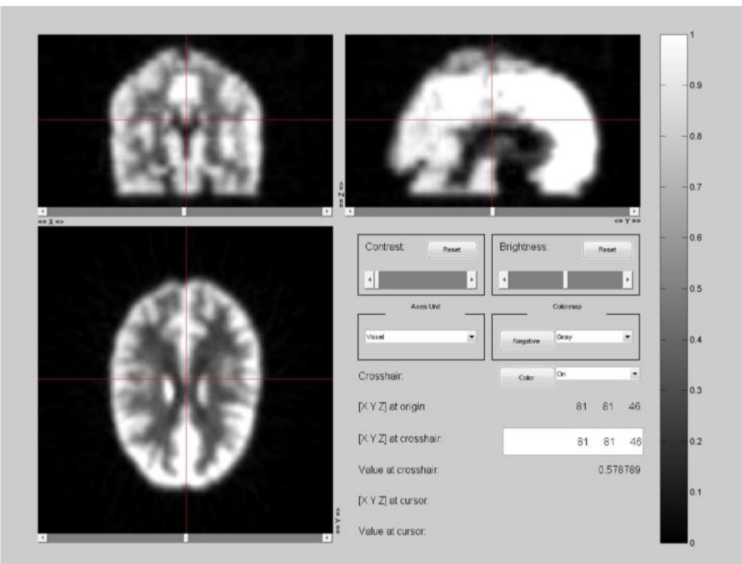
## PAT Uniform Phantom Analysis

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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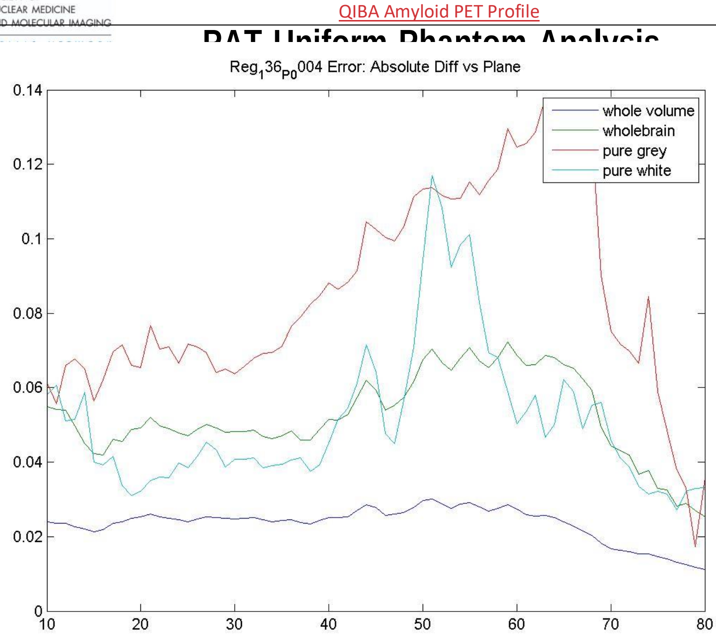




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# ~~7.11~~6.9 Appendix I: Kinetic Modeling and Comparison to SUVR

### *6.9.1 Introduction*

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.

### *6.9.2 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").

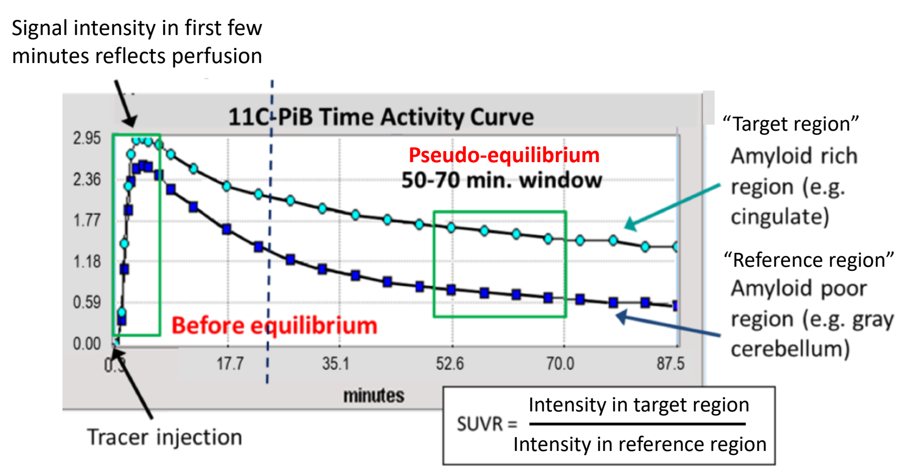


Figure 1. Time activity curves.

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

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

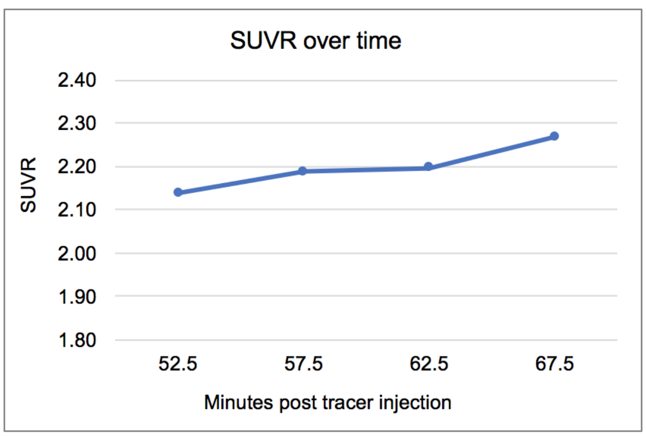


Figure 2. SUVR over time based upon the TAC values in Figure 1.

### *6.9.3 Kinetic modeling*

Several different models have been developed that use simultaneous differential equations to solve for the “flux” into and out of compartments, and ultimately the amount of tracer bound to target (in this case, amyloid). The gold standard approach uses arterial blood measurements to obtain the actual tracer concentration in blood. This method has some disadvantages due to patient and staff burden and variability in the blood measurements (Lopresti 2005, Tolboom 2009). Alternate modeling approaches

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make use of regional measurement of carotid artery radioactivity (Lopresti 2005) or eliminate the need for blood sampling by making use of reference measurements in tissue that does not contain the binding target. For amyloid tracers, this is often the cerebellar cortex, which is generally devoid of amyloid except in latest stages of Alzheimer's disease (ref) and certain familial forms of AD (Sepulveda-Falla 2011). The validity of the reference region approach as an approximation for blood based modeling must be tested for each new tracer, as it has been for 11-PIB (Price 2005), Amyvid (florbetapir, Wong 2010), Vizamyl (flutemetamol, Nelissen 2009), and Neuroseq (florbetaben, Becker 2013). All kinetic models make use of the entire time course of tracer measurement (TAC) from time of injection to a point at which a "pseudo-equilibrium" has been reached. All of these models have the advantage of segregating the contribution of blood flow and clearance from that of bound tracer. In the process, they provide a measure of "R1", i.e perfusion relative to reference perfusion. Given the correlation between blood flow and cerebral glucose metabolism that exists in many cases, this provides an additional "FDG like" image reflecting neuronal function. The creation of a full TAC using an early time window and late time window has also been demonstrated (Bullich 2017). The measure of target burden (in this case amyloid) derived from a kinetic model is called the Distribution Volume Ratio (DVR or $V_{tissue}/V_{nondisplaceable}$), equal to non-displaceable Binding Potential (BPnd) + 1. Published studies that used kinetic modeling may state the DVR value or may alternatively state the BPnd value when stating amyloid burden.

### *6.9.4 Standardized Uptake Value Ratio*

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

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

### *6.9.5 Bias in SUVR measurements*

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The fact that true equilibrium is never reached can create an upward bias in SUVR value relative to DVR (Slifstein et al, 2007, Carson et al, 1993, Frokjaer et al, 2007, van Berckel et al, 2013). To illustrate this conceptually, from the TACs in Figure 1, it can be seen that the "receptor poor" reference region TAC asymptotes, or flattens, more rapidly than the "receptor rich" TAC. This is because tracer binding slows

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tracer flux back into the bloodstream. Even in late timeframes, neither curve is flat, which would be the case if equilibrium were reached and net flux were zero. However, the receptor poor curve approaches a "flatter" stage first, as the concentration difference between tissue and plasma is lower. The difference between the rate of change in the receptor rich TAC (the SUVR numerator) and the reference TAC (the SUVR denominator) creates an artificially high value. A mathematical expression of this is provided in Slifstein et al (2007), which the reader is encouraged to review for further detail along with other references cited. In brief, as described mathematically in Slifstein, a change in concentration in a given region is depicted by $[k_1*C_{plasma}]$ minus $[k_2*C_{tissue}]$, where $k_1$ is the transport coefficient from plasma to tissue, $C_{plasma}$ is the concentration in plasma, $k_2$ is the transport coefficient from tissue to plasma, and $C_{tissue}$ is the concentration in tissue. At equilibrium, these would sum to zero consistent with a lack of net concentration change. The expression $C_{tissue}/C_{reference}$, which is the SUVR, would equal the DVR (where DVR $= V_{tissue}/V_{ND}$ and ND refers to nondisplaceable binding in reference region). However, only "pseudo-equilibrium" is reached and instead, $C_{tissue}/C_{reference} = [V_{tissue}*(k_1\ C_{plasma} + |dC_{tissue}/ct|)]/[V_{tissue}*(k_1\ C_{plasma} + |dC_{reference}/ct|)]$. The rate of change in tissue $|dC_{tissue}/ct|$ in the numerator of this expression is greater than the rate of change $|dC_{reference}/ct|$ for the reference tissue (which "flattened" earlier) in the expression denominator. This erroneously increases the value of the $C_{tissue}/C_{reference}$, the SUVR.

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.

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

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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.

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

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:

1. the level of non-specific binding is the same in target and reference regions
2. the ratio K1/k2 is the same for target and reference regions.

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

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

### *6.9.6 Logistical considerations for dynamic modeling*

Acquisition of discrete timeframe data for dynamic modeling requires several short duration frames occurring immediately following tracer injection, followed by longer timeframes later on. The scanner must be capable of acquiring multi-frame data and must have adequate memory storage to support what will likely be more than 20 frames in a single session (this issue has decreased with newer scanners). The site must also either have scanner equipment that provides for a button enabling start of scan along with tracer injection, or a second staff person available to initiate scanner data acquisition at time of injection. There are further considerations with the length of the IV line depending upon the tracer (due to affinity for tubing walls for some tracers), and the position of the subject within the scanner. As additional

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considerations, scanner utilization time and patient burden are increased. A dual “early” (first minutes post injection) and “later” (pseudo equilibrium) data acquisition approach has been demonstrated that allowed extrapolation of a full TAC for kinetic modeling while also allowing the subject to have a “break” (Bullich 2017). However, the potential benefit of allowing a site to fit an extra scan within that “break” period is offset by the potential occurrence of a delay in continuing the scan, and associated introduction of technical variability. To assess blood flow changes, alternate modalities such as arterial spin labeling (ASL) MRI have been proposed; however, these require validation for use in this context and do not capture clearance changes.

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

### *6.9.7 Conclusions*

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Longitudinal changes in SUVR arising from systematic changes in blood flow ratios and clearance rates mentioned in this section are not accounted for in the coefficient of variation in the profile Claim, which captures non-systematic variability. The impact of systematic changes is highly dependent upon the study population and therapeutic agent. When evaluating patient populations where the disease process may impact blood flow or clearance rate, or where a therapeutic intervention could impact these factors, it is strongly recommended to conduct at least an initial study using full dynamic modeling in order to determine whether the SUVR approach is an acceptable substitute. Despite the logistical challenges of conducting full dynamic imaging, there are certain sites that routinely acquire data of this type. The benefit of characterizing potential erroneous signal changes due to changes in blood flow or clearance merits inclusion of such studies prior to broadening a longitudinal amyloid measurement trial through use of SUVR.

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## 6.10 Appendix I: SNMMI PAT Uniform Phantom Analysis sample report

SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING
CLINICAL TRIALS NETWORK

### Introduction

The Uniform Phantom Analysis is meant to provide five distinct measures of scanner performance. These are relevant for daily clinical performance as well as qualifying a scanner for use in trials.

1. Scanner Quantitative Calibration Accuracy
2. Uniformity in the axial (across planes) direction
3. Uniformity in the radial (within planes) direction
4. Spatial resolution in the axial direction
5. Spatial resolution in the radial direction

### Phantom Data Acquisition and Reconstruction

This phantom study is meant to quantify some of the most fundamental metrics associated with your PET scanner performance. To get accurate measures this test is meant to be performed using:

1. A lengthy two-bed position (at least) scan of your 20 cm diameter uniform phantom (15-30 minutes per bed position). The phantom is tilted on a slight incline (front edge raised approximately 2 cm) so that spatial resolution can be accurately assessed from the edge of the phantom given that its physical edge occurs at a gradual progression of y-locations (floor to ceiling) in different axial slices. The long acquisition minimizes statistical noise.

2. Your standard clinical oncology reconstruction to get an accurate assessment of resolution using your clinically-used reconstruction algorithm and parameters.

### Software Functioning

The software expects the uniform phantom data to be acquired on a slight incline. It understands the cylindrical geometry of the phantom and analyzes the images to determine the 3D equation of the central axis of the cylinder. Given this information, a series of measurements is made without requiring user interaction.

- **Calibration Accuracy:** A large cylindrical VOI is placed in the center of the phantom (avoiding edge effects).
- **Uniformity in the Axial Direction**: Individual approximately 15 cm diameter circular ROIs are placed in the center of each axial slice.
- **Uniformity in the Radial Direction**: Five individual circular regions of interest approximately 4 cm in diameter are placed in each axial slice anterior, posterior, left, right, and center.
- **Spatial Resolution in the Axial Direction**: An edge profile is drawn for the central axial slice, and several slices in front and several slices behind. Using the measured phantom axis angle to calculate fractional offset of the adjacent edge curves, a highly sampled edge response curve can be pieced

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PAT Uniform Phantom Analysis

together. A mathematical function is fit to this curve in order to measure the axial resolution.

- **Spatial Resolution in the Radial Direction**: An edge profile is drawn on the central coronal slice and several slices to the left and right. In a manner similar to the previous step, piecing these several profiles together creates a highly sampled edge response function that can be used to assess the radial resolution.

## Caveats

The software expects the phantom data to be collected at a slight incline. If it is not, and the scan is performed with the phantom parallel to the axis of the scanner then all measurements will still be valid EXCEPT the resolution measurements, which require the higher sampling afforded by the inclined phantom.

## Report Header

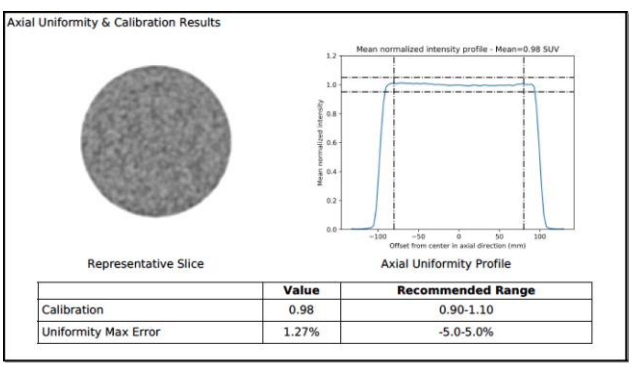
The header of the report is at the top of the first page. Example below.

Facility: University of Iowa Hospitals — Phantom: Uniform — Concentration: 0.21µCi/ml
Scanner Model: SIEMENS Biograph64_Vision 600 — Scan: 08/02/2019 — Time Per Bed: 3.0min.
Reconstruction: PSF+TOF 4i5s Gauss3.00

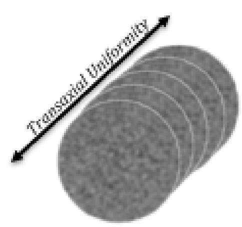
This Section reads the facility name, scanner make and model, reconstruction, scan date, and time per bed position from the DICOM Tags. It also reports the actual concentration in the phantom based upon the reported activity injected into the phantom, and the phantom volume.

## Scanner Calibration and Axial Uniformity

The scanner calibration accuracy is reported at the bottom of the first box. The "Calibration" reported is the PET measured concentration from a large cylindrical VOI automatically placed on the image data, divided by the actual concentration at scan time as determined by the decay corrected concentration as calculated from the data entered into PAT (activity injected into the phantom, time of dose measurement, the phantom fill volume). The Calibration reported should ideally be 1.00 with an acceptable range between 0.90 -1.10 (within ±10% of actual concentration).




| | Value | Recommended Range |
|---|---|---|
| Calibration | 0.98 | 0.90-1.10 |
| Uniformity Max Error | 1.27% | -5.0-5.0% |

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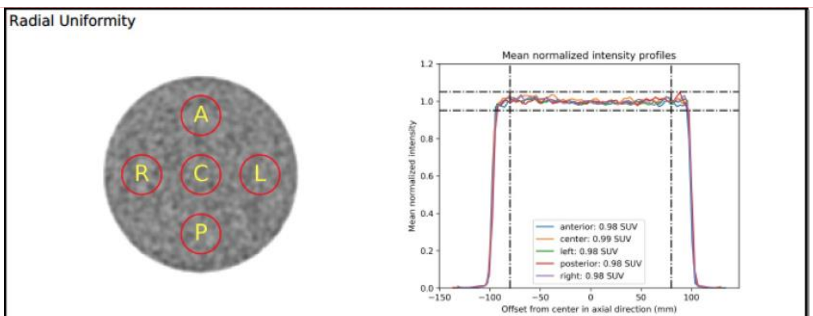
## PAT Uniform Phantom Analysis

Axial uniformity is reported both graphically as a profile through all axial slices of the scanner, and numerically in a downloadable spreadsheet available from PAT. For purposes of uniformity (but not of accuracy) the plot is normalized to the mean measured across the scanner's axial field of view, and will always be centered around 1.0. A circular region of interest of approximately 15 cm is centered in each slice around the centroid pixel to determine the mean concentration per slice.

For purposes of uniformity assessment, only the central 80% of slices are analyzed (designated by two dotted vertical lines in the plot) so as to avoid edge/resolution effects. Two horizontal dotted lines are provided at ± 5%. Typically, a scanner should have uniformity that stays within that ± 5% window. The largest deviation from 1.0 is reported in the first box underneath the Calibration measure. One should *not* observe a gradient from front to back (or vice versa), and this would be evidence of a problem, even if it were to stay within the ± 5% boundaries.

## Radial Uniformity

Radial uniformity is reported both graphically and numerically in the second box as a profile through all axial slices of the scanner. For this measurement, five individual circular regions of interest approximately 4 cm in diameter are placed in each axial slice anterior, posterior, left, right, and center to assess radial uniformity in each slice. Like the first box, this plot is normalized to the mean measured across the scanners axial field of view, and so will always be centered around 1.0.




| | Value | Location | Recommended Range |
|---|---|---|---|
| Uniformity Max Error | 3.40% | center | -5.0-5.0% |

For purposes of uniformity assessment, only the central 80% of slices are analyzed (designated by two dotted vertical lines in the plot) so as to avoid edge/resolution effects. Two horizontal dotted lines are provided at ± 5%. Typically, all five regions should have uniformity that stays within that ± 5% window, however because these are smaller regions, noise may result in excursions slightly above and below the 5% line, which is to be expected and is likely of no consequence. Here we are looking for geometric bias. Is the anterior region systematically different than the posterior region? Is the left different than the right? Is the center region higher or lower than the peripheral regions (as might be seen if either attenuation or scatter corrections are not being performed appropriately)? It is up to the reader to make these determinations, as no automated detection of regional bias is performed.

The largest deviation from 1.0 is reported in the first box underneath the Calibration measure, along with which region this occurred in.



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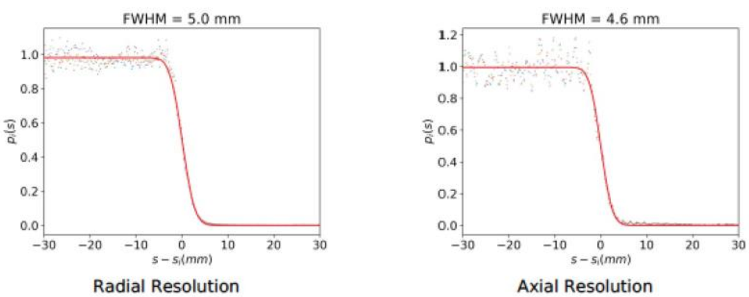
PAT Uniform Phantom Analysis

## Resolution Measurement

Spatial resolution measurements of PET scanners have historically been performed using point sources of F-18 in air reconstructed using filtered back-projection. This is the NEMA approach, which has the explicit purpose of measuring the *intrinsic* resolution of a PET scanner; it does not, however, provide a meaningful measurement of resolution under clinical scanning conditions.

The PAT approach targets providing sites with a meaningful measure of spatial resolution under more clinically relevant conditions. PAT implements an algorithm developed by Lodge[1] that uses the edge response function measurement from the uniform phantom acquired at a slightly oblique angle to measure both axial and radial resolution. This approach uses the phantom data reconstructed with the site's clinical reconstruction method in the presence of scatter and attenuation material to generate a clinically meaningful measurement of resolution.

The table provided in the PAT report includes the composite edge response function for the radial and axial planes, along with the functional fit to the data. The table below documents the axial and radial resolution measurements. The dots indicate the data and the curves indicate the function fit from which the resolution measure is derived.




| | Value | Recommended Range |
|---|---|---|
| Radial Reconstructed Resolution | 5.0mm | <9mm |
| Axial Reconstructed Resolution | 4.6mm | <9mm |

## DICOM and Fill Information

Relevant DICOM header and fill information is displayed in fourth box. This is provided to provide a simple means to check the fill and reconstruction information.

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## PAT Uniform Phantom Analysis

| Name | Value |
|---|---|
| Institution | University of Iowa Hospitals |
| Phantom | Uniform |
| Series Description | PET WB ultraHD |
| Scan Date | 08/02/2019 |
| Scan Time | 14:58:07 |
| Assay Time | 14:32:00 |
| Background Volume | 6303.0g |
| Background Activity | 1.59 |
| Uptake Time | 26.1 |
| Minutes per Bed | 3.00 |
| Voxel Dimensions | 1.65x1.65x3.00mm |
| Matrix Dimensions | 440x440x88 |
| Scanner Make and Model | SIEMENS Biograph64_Vision 600 |
| Reconstruction Method | PSF+TOF 4i5s |
| Reconstruction Parameters | |
| Reconstruction Filter | XYZ Gauss3.00 |

# References

*Measuring PET Spatial Resolution Using a Cylinder Phantom Positioned at an Oblique Angle.*

Lodge MA, Leal JP, Rahmim A, Sunderland JJ, Frey EC. J Nucl Med. 2018 Jun 14



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## 6.11 Appendix K: Conformance Checklists

### *6.11.1 INSTRUCTIONS*

## Amyloid PET Imaging

This Checklist is organized by "Actor" for convenience. If a QIBA Conformance Statement is already available for an actor (e.g. your analysis software), you may choose to provide a copy of that statement rather than confirming each of the requirements in that Actors checklist yourself.

Within an Actor Checklist the requirements are grouped by the corresponding Activity in the QIBA Profile document. If you are unsure about the meaning or intent of a requirement, additional details may be available in the Discussion section of the corresponding Activity in the Profile.

Conforms (Y/N) indicates whether you have performed the requirement and confirmed conformance. When responding N, please explain why.

An additional Site Opinion column is included during the Technical Confirmation process to allow you to indicate how the requirement relates to your current, preferred practice. When responding Not Feasible or Feasible, will not do (i.e. not worth it to achieve the Profile Claim), please explain why.

An additional column has been included to assess the impact of a given step for the purposes of checklist finalization. This can be translated into a quantitative or other impact or note in future versions.

Feedback on all aspects of the Profile and associated processes is welcomed.



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### 6.11.2 SITE CHECKLIST

| Parameter | Conforms (Y/N) | Requirement (Site) |
|---|---|---|
| Acquisition Devices | | Shall confirm all participating acquisition devices conform to this Profile. |
| Reconstruction Software | | Shall confirm all participating reconstruction software conforms to this Profile. |
| Image Analysis Tools | | Shall confirm all participating image analysis tools conform to this Profile. (not applicable in clinical trial with central data QC, processing, analysis) |
| Radiologists | | Shall confirm all participating radiologists conform to this Profile. |
| Physicists | | Shall confirm all participating physicists conform to this Profile. |
| Technologists | | Shall confirm all participating technologists conform to this Profile. |

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### 6.11.3 IMAGING FACILITY COORDINATOR CHECKLIST

| Section | Parameter | Conforms (Y/N) | Requirement (Imaging Facility Coordinator) | Inclusion notes |
|---|---|---|---|---|
| 3.8.2 | Accreditation / Qualification | | 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.). | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.2 | Personnel Roster | | Each site shall have the support of certified technologists, physicists, and physicians experienced in the use of amyloid-PET/CT in the conduct of clinical trials. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.2 | Technologist | | Technologist certification shall be equivalent to the recommendations published by the Society of Nuclear Medicine and Molecular Imaging Technologists Section (SNMMI-TS) and the American Society of Radiologic Technologists (ASRT) and meet all relevant regulatory requirements. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.2 | Medical Physicist | | Medical physicists shall be certified in Medical Nuclear Physics or Radiological Physics by the American Board of Radiology (ABR) or equivalent certification. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.2 | Physician | | Physicians overseeing PET/CT scans shall have board certification by the American Board of Nuclear Medicine (ABNM) or equivalent. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.8.3.2 | Scanner hardware | | The same scanner will be used for all longitudinal scans acquired for the same subject. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.3.2 | Scanner operating software | | The same scanner software will be used for all longitudinal scans acquired for the same subject (or requalified if update is necessary). | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.1 | PET scanner | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |

### *6.11.4 NUCLEAR MEDICINE PHYSICIAN / RADIOLOGIST CHECKLIST*

(Note: This Profile addresses quantitation and does not cover visual reads, which would involve additional requirements for the Nuclear Medicine Physician or Radiologist. Certification of the physicians is covered under the Facility Coordinator as an actor.)

| **Section** | **Parameter** | **Conforms (Y/N)** | **Requirement (Physician)** | **Inclusion notes** |
|---|---|---|---|---|
| 3.3.3.1.2 | Administered amyloid radiotracer Activity | | Qualified health professional shall assay the pre-injection activity, record time of assay, inject quantity per protocol and record time of injection, assay residual activity after injection and record time of measurement | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.3.3.1.3 | Amyloid radiotracer administration | | Shall administer tracer intravenously through indwelling catheter (24 gauge or larger), with 3-way valve system attached to allow at least 10 cc normal saline flush after injection | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.3.3.1.3 | Suspected infiltration or extraneous leakage | | Shall record event and expected amount, and image infiltration site | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.4.5 | PET scanner Resolution | | Shall perform and document, on at least an annual basis or during an initial site qualification process, a qualitative resolution QC test by using the manufacturer's settings and verifying resolution of normal gross anatomic features within either a clinical image or representative brain phantom. | □High impact<br>■ Low impact<br>□ Done anyway |

PAT Uniform Phantom Analysis

## 6.11.5 MEDICAL PHYSICIST CHECKLIST

| Section | Parameter | Conforms (Y/N) | Requirement (Physician) | Inclusion notes |
|---|---|---|---|---|
| 3.8.4.4 | Uniformity measurement | | Axial uniformity shall be measured at least monthly 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. Mean axial concentrations in ROIs in the central 80% of planes shall be within ±3% of the overall average for each qualified axial slice within sufficient distance from the axial edge of the field of view (2-4 cm). A method and software such as the PAT Uniformity software available from SNMMI may be used for measurement.<br>Uniformity across planes against a gold standard reference can also be measured using a Hoffman phantom as described in Appendix H. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.4.5 | PET scanner Resolution | | 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. The FWHM resolution of the scanner should be <= 8.0 mm with a preferable target of 4 to 5 mm. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.4.6 | Phantom tests: Frequency of noise measurements | | Shall perform at baseline, quarterly and after scanner upgrades, maintenance or repairs, and new setups. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.8.4.6 | Phantom test: noise measurements | | A uniform cylinder phantom or equivalent shall be filled with an 18-F concentration in the uniform area (approximately 0.1 to 0.2 µC/ml) and scanned using the intended acquisition protocol. Using a rectangular or spherical region as close as possible to, but no smaller than, 3 cm to a side, the COV of the voxel values within the region should be below 15%, for the slices within the central 80% of the axial FOV. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.8.4.7 | Phantom test: gray/white matter ratio measurement | | Using a phantom that contains different regions having uptake ratios between 2:1 and 4:1, measure the high to low ratio and ensure that the ratio is within 10% of specified contrast. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.4.8 | Phantom test: SUVR accuracy | | The quantitative accuracy of the scanner shall be within +-10% of the cross-referenced radionuclide calibrator (when properly calibrated). | ■ High impact<br>□ Low impact<br>□ Done anyway |

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PAT Uniform Phantom Analysis

| Section | Parameter | Conforms (Y/N) | Requirement (Physician) | Inclusion notes |
|---|---|---|---|---|
| 3.8.5.1 | Radionuclide Calibrator Linearity | | Shall evaluate quarterly (or after any radionuclide calibrator event) using either 18F or Tc-99m and should be within ±2.5 % of the true value over an operating range of 37-1110 MBq (1 to 30 mCi) and the true value is determined by a linear fit (to the log data) over the same operating range. Concentric sleeve method is acceptable. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.5.2 | Scales | | Shall evaluate annually or after any repair by qualified personnel. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.8.5.3 | Scanner and site clocks | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |

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### 6.11.6 TECHNOLOGIST CHECKLIST

| Section | Parameter | Conforms (Y/N) | Requirement (Technologist) | Inclusion notes |
|---|---|---|---|---|
| 3.3.3.1.2 | Administered amyloid radio-tracer Activity | | Qualified health professional shall assay the pre-injection activity, record time of assay, inject quantity per protocol and record time of injection, assay residual activity after injection and record time of measurement | □High impact<br>□ Low impact<br>■ Done anyway |
| 3.3.3.1.3 | Amyloid radiotracer administration | | Shall administer tracer intravenously through indwelling catheter (24 gauge or larger), with 3-way valve system attached to allow at least 10 cc normal saline flush after injection | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.3.3.1.3 | Suspected infiltration or extraneous leakage | | Shall record event and expected amount, and image infiltration site | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.1 | Tracer Injection Time | | Shall enter the time of amyloid tracer injection into PET scanner console during the acquisition | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.1 | Tracer Uptake Time | | Shall ensure that the tracer uptake time for the baseline scan is within the acceptable range for the specific radiotracer | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.1 | Tracer Uptake Time | | When repeating a scan on same subject, shall apply the same time interval used at the earlier time point as closely as possible and not more than +/- 5 minutes | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.2 | Subject Positioning | | Shall position the subject according to protocol specifications consistently for all scans, with brain fully in field of view, ideally centered and with bottom of cerebellum at least 2.5 cm away from edge of axial FOV unless otherwise specified by protocol. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.2 | Subject Positioning | | Shall ensure the comfort of the subject in the head holder prior to initiating the scan, to minimize the likelihood of movement. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.2 | Subject Positioning | | Shall instruct the subject to hold as still as possible during the scan. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.2 | Subject Positioning | | Shall document the head position of the subject in the scanner FOV so that this can be replicated for subsequent scans. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.2 | Subject Positioning (non-compliance) | | Shall document issues regarding subject non-compliance with positioning. | ■ High impact<br>□ Low impact<br>□ Done anyway |

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| Section | Parameter | Conforms (Y/N) | Requirement (Technologist) | Inclusion notes |
|---|---|---|---|---|
| 3.4.1.3 | Anatomic Coverage | | Shall perform the scan such that the anatomic coverage (including the entire brain) is acquired in a single bed position according to the protocol specifications and the same for all time points. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.4.1.4.1 | PET acquisition mode | | The key PET acquisition mode parameters (e.g., time per bed position, acquisition mode, etc.) shall be set as specified by study protocol and used consistently for all patient scans. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.4.1.4.1 | PET acquisition mode | | PET shall 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.4.1.4.2 | CT acquisition mode | | 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. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.4.1.4.2 | CT acquisition mode | | 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. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.5.1 | PET image reconstruction | | The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be identical for a given subject across time points. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.1 | PET image reconstruction | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway<br>The part of this that is high impact is the need for consistency, also covered above under PET image reconstruction |
| 3.5.1 | PET image reconstruction | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway<br>The part of this that is high impact is the need for consistency, also covered above under PET image reconstruction |
| 3.5.1 | PET image reconstruction | | 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 < 2.5 mm in the | ■ High impact<br>□ Low impact<br>□ Done anyway<br>Loss of resolution |

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| Section | Parameter | Conforms (Y/N) | Requirement (Technologist) | Inclusion notes |
|---|---|---|---|---|
| | | | z direction (older scanners such as GE Advance may require up to 4.5 mm but are not as recommended). | reduces ability to detect signal change |
| 3.5.1 | Correction factors | | All quantitative corrections shall be applied during the image reconstruction process. These include attenuation, scatter, random, dead-time, and efficiency normalizations. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.2.13.5.2.2.1 | Image orientation | | The raw image will be spatially oriented per study protocol. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.3 | Data archiving: raw images | | The originally reconstructed PET images (image raw data), with attenuation correction, and CT images shall always be archived at the local site. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.8.5.1 | Radionuclide Calibrator Constancy | | Shall evaluate daily (or after any radionuclide calibrator event) using a NIST-traceable (or equivalent) simulated 18F, Cs-137, or Co-57 radionuclide calibrator standard and confirmed that measured activity differs by no greater than ±2.5 % from the expected value. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.8.5.1 | Radionuclide Calibrator Accuracy | | Shall evaluate annually (or after any radionuclide calibrator event) with a NIST-traceable (or equivalent) simulated F-18 radionuclide calibrator standard (use of other long-lived NIST standards are acceptable). Shall confirm that net measured activities differ no greater than ±2.5% from expected value. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.8.5.1 | Radionuclide Calibrator Linearity | | Shall evaluate quarterly (or after any radionuclide calibrator event) using either 18F or Tc-99m and should be within ±2.5 % of the true value over an operating range of 37-1110 MBq (1 to 30 mCi). | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.8.5.1 | PET Radiation Dose | | Shall record the radiation dose from the administered activity. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 3.8.5.2 | Scales | | Shall evaluate annually or after any repair by qualified personnel. | □ High impact<br>■ Low impact<br>□ Done anyway<br>Not required for claim |
| 3.8.5.3 | Scanner and site clocks | | 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.<br>Synchronization of all clocks used in the conduct of the amyloid-PET study shall be checked weekly and | ■ High impact<br>□ Low impact<br>□ Done anyway |

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|---|---|---|---|---|
| | | | after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur) | |
| 4.1 | CT Scanner Calibration | | Follow manufacturer's recommendations. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.1 | PET Scanner Calibration | | 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 | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.1 | Radionuclide calibrator | | Calibrated to 18F using NIST traceable source or equivalent either by site or calibrator manufacturer. | □ High impact<br>□ Low impact<br>■ Done anyway |

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### 6.11.7 IMAGE ANALYST AND WORKSTATION CHECKLIST

**IMAGE ANALYST**

| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 3.5.2.2.1 | Inter timeframe spatial alignment | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.2.2.1 | Action based on inter-timeframe consistency check | | If inter-frame alignment has been performed prior to attenuation correction, frames will be removed if inter-frame translation exceeds a recommended threshold or if inter-frame alignment has not been performed prior to attenuation correction, frames will be removed if inter-frame translation exceeds a recommended threshold. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.2.2.2 | Static Image generation | | Only timeframes identified as appropriately aligned will be included in this image generation. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.5.3 | Data archiving: post-processed images | | 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. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 3.6.2.2 | Image smoothing | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.6.3.1.1 | PET and MRI image fusion | | When coregistering a subject's PET and MRI images, accurate alignment of the images in all planes (transaxial, coronal, sagittal) will be verified. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.6.3.1.2 | Co-registration of longitudinal scans | | When coregistering a subject's longitudinal PET images, accurate alignment of the images in all directions (transaxial, coronal, sagittal) will be verified. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.6.3.2.1 | Target Region Definition | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 3.6.3.2.2 | Reference Region Definition | | The reference region definition will conform to protocol by including the specified tissue. | ■ High impact<br>□ Low impact<br>□ Done anyway |

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| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| | | | Quality control measures will be applied to ensure that longitudinal change is not attributable to technical noise or artifact in a particular reference region. | |
| 3.6.3.2.3 | Region placement | | The placement of all regions of interest and reference region(s) will be verified to be on the correct tissue | ■ High impact □ Low impact □ Done anyway |
| 3.6.3.2.3 | Region placement | | All regions will be checked to ensure that boundaries do not include empty space (scan truncation). Regions will be adjusted using a consistent approach, such as automated exclusion of voxels, with a sub-threshold value, to exclude voxels where tissue is missing. | ■ High impact □ Low impact □ Done anyway |
| 3.6.3.2.3 | Region placement | | The same portion of tissue will be measured between longitudinal scans for the same subject. | ■ High impact □ Low impact □ Done anyway |
| 4.4 | Image analysis workstation performance evaluation | | 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. | ■ High impact □ Low impact □ Done anyway |
| 4.4 | Image analysis workstation repeatability | | 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. | ■ High impact □ Low impact □ Done anyway |

## IMAGE POST PROCESSING WORKSTATION

| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.4 | Metadata | | 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. | □ High impact □ Low impact ■ Done anyway |
| 4.4 | Metadata | | Shall be able to display all information that affects SUVRs either directly in calculation (e.g., region of interest intensity) or indirectly (image acquisition parameters). | ■ High impact □ Low impact □ Done anyway |
| 4.4 | Image acquisition | | 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 | ■ High impact □ Low impact □ Done anyway |



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| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| | | | timeframe in cases where the image consists of multiple timeframes. | |
| 4.4 | Decay correction | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Image orientation | | Shall allow user to orient image per protocol in x, y, and z directions. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Intra-scan, inter-frame alignment | | Shall be able to automatically spatially align the different timeframes that may have been acquired | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Intra-scan, inter-frame alignment | | Shall allow selection of an anchor frame to which other frames are aligned | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Intra-scan, inter-frame alignment | | Shall measure and display the translational and rotational parameters necessary to align each frame to the reference frame. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Static image creation | | Shall allow exclusion of one or more frames from the static image that is created through frame averaging or summation | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Static image creation | | Shall be able to sum and/or average the selected timeframes to create a static image for analysis | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Smoothing | | Shall be able to apply a 3D smoothing filter if indicated as part of study protocol | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.4 | Data storage and transfer | | Shall be able to store images after each major step of image manipulation (e.g., after frame summation) | □ High impact<br>□ Low impact<br>■ Done anyway |

## IMAGE ANALYSIS WORKSTATION

| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.4 | Performance Evaluation | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |



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| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.4 | Repeatability | | Shall be validated to achieve repeatability with a within-subject CV of less than or equal to 2.6%. See Appendix F. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Linearity | | Shall be validated to achieve:<br>• slope $(\hat{A}_1)$ between 0.95 and 1.05<br>• R-squared ($R^2$) >0.90<br>See Appendix F. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Image Quality control: Visual inspection | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Spatial mapping: Image fusion (co-registration) | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Spatial mapping: Co-registration between visits | | Shall be able to automatically and accurately spatially align multiple PET visits to one another when this approach is implemented. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Spatial Mapping: warp to template | | Shall be able to automatically and accurately spatially map the subject's scan and template to each other when this approach is implemented. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Target and reference region definition | | 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). | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | SUVR image creation | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Region placement | | Shall be able to apply (place for measurement) pre-specified regions of interest onto the PET scan in an anatomically accurate manner. | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Region placement quality control | | 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) | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | Region of interest measurement | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |

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| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.4 | SUVR calculation | | 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). | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.4 | SUVR output | | 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. | ■ High impact<br>□ Low impact<br>□ Done anyway |

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### 6.11.8 ACQUISITION DEVICE AND RECONSTRUCTION SOFTWARE CHECKLIST

Notes:

- Requirements pertaining to acceptance of data in DICOM fields should be standard with DICOM conformant scanners. A more efficient approach to verifying those line items may be to confirm that the scanner used at the site is among an acceptable list of manufacturers and models.
- The ability to accept information into DICOM headers does not preclude errors made during entry, and Quality control should be implemented through personnel, study protocol, and use of transmittal forms where applicable.
- Similarly, the reconstruction capabilities could be covered using a list of acceptable operating software and version numbers.
- Since this Profile makes use of SUVR and DVR, height and weight are not relevant unless to detect cases where injected dose compared to weight or body mass is out of expected range.

| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.2 | PET Scanner: calibration | | Shall be able to be calibrated according to the specifications in section 3.8.4 | ■ High impact<br>□ Low impact<br>□ Done anyway |
| 4.2 | PET scanner: Weight | | 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. | □ High impact<br>□ Low impact<br>■ Done anyway<br><br>Not required for claim |
| 4.2 | PET scanner: Height | | Shall be able to record patient height in feet/inches or cm/m as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard. | □ High impact<br>□Low impact<br>■ Done anyway<br><br>Not required for claim |
| 4.2 | PET scanner: Administered Radionuclide | | 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.<br>Shall be able to enter the radionuclide type (i.e., F-18) by operator entry into the scanner interface.<br>Shall be recorded in Radionuclide Code Sequence (0054,0300) in the DICOM image header (e.g., (C-111A1, SRT, “$^{18}$Fluorine”)). | □ High impact<br>□ Low impact<br>■ Done anyway<br><br>Impacts decay correction; impact lowered for SUVR due to ratio |

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| Section | Parameter | Conforms (Y/N) | Requirement (Image Analyst) | Inclusion notes |
|---|---|---|---|---|
| 4.2 | PET scanner: Administered Radiotracer | | 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"). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Administered Radiotracer radioactivity | | 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. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Administered Radiotracer Time | | 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). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Decay Correction Methodology | | 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.<br>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). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Scanning Workflow | | Shall be able to support Profile Protocol (Section 3) PET and CT order(s) of acquisition.<br>Shall be able to pre-define and save (by imaging site) a Profile acquisition Protocol for patient acquisition. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 4.2 | PET scanner: CT Acquisition Parameters | | Shall record all key acquisition parameters in the CT image header, using standard DICOM fields. Includes but not limited to: Actual Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation Time, Exposure and Slice Width in the DICOM image header. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: PET-CT Alignment | | Shall be able to align PET and CT images within ±2 mm in any direction. | ■ High impact<br>□ Low impact<br>□ Done anyway<br>In all but the newest scanners |

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| | | | | this is a manual operation and not frame by frame. |
| 4.2 | PET scanner: CT Absorbed Radiation Dose | | Shall record the absorbed dose (CTDI, DLP) in a DICOM Radiation Dose Structured Report. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Activity Concentration in the Reconstructed Images | | 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). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: Tracer Uptake Time | | 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). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: PET Voxel size | | See Section 4.3 (PET Voxel size) under the Reconstruction Software specification requirements. | □ High impact<br>□ Low impact<br>■ Done anyway<br>This is simply a reference to another section. |
| 4.2 | PET scanner: CT Voxel size | | Shall be no greater than the reconstructed PET voxel size.<br>Voxels shall be square, although are not required to be isotropic in the Z (head-foot) axis.<br>Not required to be the same as the reconstructed PET voxel size. | □ High impact<br>■ Low impact<br>□ Done anyway |
| 4.2 | PET scanner: Subject Positioning | | 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). | □ High impact<br>■ Low impact<br>□ Done anyway |
| 4.2 | PET scanner: Documentation of Exam Specification | | 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). | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: DICOM Compliance | | All image data and scan parameters shall be transferable using appropriate DICOM fields according to the DICOM conformance statement for the PET scanner. | □ High impact<br>□ Low impact<br>■ Done anyway |

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| 4.2 | PET scanner: DICOM Data transfer and storage format | | 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.<br>PET images shall be transferred and stored without any form of lossy compression. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.2 | PET scanner: DICOM Editing | | Shall be able to edit all fields relevant for SUV calculation before image distribution from scanner.<br>Shall provide appropriate warnings if overriding of the current values is initiated. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Metadata | | Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Reconstruction section. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Data Corrections | | PET emission data must be able to be corrected for geometrical response and detector efficiency, system dead time, random coincidences, scatter and attenuation. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Reconstruction Methodology | | Shall be able to provide iterative and/or analytical (e.g., filtered back projection) reconstruction algorithms. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Methodology / Output | | Shall be able to perform reconstructions with and without attenuation correction. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Data Reconstruction 2D/3D Compatibility | | Shall be able to perform reconstruction of data acquired in 3D mode using 3D image reconstruction algorithms.<br>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. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Quantitative calibration | | Shall apply appropriate quantitative calibration factors such that all images have units of activity concentration, e.g., kBq/mL. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Voxel size | | Shall allow the user to define the image voxel size by adjusting the matrix dimensions and/or diameter of the reconstruction field-of-view. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Voxel size | | 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 | □ High impact<br>□ Low impact<br>■ Done anyway |



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| | | | 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. | |
| 4.3 | Reconstruction Software: Reconstruction parameters | | Shall allow the user to control image noise and spatial resolution by adjusting reconstruction parameters, e.g., number of iterations, post-reconstruction filters. | □ High impact<br>□ Low impact<br>■ Done anyway |
| 4.3 | Reconstruction Software: Reconstruction protocols | | Shall allow a set of reconstruction parameters to be saved and automatically applied (without manual intervention) to future studies as needed. | □ High impact<br>□ Low impact<br>■ Done anyway |

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