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

5   Version DRAFT

6   ~~10Nov2016~~10Feb2017

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47 ## Open Issues:

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

51

52

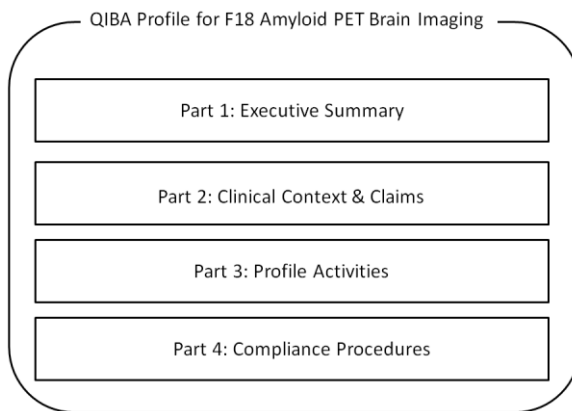| Claim Context |
| --- |
| If and how to address concern that large (>8% change in ~~SUVr~~ SUVR across time) may be accounted for by biologic change unrelated to amyloid deposition difference alone. |
| **Conformance Methodology** |
| The methodology to perform conformance testing of the image analysis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

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1. Executive Summary

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

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

68
69 Figure 1: Illustration of the Profile components

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

Summary for Clinical Trial Use

76 The QIBA Amyloid-PET Profile defines the technical and behavioral performance levels and quality control
77 specifications for brain amyloid tracer PET scans used in single- and multi-center clinical trials of neurologic
78 disease, primarily dementia. While the emphasis is on clinical trials, this process is also intended to apply
79 for clinical practice. The specific claims for accuracy are detailed below in the Claims.

80 The aim of the QIBA Profile specifications is to minimize intra- and inter-subject, intra- and inter-platform,
81 and inter-institutional variability of quantitative scan data due to factors other than the intervention under

82   investigation. ==PET studies using an amyloid tracer, performed according to the technical specifications of==
83   ==this QIBA Profile provides qualitative and/or quantitative data for multi-time point comparative==
84   ==assessments (e.g., response assessment, investigation of predictive and/or prognostic biomarkers of==
85   ==treatment efficacy). While the Profile details also apply to studies assessing subjects at a single time point, a==
86   ==cross-sectional Claim is not currently included in this Profile.==

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

91   The intended audiences of this document include:

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

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

2. Clinical Context and Claims

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

Utilities and Endpoints for Clinical Utility

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

119   This QIBA Profile specifically addresses the requirements for measurement of 18F- amyloid tracer uptake
120   with PET as an imaging biomarker for assessing the within subject change in brain amyloid burden over

121 time (longitudinal Claim) to inform the assessment of disease status or possibly to evaluate therapeutic
122 drug response. Quantitative assessment of amyloid burden at a single time point (cross sectional or bias
123 Claim) is not part of the current Profile.

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

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

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

133

Claim:

135 If Profile criteria are met, then:

136 Claim 1: A measured change in SUVR of Δ % indicates that a true change has occurred if Δ > 8 %, with 95%
137 confidence.

138 Claim 2: If Y1 and Y2 are the SUVR measurements at two time points, then the 95% confidence interval for
139 the true change is (Y2-Y1) ± 1.96 × √([Y1 ×0.~~043~~029]^2+[Y2 ×0.~~043~~029]^2).

140 ~~While the~~This Profile's ~~claim~~ Claims ~~has~~ have been informed by an extensive review of the literature (See
141 Appendix B), including a meta-analysis that was performed as part of the groundwork effort; however, it is
142 currently a consensus claim that has not yet been substantiated by studies that strictly conform to the
143 specifications ~~given here~~in this document. The Committee recognizes on the one hand that the threshold
144 change metric (8%) cited in the Claim uses a repeatability coefficient (RC) at the lower end of the range
145 identified by the meta-analysis, this threshold change metric may not be as robust as it may need to be in
146 order to be relevant for the assessment of biologic change or a modification of biologic change with a
147 therapeutic intervention. Despite these limitations, it is the Committee's opinion that by sharing the
148 outlined performance requirements contained herein, the community of professionals using amyloid
149 imaging in both clinical trials and clinical practice will be able to obtain more robust data which can then
150 refine the Claim thresholds.

151 The following important considerations are noted:

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

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

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

161   met.

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

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

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

168   7. In this Profile, SUVR will be measured using SUVmean of the target regions of interest normalized to that
169   of a reference region. SUV is a simplified metric representing the radiotracer uptake at a prescribed uptake
170   time interval post injection. SUV is a composite signal consisting of contributions from radioactivity present
171   in tissue arising from tracer signal in blood (typically 3-8% of tissue consists of blood volume), the tracer
172   free, non-specifically and/or non-selectively bound in tissue and the tracer specifically bound to a target of
173   interest, in this case amyloid (Gunn RN et al. JCBFM. 2001 Jun;21(6):635-52, Innis et al, JCBFM. 2007
174   Sep;27(9):1533-9, Schmidt KC[1], Turkheimer FE, Q J Nucl Med. 2002 Mar;46(1):70-85.) . By normalising SUV
175   to that of a reference region a simplified metric for the distribution volume ratio (DVR) is derived
176   attempting to cancel or compensate for the contributions from the free and non-specifically bound tracer
177   in tissue. However, the absolute signals and relative contributions arising from the various compartments
178   are uptake time dependent as a result of differences in perfusion and non-specific and specific binding
179   across the brain. In particular, it should be noted that perfusion does not only determine the wash-in
180   (delivery) of the tracer, but also the wash-out of the tracer. Moreover, the wash-out is affected by the
181   relative contributions of non-specific and specific binding as well, i.e., more 'binding slows down' wash-out.
182   The latter also explaining the upward bias seen in SUVR compared with DVR (van Berckel et al, J Nucl Med.
183   2013 Sep;54(9):1570-6). A detailed discussion on the various sources of bias when using the simplified
184   reference tissue model (and SUVR) can be found in (Salinas et al. JCBFM Feb;35(2):304-11, 2015). From the
185   fundamental kinetic properties of radiotracers it can be understood that both SUV and SUVR (as surrogate
186   for DVR) are perfusion dependent and that changes in perfusion across the brain as well as longitudinally
187   will result in changes in SUVR. Consequently, changes in SUVR may not represent only a change in specific
188   signal (amyloid) but could, at least in part, be the result of changes or variability in perfusion (van Berckel et
189   al, J Nucl Med. 2013 Sep;54(9):1570-6). Whether or not a change in SUVR is affected by changes in amyloid
190   and/or perfusion ideally should be first demonstrated in a small cohort before SUVR is used in the larger
191   clinical trial. At the very least these validation studies should be performed to assess the minimally required
192   decrease in SUVR that is needed in order to rule out false positive findings because of (disease and/or drug
193   related) perfusion effects.

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

199

3. Profile Activities

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

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

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

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

The imaging steps corresponding to Figure 1 are:

1) Patients or subjects are prepared for scanning. The amyloid tracer is administered. Patient waits for bio-distribution and uptake of amyloid tracer. See Section 3.1.3.1.2 for ligand-specified timing.

2) Emission and transmission data are acquired (typically the PET scan and CT scan if a PET-CT scanner).

3) Data correction terms are estimated and the attenuation and scatter corrected images are

224   reconstructed.

225   4) Images are reviewed for qualitative interpretation.

226   5) Quantitative (and/or semi-quantitative) measurements are performed.

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

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

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

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

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

3.1. Subject Handling

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

3.1.1 Subject Selection and Timing

242 The utility of correlative anatomic brain imaging, CT or MRI, can be viewed in two different contexts. From
243 a clinical perspective, the anatomic imaging study is used to assess for evidence of bleed, infection,
244 infarction, or other focal lesions (e.g., in the evaluation of subjects with dementia, the identification of
245 multiple lacunar infarcts or lacunar infarcts in a critical memory structure may be important). From the
246 perspective of establishing performance requirements for quantitative amyloid PET imaging, the purpose of
247 anatomic imaging (separate from the utility of providing an attenuation correction map) is to provide
248 assessment of cortical atrophy and consequently a falsely decreased SUVR. The image analyst should also
249 be aware of the possibility of falsely increased SUVR due to blood-brain barrier (BBB) breakdown, such as in
250 the case of intracranial bleed. The effect of differential BBB integrity inter-time point is currently not
251 quantified in the scientific literature. While the performance of anatomic imaging is not a performance

252 requirement of the Profile, the value of performing such imaging and the incorporation of its analysis with
253 the amyloid PET findings may provide additional value in the interpretation for an individual subject. This
254 should be considered in the design and implementation of the study protocol.

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

3.1.1.1 Timing of Imaging Test Relative to Intervention Activity

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

3.1.1.2. Timing Relative to Confounding Activities

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

3.1.1.3. Timing Relative to Ancillary Testing

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

3.1.2 Subject Preparation

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

3.1.2.1. Prior to Arrival

282 There are no dietary or hydration requirements or exclusions.

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

3.1.2.2. Upon Arrival

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

3.1.2.3 Preparation for Exam

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

- <mark>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.</mark>

- The waiting and preparation rooms should be relaxing and warm (> 75° F or 22° C) during the entire uptake period (and for as long as reasonably practicable prior to injection, at least 15 minutes is suggested as acceptable). Blankets should be provided if necessary.

- The subject should remain recumbent or may be comfortably seated;

- After amyloid tracer injection, the subject may use the toilet. The subject should void immediately (within 5 – 10 minutes) prior to the PET image acquisition phase of the examination.

- <mark>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.</mark>

- The amount of fluid intake and use of all medications (e.g., diuretic, sedative) must be documented on the appropriate case report form.

- The subject should remove any bulky items from their pockets such as billfolds, keys, etc. In addition, they should remove eyeglasses, earrings and hair clips/combs (and anything that could cause discomfort while the head is resting in the head holder) if present. They should also remove hearing aids if possible although it is important that they ~~be able to~~can follow instruction (and hear them if necessary) to remain still while in the scanner.

3.1.3. Imaging-related Substance Preparation and Administration

3.1.3.1. Radiotracer Preparation and Administration

3.1.3.1.1 Radiotracer Description and Purpose

The specific amyloid radiotracer being administered should be of high quality and purity. For example, the amyloid seeking radiopharmaceutical must be produced under Current Good Manufacturing Practice as specified by the FDA, EU, European Pharmacopeia or ~~other~~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.

<mark>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}.</mark>

326 3.1.3.1.2 Radiotracer Activity Calculation and/or Schedule

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

336

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

337

338

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

Parameter	Entity/Actor	Specification
		All data should be entered into the common data format mechanism (Appendix E).

339 3.1.3.1.3 Radiotracer Administration Route

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

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

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

350 3.2. Image Data Acquisition

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

359 dedicated PET scanner.

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

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

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

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

370 • CT Scout (i.e., topogram or scanogram etc.), followed by the following two acquisitions, in either
371   order (ensuring that the same sequence is performed for a given subject across time points):

372 • CT (non-contrast) for anatomic localization and attenuation correction and

373 • PET Emission scan acquisition

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

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

3.2.1 Imaging Procedure

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

3.2.1.1 Timing of Image Data Acquisition

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

393

Parameter	Florbetapir (Amyvid) [1]	Flutemetamol (Vizamyl) [2]	Florbetaben (Neuraceq) [3]	NAV4694
Tracer Uptake Time	30 – 50 mpi	90 - mpi	45 - 130 mpi	50 – 70 mpi

(mpi = mins post injxn)				
Duration of Imaging Acquisition	10 min	20 min	15 – 20 min	20 min

394

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

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

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

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

410 The following sections describe the imaging procedure.

411 **3.2.1.2 Subject Positioning**

412 Proper and consistent subject head positioning is critically important for amyloid PET imaging. It is
413 important to take the time necessary to ensure not only that the subject is properly positioned but can
414 comfortably maintain that position throughout the duration of the scanning session. Excessive motion and
415 in particular a difference in the subjects' position between the emission scan and the transmission scan
416 used for attenuation correction is the single most common cause of failed studies.

417 NOTE: The successful implementation of strategies to minimize head motion (and maximize signal to noise)
418 is critical to overall conformance to the Profile requirements. This can be addressed both at the time of
419 image acquisition (through the use of head immobilization techniques described in the paragraphs
420 immediately below) and at the time of image acquisition set-up and reconstruction, described in Section
421 3.3.2.2.1.

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

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

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

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

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

439

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

440

Parameter	Entity/Actor	Specification
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).

441

442

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

443

444 **3.2.1.3 Scanning Coverage and Direction**

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

446   the cerebellum. The anatomic coverage should be included in a single bed position.

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

447

3.2.1.4 Scanner Acquisition Mode Parameters

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

454   *PET Acquisition*

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

459

Parameter	Entity/Actor	Specification
PET acquisition mode	Study Sponsor	The key <mark>3-D</mark> PET acquisition mode parameters (e.g., time per bed position, acquisition mode, etc.) <u>shall be specified</u> in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key acquisition mode parameters shall be specified according to pre-determined harmonization parameters.
PET acquisition mode	Technologist	The key PET acquisition mode parameters (e.g., time per bed position, acquisition mode, etc.) <u>shall be set as specified</u> by study protocol and used consistently for all patient scans.
		PET should be acquired in listmode format (best) or dynamic time frames of no more than 5 minutes each.

460

461   *CT Acquisition*

462   For the CT acquisition component of the PET/CT scan, this Profile only addresses the aspects related to the
463   quantitative accuracy of the PET image. In other words, aspects of CT diagnostic accuracy are not addressed
464   in this Profile. In principle, any CT technique (parameters include kVp, mAs, pitch, and collimation) will

465 suffice for accurate corrections for attenuation and scatter. However, it has been shown that for estimating
466 PET tracer uptake in bone, lower kVp CT acquisitions can be more biased. Thus higher kVp (greater than or
467 equal to 80kVp100 kVp) CT acquisitions are recommended in general (Abella et al). In addition, if there is
468 the potential for artifacts in the CT image due to the choice of acquisition parameters (e.g., truncation of
469 the CT field of view), then these parameters should be selected appropriately to minimize propagation of
470 artifacts into the PET image through CT-based attenuation and scatter correction.

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

478

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

479

480

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

Parameter	Entity/Actor	Specification
Dose Exposure		lowest radiation dose necessary to achieve the diagnostic objective.

481

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

489 3.3. Imaging Data Reconstruction and Post-Processing

490 3.3.1 Imaging Data Reconstruction

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

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

503

Parameter	Entity/Actor	Specification
PET image reconstruction	Study Sponsor	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key PET image reconstruction parameters shall be specified according to pre-determined harmonization parameters.
PET image reconstruction	Technologist	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be identical for a given subject across time points.
PET image reconstruction	Technologist	If available, any reconstruction algorithm that uses point spread function (PSF) modeling should NOT be used.

PET image reconstruction	Technologist	If available, the time of flight (TOF) option can be used; <mark>the use or non-use of TOF must be consistent for a given subject across time points.</mark>
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 <mark>$\leq$ 2.5 mm in the x and y dimensions and $\leq$ 3 mm in the z dimension</mark>. The final size shall not be achieved by re-binning, etc., of the reconstructed images.
Correction factors	Technologist	All quantitative corrections shall be applied during the image reconstruction process. These include attenuation, scatter, random, dead-time, and efficiency normalizations. However, no partial volume correction should be performed.
Calibration factors	Scanner	All necessary calibration factors needed to output PET images in units of Bq/ml shall be automatically applied during the image reconstruction process.

504

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

509 3.3.2 Image Data Post-processing

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

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

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

522 3.3.2.1 **Ensure image orientation**

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

528

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

529

3.3.2.2   Create Static Image

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

541

3.3.2.2.1   Intra-scan inter-timeframe assessment and alignment

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

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

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

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

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

587

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

588

589 **3.3.2.2.2   Combine discrete timeframes**

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

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

599

3.3.3 Imaging Data Storage and Transfer

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

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

612 **Post-processed image data** are images that have been transformed after reconstruction in some manner.
613 This is typically a stack of DICOM slices/files constituting a PET image volume that can still be analyzed on
614 one or more of the following: PET scanner console, PET image display workstation, PACS system, etc.
615 For archiving at the local site or imaging core lab (if relevant), the most important data are the original
616 images, i.e. the image raw data. In the unlikely event that the scanner raw data (which should be archived
617 by the local site) is required for later reprocessing; this should be made clear in the protocol.
618

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

Parameter	Entity/Actor	Specification
Data archiving: post-processed images	Image analyst	If a static image has been generated by aligning frames and summing or averaging discrete timeframes, or through other parametric image generation, the image will be archived at the site where the static image generation occurred.

619

3.4. Image Analysis

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

3.4.1 Input Data

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

3.4.2 Image Quality Control and Preparation

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

640

641 **3.4.2.1 Correction for Partial Volume Effects**

642 Partial Volume Effects Correction (PVEc) is NOT recommended as a "by default" step in this Profile due to
643 the fact that the process itself can introduce a great deal of variability, countering the tolerance goals of the
644 Profile. However, we discuss this step here, as it may be included in certain study protocols particularly if
645 methodology is systematically employed that does not increase variability. As background on this topic, due
646 to the limits of PET scanner resolution, the signal measured at the borders of white and gray tissue, or
647 tissue and cerebrospinal fluid (CSF) can contain contributions from both types of tissue within the
648 boundaries of the same voxel. In particular, some amyloid PET tracers have high levels of nonspecific white
649 matter uptake, producing high signal intensity that "spills into" neighboring gray tissue measures. In
650 addition, neurodegenerative patients may exhibit substantial, progressive atrophy, increasing spill-in from
651 CSF that can dilute increases or accentuate decreases originating from the atrophic tissue elements.
652 Several different mathematical algorithms and approaches have been developed to correct or compensate

653 for PVE and tissue atrophy. However, these approaches are not necessarily sensible in the setting of
654 amyloid imaging and quantification. Simply applying correction for the loss of cerebral gray matter results
655 in upscaling of image signal intensity, and is most appropriate when the tissue origin of the signal is lost,
656 resulting in the atrophy (ex loss of synaptic neuropil in FDG cerebral glucose metabolism imaging). In the
657 case of amyloid deposits in neurodegenerative dementia, however, the deposits are not contained with
658 normal cerebral gray matter elements; amyloid plaques are extracellular accumulations and are unlikely to
659 degenerate as gray matter atrophies due to losses of synapses and neurons ensues. Thus, applying gray
660 matter atrophy-correction PVEc may inappropriately "upscale" the amyloid signal from atrophic cortical
661 regions. Usual PVEc approaches result in a new image, typically containing only gray matter, and has been
662 shown to increase the apparent amyloid in AD patients by as much as 30% to 56%. The most sensible
663 approach to PVEc in amyloid images is to apply correction for spillover from subcortical white matter into
664 the gray matter regions, which is likely to become increasingly problematic as the cortical gray matter
665 becomes atrophic. Appropriate use of PVEc can potentially help to increase sensitivity to longitudinal
666 change, and to reduce error associated with changes in atrophy or white matter uptake. However, PVEc
667 methods can also introduce variability, and results are highly sensitive to subjective selections of the
668 parameters used in calculating the correction. Effects upon measurement of longitudinal change have
669 varied from no effect to an increase in measured change. The tradeoff between benefit vs. these
670 considerations must be considered and the decision as to whether or not to use may be study dependent.
671 The point in the process at which PVE correction is applied may vary, for example either applied to spatially
672 normalized images or to native images, prior to or after the creation of a SUVR image.

673 **3.4.2.2 Image Smoothing**

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

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

686

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.

687

3.4.3 Methods to Be Used

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

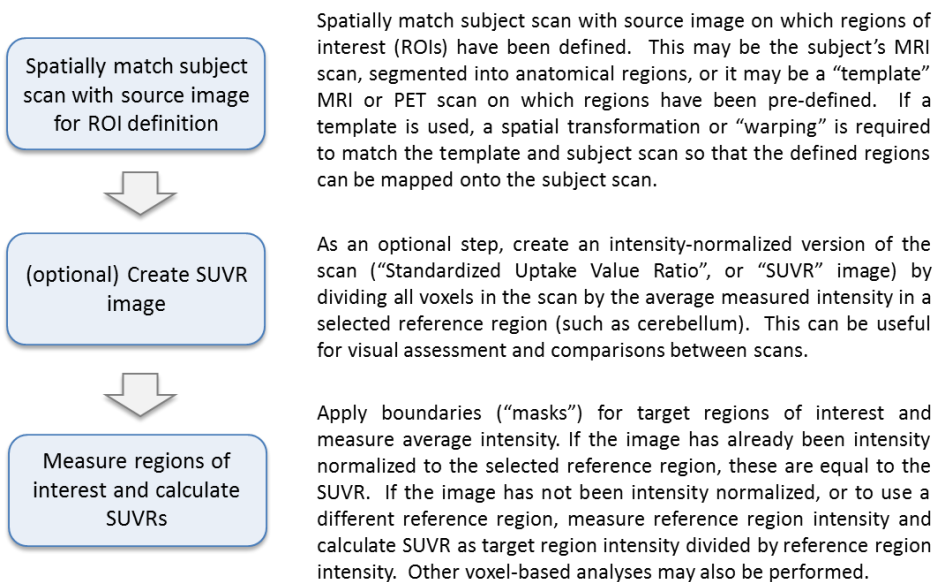| Spatially match subject scan with source image for ROI definition	Spatially match subject scan with source image on which regions of interest (ROIs) have been defined. This may be the subject's MRI scan, segmented into anatomical regions, or it may be a "template" MRI or PET scan on which regions have been pre-defined. If a template is used, a spatial transformation or "warping" is required to match the template and subject scan so that the defined regions can be mapped onto the subject scan.
(optional) Create SUVR image	As an optional step, create an intensity-normalized version of the scan ("Standardized Uptake Value Ratio", or "SUVR" image) by dividing all voxels in the scan by the average measured intensity in a selected reference region (such as cerebellum). This can be useful for visual assessment and comparisons between scans.
Measure regions of interest and calculate SUVRs	Apply boundaries ("masks") for target regions of interest and measure average intensity. If the image has already been intensity normalized to the selected reference region, these are equal to the SUVR. If the image has not been intensity normalized, or to use a different reference region, measure reference region intensity and calculate SUVR as target region intensity divided by reference region intensity. Other voxel-based analyses may also be performed.

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

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

3.4.3.1 Spatially Match Subject and Template

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

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

3.4.3.1.1   "Fuse" MRI and PET images

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

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

Parameter	Entity/Actor	Specification

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

747

3.4.3.1.2 Longitudinal PET co-registration

748

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

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

759

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.

760

3.4.3.1.3 Spatial Mapping of Subject Image and Template Image

761

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

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

774 When an MRI is not available, the subject PET scan can be transformed directly to the template PET. Since
775 the signal within gray matter and the intensity contrast between gray and white matter in a negative
776 amyloid scan are substantially different than those in an amyloid positive scan, images at the extremes of
777 positive and negative may not spatially normalize well. To address this, various approaches have been
778 developed that test the fit to a series of templates (Lundqvist et al, 2013), selecting the best fit. Other

779 confounds in PET-based spatial normalization can occur when the amyloid PET image has high intensity
780 signal in portions of dura or skull, or missing (truncated) tissue at the top or bottom of the brain. Various
781 additional steps have been employed to address these issues.

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

787

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.

788 **3.4.3.2 VOI Placement: Target / Reference**

789 **3.4.3.2.1   Determine Target Regions for Measurement**

790 The selection and delineation of target regions for amyloid measurement vary depending upon study
791 objectives and should be specified in the protocol. For clinical application, some manufacturers have
792 specified predefined VOIs associated with a threshold SUVR that they have correlated to autopsy data.
793 Some clinical trials have used a cortical average consisting of 4 – 6 regions, with individual regional amyloid
794 measures providing further information. When "emerging" subjects with amyloid levels nearer to threshold
795 are studied in clinical trials, analysis of specific sub-regions may become important.
796

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

801 • *Region Boundaries:* Some approaches use the entire anatomical region, whereas others define a sub-
802   region empirically determined to accumulate greatest amyloid burden.

803 • *Method to match the region to subject's anatomy:* Some methods apply a standard atlas of region
804   definitions (pre-defined anatomical boundaries based upon reference brains), and rely upon the
805   transformation between the subject's morphology and the atlas template to match the atlas regions to
806   the subject. These may be referred to as "probabilistic" regions. Other approaches estimate anatomical
807   boundaries based upon the individual subject's MRI, incorporating atlas reference information in a
808   more complex way (e.g., Freesurfer).

809 • *Region confinement to gray tissue:* When atlas based regions are applied, these may or may not be
810   thresholded (restricted) using the gray tissue segment from the subject's MRI. This masking can help to
811   assure alignment between template regions and the subject's actual morphology, and can be done
812   using either native space images or warped images.

813 • *Region erosion from surrounding tissue or CSF:* VOI boundaries may be eroded (e.g., perimeter reduced

814   by one to two voxels) away from the neighboring CSF and white tissues, in order to reduce atrophy
815   effects and spillover from non-gray tissue types. This is most often applied to probabilistic regions that
816   tend to be larger and incorporate tissue adjacent to gray matter.

817   • *"Native space" vs. "Template space":* VOIs may be defined only in template space, for measuring the
818   subject's warped scan, or may be transformed to the subject's native scan. Use of the native scan can
819   reduce interpolation and signal changes arising from stretching or compressing subject anatomy.
820

821   Comparisons of different approaches to regional definition, including whether native vs. template scans are
822   used, have yielded high correlation coefficients (Landau et al, 2013). However, it is important to note that
823   <u>measurement of different portions of tissue will give different results</u>. It is therefore important that the
824   same tissue definition be applied across scans and across subjects within a study.
825

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.

826

827   ### 3.4.3.2.2   Determine Reference Region

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

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

840   The cerebellar cortex (gray matter) has been a reference region of choice in numerous studies of amyloid
841   since it typically does not accumulate fibrillar amyloid and because its gray tissue kinetics are assumed be
842   reasonably matched to those of gray tissue target regions. Because of its low signal and lack of binding, the
843   cerebellar cortex provides the most sensitive reference for measuring cross sectional differences.
844   However, due to its low signal level, small swings in value will create large swings in calculated SUVR.
845   Further, the physical location of the cerebellum toward the edge of the scanner transaxial field of view
846   makes it susceptible to edge noise, scatter, and tissue exclusion (particularly in scanners with a shorter axial
847   field of view). In head rotation and in emission-transmission scan misalignment, the posterior edge of the
848   cerebellar cortex can be particularly impacted. In addition, slight shifts in position can cause a blending of
849   white and gray tissue that will impact the reference measurement. Further, the cerebellum is located in
850   transaxial slices that are not in proximity to several typical target VOIs, and signal in those slices may not
851   change in the same way due to technical factors. In longitudinal studies, for one radiotracer, the cerebellar
852   cortex has been demonstrated to show stability over time (Villemagne, AAIC 2015) while for others

853 variability with regard to measured change has been shown, decreasing statistical power. Even in cross-
854 sectional measurements, technical noise embedded in the cerebellum (or any reference region) may cause
855 a subject whose amyloid burden is at the threshold of positivity to "tip" in one direction or another. At a
856 minimum, the inferior margin of the cerebellar reference boundaries should not extend to the edge of the
857 FOV, where the greatest technical variability occurs. Alternate reference region comparisons are also
858 recommended to ensure that noise has not driven the SUVR result.

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

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

885

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

886

887 **3.4.3.2.3   Apply Regions to Subject Scans for Measurement**

888 Target VOIs may be applied for measurement either to the non-intensity normalized image, or to an SUVR

889 image that was first generated by dividing each voxel by the average value in the reference region. When
890 placing VOIs, it is critical to ensure accurate fit, and that only appropriate tissue is included. Potential
891 sources of error include the following:
892

893 Differences in tissue composition: Positioning of a cortical VOI toward the edge of gray matter in one scan
894 vs. toward white matter in a second longitudinal scan will introduce measurement error due to the tissue
895 composition and partial volume effects. In cross-sectional measurement, these differences can also be
896 significant for subjects at threshold of positivity.
897

898 Tissue truncation: If the scan does not have a complete cerebellum or other region, and the VOI samples
899 the empty space, a large error can result depending upon proportion of missing tissue for the VOI.
900

901 Differences in tissue sampled: Measuring different portions of tissue (e.g., the full region in one scan vs.
902 only a part of the region due to tissue truncation in the second scan) across longitudinal scans can
903 introduce errors of a few to several percent.
904

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.

905

906 ### 3.4.3.2.4   Generate SUVR Image

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

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

913 ### 3.4.3.3 Create SUVR

914 ### 3.4.3.3.1   Measure Regional Values

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

917 ### 3.4.3.3.2   Calculate SUVR

918 The SUVR is calculated by dividing the VOI value by the reference region value (which will be 1.0 if

919 measured on a SUVR image). If a parametric image was generated using full dynamic scanning, or if a
920 kinetic model is being applied to a multi-timeframe dynamic image, a DVR value is generated instead.

921 ### 3.4.3.3.3   Relating SUVR values to other studies

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

942 ## 3.4.4 Required Characteristics of Resulting Data

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

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

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

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

3.5. Image Interpretation and Reporting

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

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

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

3.6. Quality Control

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

3.6.1 Imaging Facility

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

- Identification of appropriate imaging equipment intended for use in the trial

- Documented performance of required quality control procedures of the scanner and ancillary equipment (e.g., radionuclide calibrator)

- Radiotracer quality control procedures

- Experience of key personnel (technologists, radiologists, physicists and/or other imaging experts)

- Procedures to ensure imaging protocol conformance during the trial

3.6.1.1   Site Accreditation/Qualification Maintenance

Whilst imaging facility accreditation is generally considered to be adequate for routine clinical practice purposes (e.g., ACR, IAC, and TJC), facility qualification (e.g., EARL, SNMMI-CTN, ACRIN, and imaging core labs) -may be required for clinical research/clinical trial participation. In order to be considered to be conformant with this Profile, an imaging scanner/facility must provide documentation of current qualified status. Appropriate forms, checklists or other process documents should be maintained and presented upon request to verify that ongoing quality control procedures are being performed in a timely manner as dictated by specific clinical study requirements. If exceptions to any of the performance standards stated

993 below occur and cannot be remediated on site, the site should promptly communicate the issue to the
994 appropriate internal overseer for advice as to how the irregularity should be managed. In addition to
995 documenting the level of performance required for this Profile (and the level of performance achieved), the
996 frequency of facility accreditation/qualification also needs to be described.

997 It is important to note that that imaging facility Accreditation and/or Qualification, as defined in this Profile,
998 are considered necessary, but are not sufficient for being conformant with this Profile. In order to be
999 conformant with the Profile, and thus to support the claims of the Profile, all normative requirements must
1000 be met.

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

1001 *3.6.2 Imaging Facility Personnel*

1002 For each of the personnel categories described below, there should be training, credentialing, continuing
1003 education and peer review standards defined. Guidelines for training/credentialing for each resource
1004 category are summarized below (UPICT Protocol Section 2.1). Note that only physicians reading the PET/CT
1005 amyloid scans need specific training and certification for PET amyloid interpretation.

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

Parameter	Entity/Actor	Specification
		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.

1006

3.6.3 Amyloid- PET Acquisition Scanner

1007

1008 Amyloid-PET studies as described in this Profile require either a PET/CT scanner or a dedicated PET scanner
1009 with the ability to acquire a transmission image. PET/MR scanners may be added in future versions of this
1010 Profile. The scanners should be identified based on manufacturer, name and model. Hardware
1011 specifications should be documented. Scanner software name and version should be documented at the
1012 time of trial initiation and at the time of any and all updates or upgrades.

1013 The scanner must undergo routine quality assurance and quality control processes (including preventive
1014 maintenance schedules) appropriate for clinical applications, as defined by professional and/or regulatory
1015 agencies. In order to assure adequate quantitative accuracy and precision of imaging results, additional
1016 quality assurance measures are required, as discussed below.

1017 For consistency, clinical trial subjects should be imaged on the same device over the entire course of a
1018 study. A replacement scanner of the same make and model may be used if it is properly qualified. It is
1019 imperative, however, that the trial sponsor be notified of scanner substitution if it occurs.

1020 For clinical trials with quantitative imaging requirements, a subject should have all scans performed on only
1021 one scanner unless quantitative equivalence with a replacement scanner can be clearly demonstrated.
1022 However, it should be noted that there are currently no accepted criteria for demonstrating quantitative
1023 equivalence between scanners. It is anticipated that future version of this Profile will provide such criteria."

1024

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

1025 **3.6.3.1 Ancillary Equipment**

1026 3.6.3.1.1 Radionuclide Calibrator

1027 The following guidelines are collected from ANSI standard N42.13, 2004 and IAEA Technical Report Series
1028 TRS-454. All requirements assume measurements on unit doses of amyloid tracer and that calibration
1029 sources are in the 'syringe' geometry (i.e., no bulk doses).

1030 The Constancy test ensures reproducibility of an activity measurement over a long period of time by
1031 measuring a long-lived source of known activity.

1032 The Accuracy test ensures that the activity values determined by the radionuclide calibrator are correct and
1033 traceable to national or international standards within reported uncertainties.

1034 The Linearity test confirms that, for an individual radionuclide, the same calibration setting can be applied
1035 to obtain the correct activity readout over the range of use for that radionuclide calibrator.

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

1036

1037 3.6.3.1.2 Scales and stadiometers

1038 Scales and stadiometers should be inspected and calibrated at installation and annually.

1039

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

1040

1041   3.6.3.1.4 Clocks and timing devices

1042   The PET and CT scanner computers and all clocks in an imaging facility used to record activity/injection
1043   measurements should be synchronized to standard time reference within +/-1 minute. These include any
1044   clocks or timekeeping systems that are connected with a subject's amyloid-PET study, in particular those
1045   associated with the radionuclide calibrator, the injection room, the scanner, and the acquisition
1046   computer(s). The synchronization of all clocks (to date, time of day and to time zone) should be monitored
1047   periodically as part of ongoing QA program. In particular, clocks should be inspected immediately after
1048   power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur). Correct synchronization
1049   could be achieved using the Consistent Time Integration Profile as defined in the IHE IT Infrastructure
1050   Technical Framework. The Consistent Time Profile requires the use of the Network Time Protocol (NTP)
1051   (www.NTP.org).

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

1052

1053   ## 3.6.4 Phantom Imaging

1054   ### 3.6.4.1 Uniformity and Calibration

1055   Verification of scanner normalization with a uniform phantom is a minimum requirement for all scanners
1056   used in clinical trials including those that only have qualitative endpoints. A Hoffman or equivalent
1057   phantom may be used in place of a uniform phantom to verify scanner normalization via in-plane and axial
1058   comparisons to an analytical gold standard for that phantom over the complete field of view to be used by
1059   the amyloid measurand. For trials with quantitative PET measurements, this assessment should also include
1060   a comparison against a radionuclide calibrator to ensure quantitative accuracy; that is, a comparison of the
1061   absolute activity measured versus the measured amount injected should be performed. This comparison is
1062   particularly important after software or hardware upgrades. If the trial requires absolute quantification in
1063   baseline images or absolute changes in longitudinal studies, it should be considered to include an image
1064   quality and/or contrast recovery QC assessment as part of the routine QC procedures and/or scanner
1065   validation process. Clinical trials using only relative changes in longitudinal studies may not require contrast
1066   recovery assessments provided there is appropriate consideration for the minimum size of target lesions
1067   based on the partial volume effect.

1068 An essential requirement for extracting quantitative data from images is that there be known calibration
1069 accuracy and precision and/or cross calibration of the PET system against the (locally) used radionuclide
1070 calibrator (within 10%). The QC procedures should utilize the same acquisition/reconstruction protocol,
1071 software and settings that are used for the subject scans.

1072

Parameter	Entity/Actor	Specification
Phantom tests: Frequency of uniformity measurements	Imaging Site	Shall perform at baseline, quarterly and after scanner upgrades, maintenance or repairs, and new setups.
Uniformity QC	Technologist	At least quarterly and following software upgrades, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom. 1. Visual check that no streak artifacts or axial plane non-uniformities are present. 2. The standard deviation of a large central 2D ROI shall be compared with similar previous scans to check for measurable differences. 3. The mean values of a large central 2D ROI for all image slices shall be compared with similar previous scans to check for measurable differences.
Phantom tests: transaxial uniformity measurement	Imaging Site	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.
Phantom tests: axial uniformity measurement	Imaging Site	Using uniform cylinder phantom or equivalent shall obtain a slice-to-slice variability of less than 10%.
		Using uniform cylinder phantom or equivalent shall obtain a slice-to-slice variability of less than 5%.
		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.

1073

1074 **3.6.4.2 Resolution**

1075 The assessment of adequate resolution should include both a qualitative evaluation (using clinical or
1076 anthropomorphic phantom images) and quantitative assessment (using phantom-defined criteria).

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

1077

1078 **3.6.4.3 Noise**

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

1079

1080 **3.6.4.3 Amyloid-PET Specific Phantom Measurements**

1081 The above more general phantom evaluations of a PET scanner are needed to qualify it for clinical practice
1082 or a clinical trial. However, more purpose-specific phantoms are also needed to simulate the human brain,
1083 amyloid uptake patterns, and the amyloid SUVR measurand. Purpose-specific phantom options that might
1084 be considered on a per-protocol basis include, but are not limited to:

1085   1. Each site uses a single phantom for the duration of the trial but not necessarily the same model of
1086   phantom used at other sites.

1087   2. All sites use phantoms of the same model for the duration of the trial.

1088   3. All sites use phantoms built to precise specifications for the duration of the trial.

1089   4. All sites share a single phantom for the duration of the trial.

1090 The phantom scans and performance evaluation should be performed prior to the start of a trial and
1091 repeated during the course of the trial as specified by the individual protocol. Any changes to scanner
1092 equipment, either hardware or software, should be immediately reported to the trial sponsor and/or
1093 imaging CRO and may result in the need for re-qualification prior to imaging additional trial subjects. In
1094 particular, it is strongly recommended that subjects in a longitudinal study be scanned on the same PET
1095 system with the same software version whenever possible.

1096 Generally, the purpose-specific phantom scans must provide a metric to characterize these imaging
1097 properties:

1098 - Spatial resolution – PET scanner hardware, reconstruction methods and reconstruction parameter
1099   selections can result in dramatically different spatial resolutions in the reconstructed images.
1100   Because partial volume effects (especially between gray and white matter regions) can bias many
1101   amyloid PET measurands, it is essential to calibrate the spatial resolution of each scanner using the
1102   acquisition and reconstruction protocol planned for patient imaging. A post-reconstruction
1103   smoothing operation can then be applied for calculation of a measurand at a uniform spatial
1104   resolution between scanners.

1105 - Uniformity – In-plane and axial uniformity of the purpose-specific phantom should be within 10%
1106   throughout the scanner field of view to be used in the calculation of the amyloid PET measurand.

1107 - Absence of reconstruction artifacts – Reconstructed purpose-specific phantom data should be
1108   visually free of reconstruction artifacts, such as streaks due to failing detectors or axial plane non-
1109   uniformities due to errors in normalization.

1110 - Qualitative and quantitative accuracy – Measurands using ratios, such as the SUVR must
1111   demonstrate accuracy with 10% of an analytical or otherwise known gold standard.

1112 An anthropomorphic phantom, such as the 3D Hoffman phantom or equivalent, ideally with a spatial
1113 distribution similar to the cortical gray/white matter is required to characterize the five imaging properties
1114 listed above. A uniform phantom or a point source phantom by themselves is not adequate to sufficiently
1115 characterize the amyloid imaging properties of a PET scanner. The phantom should be adequate to model
1116 and characterize effects of attenuation correction and scatter correction. Contrast ratios of amyloid tracer
1117 uptake vary between normal and abnormal subjects, and also between different amyloid tracers. However,
1118 it is recommended that the phantom be filled such that the activity concentration in the highest uptake
1119 regions be similar to the expected white matter uptake in subjects with amyloid deposition. For the
1120 Hoffman phantom, it is recommended that the activity at the start of the scan be 0.5-0.6 mCi (18.5-22.2
1121 MBq) to obtain approximately a 15 kBq/ml activity in the gray matter regions of the phantom. See
1122 Appendix H for best practices guidance for this phantom.

1123 The Hoffman phantom should be centered in the FOV of the PET scanner and data acquired for 20 minutes.
1124 Moreover, image reconstruction methods and settings should equal those specified in the study. The post-
1125 processing and data analysis should be as similar as possible to those used with patient data.

1126 A baseline assessment of the scanner imaging properties is required before any subjects are scanned in the
1127 trial, and after any major hardware of software modifications that could affect these properties. Following
1128 a baseline qualification assessment using the Hoffman phantom, routine manufacturer-recommended QA
1129 procedures (e.g. daily QC checks, quarterly normalization, etc.) using simpler phantoms may be adequate to
1130 demonstrate acceptable scanner performance over the course of a clinical trial. A baseline qualification
1131 assessment is required at least every one year in an extended study.

1132

1133 The normative list below is based on the Hoffman anthropomorphic, NEMA Image Quality, ACR, and
1134 uniform cylinder phantoms as appropriate.

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

1135

1136

1137 **3.6.4.4 Phantom imaging data analysis**

1138 For amyloid-PET image analysis, there are many combinations of hardware and software that are used. The
1139 software alone comprises multiple layers including the operating system, several base modules for input
1140 and display, and the components that draw/calculate ROIs and calculate the SUVR. See Section 4.4 and
1141 Appendix F.

1142

3.6.5 Quality Control of Amyloid-PET studies

3.6.5.1   Data Integrity

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

3.6.5.2   Determination of Image Quality

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

3.6.5.3   Determination of subjects unsuitable for Amyloid-PET analysis

3.6.6 Quality Control of Interpretation

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

4. Conformance Procedures

Relation of this Profile to Expectations for QIBA Profile Conformance

Definitions (from Appendix C):

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

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

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

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

4.1. Performance Assessment: Image Acquisition Site

Typically clinical sites are selected due to their competence in neurology and access to a sufficiently large

1179 subject population under consideration. For imaging sites it is important to have availability of:

1180 • Appropriate imaging equipment and quality control processes,

1181 • Appropriate ancillary equipment and access to radiotracer and contrast material,

1182 • Experienced Technologists (CT and PET trained) for the subject handling and imaging procedure,

1183 • Appropriately trained Radiologists/Nuclear Medicine Physicians for image analysis and diagnostic
1184   interpretation,

1185 • Appropriately trained image analysts, with oversight by a Radiologist or Nuclear Medicine Physician,

1186 • Medical Physics support to ensure appropriate scanner and equipment calibration,

1187 • Processes that assure imaging QIBA Profile-conformant image generation in appropriate time window

1188   A QA/QC program for PET scanners and ancillary devices must be in place to achieve the goals of the
1189   clinical trial. The minimum requirements are specified above. This program shall include (a) elements to
1190   verify that imaging facilities are performing imaging studies correctly and (b) elements to verify that
1191   facility's PET scanners are performing within specified calibration values. These may involve additional
1192   PET and CT phantom testing that address issues relating to both radiation dose and image quality
1193   (which may include issues relating to water calibration, uniformity, noise, spatial resolution – in the
1194   axial plane-, reconstructed slice thickness z-axis resolution, contrast scale, and others) and constancy.
1195   There is agreement that some performance testing (e.g. constancy phantom) adds value; however,
1196   acceptable performance levels, frequency of performance, triggers for action and mitigation strategies
1197   need further definition before these can be required. This phantom testing may be done in addition to
1198   the QA program defined by the device manufacturer as it evaluates performance that is specific to the
1199   goals of the clinical trial.

1200

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

Parameter	Entity/Actor	Specification
Radionuclide calibrator		Calibrated to 18F using NIST traceable source or equivalent.

1201

4.2. Performance Assessment: PET Acquisition Device

1202

1203 Distinct from the performance specifications and frequency of testing described in Section 4.1, which apply
1204 to quality control of the Acquisition Device at the imaging facility, this Section defines performance
1205 specifications of the Acquisition Device to be met upon leaving the manufacturing facility. In order to be in
1206 conformance with this Profile, the Acquisition Device should be held to the same standard whether a
1207 mobile utility or a fixed installation; a mobile scanner may require additional calibration to achieve this
1208 performance.

1209 The PET scanner should use DICOM attributes to follow version numbers of software for: 1 Acquisition, 2
1210 Reconstruction, 3 Post-processing, 4 Display/ROI analysis, 5 Dynamic Analysis. Performance requirements
1211 regarding software version identification, documentation and tracking across time are described in Section
1212 4.5.

1213 The PET scan acquisition start time should be used for the decay reference time and the integral model
1214 should be used for decay correction. The scanner should perform all decay corrections (i.e. not the
1215 operator). Image data are to be given in units Bq/ml. "Derived" images (distinct from "Original") should be
1216 flagged following the DICOM standard and should retain the scan acquisition date and time fields.

1217

1218 All needed information for fully corrected administered activity (e.g., residual activity, injection time,
1219 calibration time) is required. Note that use of the term administered activity below refers to fully corrected
1220 net radioactivity.

1221

1222 Baseline level conformance requires that the DICOM image set from the subject's PET scan and necessary
1223 metadata (that is not currently captured by all PET scanner acquisition processes) is captured in trial
1224 documentation, e.g., case report forms. The metadata is required to perform the quantitative analysis and
1225 perform quality control on SUV covariates. This includes for example, post-injection residual activity and
1226 subject height. This data should be captured in the 'Common Data Format Mechanism' as described in
1227 Appendix E.

1228 The DICOM format used by the PET scanner should meet the Conformance Statement written by
1229 manufacturer of the PET system. PET data shall be encoded in the DICOM PET or Enhanced PET Image
1230 Storage SOP Class, and in activity-concentration units (Bq/ml) with additional parameters in public DICOM
1231 fields to calculate SUVs (e.g., height, weight, scale factors). CT data should be encoded in CT or Enhanced CT
1232 Image Storage SOP Class. DICOM data shall be transferred using the DICOM Part 8 network protocol or as
1233 offline DICOM Part 10 files for media storage including CDs and DVDs. They shall be transferred without any
1234 form of lossy compression.

1235 The meta-information is the information that is separate, or in addition to, the image values (in units of
1236 Bq/ml) that is deemed necessary for quantitatively accurate representation of PET SUVs. The meta-
1237 information may also include other information beyond that need for calculation of SUVs, i.e. the type and
1238 or sequencing of therapy, the blood glucose levels, the scanner SUV stability history, etc. The actual
1239 mechanism of capturing the information is not specified in this Profile. The intent here is to list what

1240 information should be captured rather than the mechanism itself. The mechanism can range from paper
1241 notes, to scanned forms or electronic data records, to direct entry from the measurement equipment into
1242 pre-specified DICOM fields (i.e., from the PET scanner or auxiliary measurement devices such as the
1243 radionuclide calibrator). Ideally all of the specified meta-data will be captured by direct electronic entry to
1244 DICOM fields, after suitable modification of the DICOM format for PET imaging.

1245 In some facility workflows, the Acquisition Device may also provide workstation/analysis tool functionality.
1246 For example, the display of an SUV statistic (considered in Section 4.4.1) or display of Tracer Uptake Time
1247 (considered in Section 4.4), may also apply to the Acquisition Device, if used in this manner.

1248 The concept endorsed here is that the needed meta-data is identified. Through revisions of this Profile, the
1249 DICOM standard, and technology the meta-data is inserted into the analysis stream (Figure 3) in a more
1250 direct manner and technology and accepted standards evolve.

1251

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

Parameter	Entity/Actor	Specification
		header, as per DICOM standard.
		Patient weight shall be specifiable with 4 significant digits.
		Patient weight shall be transferrable directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Height	Acquisition Device	Shall be able to record patient height in feet/inches or cm/m as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard.
		Patient height shall be specifiable with 3 significant digits.
		Patient height shall be transferrable directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Administered Radionuclide	Acquisition Device	Shall be able to accept the radionuclide type (i.e., 18F) from the DICOM Modality Worklist either from the NM/PET Protocol Context, if present, or by deriving it from the Requested Procedure Code via a locally configurable tables of values.
		Shall be able to enter the radionuclide type (i.e., 18F) by operator entry into the scanner interface.
		Shall be recorded in Radionuclide Code Sequence (0054,0300) in the DICOM image header (e.g., (C-111A1, SRT, "^18^Fluorine")).
		Shall be able to accept the radionuclide type (i.e., F-18) directly from the measurement device (dose calibrator) or management system, using the Sup 159 Radiopharmaceutical Administration Radiation Dose Report bypassing all operator entry, but still permitting operator correction.
Administered Radiotracer	Acquisition Device	Shall be able to record the specific radiotracer as supplied by operator entry into the scanner interface. Shall be recorded in Radionuclide Code Sequence field (0054,0300) in the DICOM image header, e.g., (C-B1031, SRT, "Fluorodeoxyglucose F^18^").
Administered Radiotracer radioactivity	Acquisition Device	Shall be able to enter the administered radioactivity, in both MBq and mCi, as supplied by operator entry into the scanner interface. Shall be recorded in Radionuclide Total Dose field (0018,1074) in the DICOM image header in Bq.
		Shall be able to record with separate entry fields on scanner interface: (1) the pre-injection 18F-Amyloid tracer radioactivity (2) time of measurement of pre-injection 18F-Amyloid tracer

Parameter	Entity/Actor	Specification
		radioactivity (3) the residual activity after injection (4) time of measurement the residual radioactivity after injection Shall automatically calculate the administered radioactivity and store in the Radionuclide Total Dose field (0018,1074) in the DICOM image header. Alternatively, shall be able to receive this information as per DICOM Supplement 159.
		Patient Administered Radiotracer radioactivity information shall be transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still permitting operator correction.
Administered Radiotracer Time	Acquisition Device	Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072).
		Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078). I.e. not Radiopharmaceutical Start Time field (0018,1072). Shall be able to record the time of the stop of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Stop Date Time field (0018,1079).
Decay Correction Methodology	Acquisition Device	Encoded voxel values with Rescale Slope field (0028,1053) applied shall be decay corrected by the scanner software (not the operator) to a single reference time (regardless of bed position), which is the start time of the first acquisition, which shall be encoded in the Series Time field (0008,0031) for original images. Corrected Image field (0028,0051) shall include the value "DECY" and Decay Correction field (0054,1102) shall be "START", which means that the images are decay corrected to the earliest Acquisition Time (0008, 0032).
Scanning Workflow	Acquisition Device	Shall be able to support Profile Protocol (Section 3) PET and CT order(s) of acquisition. Shall be able to pre-define and save (by imaging site) a Profile acquisition Protocol for patient acquisition.

Parameter	Entity/Actor	Specification
		Shall be able to interpret previously-reconstructed patient images to regenerate acquisition protocol.
		Shall be configurable to store (or receive) acquisition parameters as pre-defined protocols (in a proprietary or standard format), to allow re-use of such stored protocols to meet multi-center specifications and to achieve repeatable performance across time points for the same subject.
CT Acquisition Parameters	Acquisition Device	Shall record all key acquisition parameters in the CT image header, using standard DICOM fields. Includes but not limited to: Actual Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation Time, Exposure and Slice Width in the DICOM image header.
CT based attenuation correction	Acquisition Device	Shall record information in PET DICOM image header which CT images were used for corrections (attenuation, scatter, etc.).
PET-CT Alignment	Acquisition Device	Shall be able to align PET and CT images within ±2 mm in any direction.
		Shall be able to align PET and CT images within ±2 mm in any direction under maximum load over the co-scan length.
CT Absorbed Radiation Dose	Acquisition Device	Shall record the absorbed dose (CTDI, DLP) in a DICOM Radiation Dose Structured Report.
Activity Concentration in the Reconstructed Images	Acquisition Device	Shall be able to store and record (rescaled) image data in units of Bq/ml and use a value of BQML for Units field (0054,1001).
Tracer Uptake Time	Acquisition Device	Shall be derivable from the difference between the Radiopharmaceutical Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072) and the Series Time field (0008,0031) or earliest Acquisition Time field (0008,0032) in the series (i.e., the start of acquisition at the first bed position), which should be reported as series time field (0008,0031).
PET Voxel size	Acquisition Device	See Section 4.3 (PET Voxel size) under the Reconstruction Software specification requirements.
CT Voxel size	Acquisition Device	Shall be no greater than the reconstructed PET voxel size.
		Voxels shall be square, although are not required to be isotropic in the Z (head-foot) axis.
		Not required to be the same as the reconstructed PET voxel size.
Subject	Acquisition	Shall be able to record the subject position in the Patient Orientation

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

1252

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

1253

1254 4.3. Performance Assessment: Reconstruction Software

1255 Reconstruction Software shall propagate the information collected at the prior Subject Handling and
1256 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.

1257 Data can be reconstructed including all corrections needed for quantification as well as without scatter and
1258 attenuation correction. Analytical or iterative reconstruction methods should be applied. If the system is
1259 capable of providing resolution recovery and/or time of flight, then the decision to 'turn on' or 'turn off'
1260 this /these capabilities should be made prospectively, as dictated by the specific protocol, and should be
1261 consistent for a given subject across multiple time points.

1262 Standardization of reconstruction settings is necessary to obtain comparable resolution and SUV recoveries
1263 across the same subject and inter-subject across sites.

Parameter	Entity/Actor	Specification
Data Corrections	Reconstruction Software	PET emission data must be able to be corrected for geometrical response and detector efficiency, system dead time, random coincidences, scatter and attenuation.
Reconstruction Methodology	Reconstruction Software	Shall be able to provide iterative and/or analytical (e.g., filtered back projection) reconstruction algorithms.
		Shall be able to indicate, for both TOF and Resolution recovery, if either is being used for purposes of image reconstruction.
Reconstruction Methodology / Output	Reconstruction Software	Shall be able to perform reconstructions with and without attenuation correction.
Data Reconstruction 2D/3D Compatibility	Reconstruction Software	Shall be able to perform reconstruction of data acquired in 3D mode using 3D image reconstruction algorithms.
		If 3D mode data can be re-binned into 2D mode, shall be able to perform reconstruction of data acquired in 3D mode using 2D image reconstruction algorithms.
Quantitative calibration	Reconstruction software	Shall apply appropriate quantitative calibration factors such that all images have units of activity concentration, e.g., kBq/mL.
Voxel size	Reconstruction software	Shall allow the user to define the image voxel size by adjusting the matrix dimensions and/or diameter of the reconstruction field-of-view.
		Shall be able to reconstruct PET voxels with a size 2.5 mm or less in the transaxial directions and 2.5 mm or less in the axial dimension (as

Parameter	Entity/Actor	Specification
		recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices).
		Pixels shall be square, although voxels are not required to be isotropic in the z (head-foot) axis.
		Shall be able to reconstruct PET voxels with a size of 2 mm or less in all three dimensions (as recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices). Voxels shall be isotropic.
Reconstruction 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.

1264

4.4. Performance Assessment: Image Analysis Workstation

1266 .-Currently, there is no commercially available tool with which image analysis workstation conformance can
1267 be assessed. Versions of a Hoffmann brain DRO have been used by some labs to perform some of the
1268 necessary tasks, but not all requirements, as defined in this Profile can be assessed with this/these DROs.

1269 A digital reference object (DRO) series of synthetic PET volumes derived from a single patient's MRI scan
1270 (also provided) shall be used in order toto evaluate conformance of the image analysis workstation (IAW).
1271 Users should use the DRO series (as per the DRO user's guide in Appendix F) to verify correct
1272 implementation of VOI placement for both target and reference regions, SUVR calculations, PET alignment
1273 to standardized atlases (when applicable), system linearity and system reproducibility.

Parameter	Entity/Actor	Specification
Performance Evaluation	Image Analyst & Analysis Workstation	Shall use the DRO series to verify adequate performance as described in Appendix F and save the results with any study compliant with this Profile.

1274

1275 The post-processing software, which may be integral to the scanner workstation or provide by a third-party
1276 vendor, shall have the ability to perform the operations specified in Section 3.3.2, Image Data Post-
1277 processing.

Parameter	Entity/Actor	Specification
Metadata	Image Post-processing workstation	Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Image Analysis Workstation section.
		Shall be able to display all information that affects 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.

1278

1279 The Image Post-processing workstation will allow for the following operations that may or may not have
1280 been performed as part of image reconstruction.
1281

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

Parameter	Entity/Actor	Specification
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)

1282

1283 The features required of the analysis workstation are dependent in part upon the methods chosen for
1284 definition and application of the target and reference regions of interest to the PET scan. Certain
1285 additional features such as kinetic modeling for full dynamic scans, partial volume correction, and MRI
1286 segmentation to create regions of interest may also be relevant per study protocol, but their
1287 description is beyond the scope of this document.

1288

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

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

4.5. Performance Assessment: Software version tracking

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

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

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1415

Appendices

Appendix A: Acknowledgements and Attributions

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

The Amyloid PET Biomarker Committee members (in alphabetical order):

List members here

The Amyloid PET Biomarker Committee and Nuclear Medicine Coordinating Committee are deeply grateful for the support and technical assistance provided by the staff of the Radiological Society of North America.

Appendix B: Background Information for Claim

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

~~References~~

Appendix C: Conventions and Definitions

Convention Used to Represent Profile requirements

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

Illustrative example:

Parameter   Entity/Actor   Normative text: Clear boxes are current requirements

1452	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.

1453 Items within tables are normative (i.e. required to be conformant with the QIBA Profile). The intent of the
1454 normative text is to be prescriptive and detailed to facilitate implementation. In general, the intent is to
1455 specify the final state or output, and not how that is to be achieved.

1456 All other text outside of these tables is considered informative only.

1457 ## *Definitions*

1458 MCI: Mild Cognitive Impairment

1459 AD: Alzheimer's Disease

1460 mpi: minutes post injection

1461 CTDI: Computed tomography dose index

1462 DLP: Dose length product

1463 ALARA: As Low As Reasonably Achievable

1464

1465 ROI: Region of interest. A region in an image that is specified in some manner, typically with user-controlled
1466 graphical elements that can be either 2D areas or 3D volumes. These elements include, but not limited
1467 to, ellipses, ellipsoids, rectangles, rectangular volumes, circles, cylinders, polygons, and free-form
1468 shapes. An ROI can also be defined by a segmentation algorithm that operates on the image.
1469 Segmentation algorithms include, but are not limited to, fixed-value thresholding, fixed-percentage
1470 thresholding, gradient edge detection, and Bayesian methods. With the definition of an ROI, metrics are
1471 then calculated for the portion of the image within the ROI. These metrics can include, but are not
1472 limited to, mean, maximum, standard deviation, and volume or area. Note that the term ROI can refer
1473 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
1474 area and the term volume of interest (VOI) is used to refer to a 3D volume. In this Profile the term ROI is
1475 used to refer to both 2D areas and 3D volumes as needed.

1476 VOI: Volume of interest. See definition for ROI.

1477 Dose: Can refer to either radiation dose or as a jargon term for 'total radioactivity'. For example, 10 mCi
1478 mCi of 18F-FDG is often referred to as a 10 mCi dose.

1479 Profile:

1480 PET: Positron emission tomography (PET) is a tomographic imaging technique that produces an image of
1481 the in vivo distribution of a radiotracer, typically FDG.

1482 PET/CT: Positron emission tomography / computed tomography (PET/CT) is a medical imaging system that
1483 combines in a single gantry system both Positron Emission Tomography (PET) and an x-ray Computed

1484 Tomography (CT) scanners, so that images acquired from both devices can be taken nearly-
1485 simultaneously.

1486 CT: X-ray computed tomography (CT) is a medical imaging technique that utilizes X-rays to produce
1487 tomographic images of the relative x-ray absorption, which is closely linked to tissue density.

1488 TOF: Time of Flight (TOF) is a PET imaging technique utilizing differential annihilation photon travel times
1489 to more accurately localize the in vivo distribution of a radiotracer.

1490 UPICT: Uniform Protocols For for Imaging in Clinical Trials (UPICT). A RSNA-QIBA initiative that seeks to
1491 provide a library of annotated protocols that support clinical trials within institutions, cooperative
1492 groups, and trials consortia. The UPICT protocols areprotocols are based on consensus standards that
1493 meet a minimum set of criteria to ensure imaging data quality.

1494 DICOM: Digital Imaging and Communications in Medicine (DICOM) is a set of standards for medical images
1495 and related information. It defines formats for medical images that can be exchanged in a manner that
1496 preserves the data and quality necessary for clinical use.

1497 CRF: Case Report Form (CRF) is a paper or electronic questionnaire specifically used in clinical trial research.
1498 The CRF is used by the sponsor of the clinical trial (or designated CRO etc.) to collect data from each
1499 participating site. All data on each patient participating in a clinical trial are held and/or documented in
1500 the CRF, including adverse events.

1501 mCi: millicuries. A non-SI unit of radioactivity, defined as 1 mCi = 3.7 × 10^7 decays per second. Clinical
1502 FDG-PET studies inject (typically) 5 to 15 mCi of 18F-FDG.

1503 MBq: megabequerel. An SI-derived unit of radioactivity defined as 1.0 × 10^6 decays per second.

1504 QA: Quality Assurance. Proactive definition of the process or procedures for task performance. The
1505 maintenance of a desired level of quality in a service or product, esp. by means of attention to every
1506 stage of the process of delivery or production.

1507 QC: Quality Control. Specific tests performed to ensure target requirements of QA program are met.
1508 TypicallyTypically, by testing a sample of the output against the specification.

1509 Accreditation: Approval by an independent body or group for broad clinical usage (requires ongoing
1510 QA/QC) e.g. ACR, IAC, TJC.

1511 Qualification: Approved by an independent body or group for either general participation in clinical
1512 research (ACRIN-CQIE , SNM-CTN others) or for a specific clinical trial (requires ongoing QA/QC). This
1513 includes CROs, ACRIN, SNM-CTN, CALGB and other core laboratories.

1514 Conformance: Meeting the list of requirements described in this document, which are necessary to meet
1515 the measurement claims for this QIBA Profile.

1516 AC: Attenuation Correction. Attenuation is an effect that occurs when photons emitted by the radiotracer
1517 inside the body are absorbed by intervening tissue. The result is that structures deep in the body are
1518 reconstructed as having falsely low (or even negative) tracer uptake. Contemporary PET/CT scanners
1519 estimate attenuation using integrated x-ray CT equipment. While attenuation-corrected images are
1520 generally faithful representations of radiotracer distribution, the correction process is itself susceptible
1521 to significant artifacts.

1522

1523 *Organizations*

1524 QIBA: Quantitative Imaging Biomarkers Alliance. The Quantitative Imaging Biomarkers Alliance (QIBA) was
1525 organized by RSNA in 2007 to unite researchers, healthcare professionals and industry stakeholders in the
1526 advancement of quantitative imaging and the use of biomarkers in clinical trials and practice.

1527 RSNA: Radiological Society of North America (RSNA). A professional medical imaging society with more than
1528 47,000 members, including radiologists, radiation oncologists, medical physicists and allied scientists. The
1529 RSNA hosts the world's largest annual medical meeting.

1530 SNMMI: Society of Nuclear Medicine and Molecular Imaging (formerly called the Society of Nuclear
1531 Medicine (SNM)). A nonprofit scientific and professional organization that promotes the science,
1532 technology and practical application of nuclear medicine and molecular imaging. SNMMI represents 18,000
1533 nuclear and molecular imaging professionals worldwide. Members include physicians, technologists,
1534 physicists, pharmacists, scientists, laboratory professionals and more

1535 CTN: The Clinical Trials Network (CTN) was formed by SNMMI in 2008 to facilitate the effective use of
1536 molecular imaging biomarkers in clinical trials.

1537 AAPM: The American Association of Physicists in Medicine is a member society concerned with the topics
1538 of medical physics, radiation oncology, imaging physics. The AAPM is a scientific, educational, and
1539 professional organization of 8156 medical physicists.

1540 EANM: The European Association of Nuclear Medicine (EANM) constitutes the European umbrella
1541 organization of nuclear medicine in Europe

1542 EARL: EANM Research Ltd (EARL) was formed by EANM in 2006 to promote ~~multicentre~~ multicenter nuclear
1543 medicine and research.

1544 ABNM: American Board of Nuclear Medicine

1545 ABR: The American Board of Radiology

1546 ABSNM: The American Board of Science in Nuclear Medicine

1547 ACR: The 36,000 members of |include radiologists, radiation oncologists, medical physicists, interventional
1548 radiologists, nuclear medicine physicians and allied health professionals.

1549 ACRIN: The American College of Radiology Imaging Network (ACRIN) is a program of the American College
1550 of Radiology and a National Cancer Institute cooperative group. Focused on cancer-related research in
1551 clinical trials.

1552 ANSI: American National Standards Institute

1553 ECOG-ACRIN: A National Cancer Institute cooperative group formed from the 2012 merger of the Eastern
1554 Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN).

1555 IAC: The Intersocietal Accreditation Commission (IAC) provides accreditation programs for Vascular Testing,
1556 Echocardiography, Nuclear/PET, MRI, CT/Dental, Carotid Stenting and Vein Center.

1557 TJC: The Joint Commission (TJC) accredits and certifies health care organizations and programs in the
1558 United States.

1559 CRO: Contract Research Organization. A commercial or not-for-profit organization designated to perform a
1560 centralized and standardized collection, analysis, and/or review of the data generated during a clinical trial.
1561 Additional activities which may be performed by an imaging core lab include training and qualification of
1562 imaging centers for the specific imaging required in a clinical trial, development of imaging acquisition

1563 manuals, development of independent imaging review charters, centralized collection and archiving of
1564 images received from study sites, performing pre-specified quality control checks/tests on incoming images
1565 and development and implementation of quality assurance processes and procedures   to ensure that
1566 images submitted are in accord with imaging time points specified in the study protocol and consistent with
1567 the quality required to allow the protocol-specified analysis /assessments

1568 CQIE: The Centers of Quantitative Imaging Excellence (CQIE) program was developed by ACRIN in response
1569 to a solicitation for proposals issued in December 2009 by SAIC-Frederick on behalf of the National Cancer
1570 Institute (NCI). The primary objective of the CQIE Program is to establish a resource of 'trial ready' sites
1571 within the NCI Cancer Centers Program that are capable of conducting clinical trials in which there is an
1572 integral molecular and/or functional advanced imaging endpoint.

1573 CLIA: Clinical Laboratory Improvement Amendments: Accreditation system for establishing quality
1574 standards for laboratory testing.

1575 USP: United States Pharmacopeial Convention establishes written and physical (reference) standards for
1576 medicines, food ingredients, dietary supplement products and ingredients in the U.S.

1577 EMA: European Medicines Agency is a European Union agency for the evaluation of medicinal products.
1578 Roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization.

1579 FDA: Food and Drug Administration is responsible for protecting and promoting public health in the U.S.
1580 through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription
1581 and over-the-counter pharmaceutical medications, vaccines, biopharmaceuticals, blood transfusions,
1582 medical devices, electromagnetic radiation emitting devices, and veterinary products.

1583 NIST: National Institute of Standards and Technology is a measurement standards laboratory which is a
1584 non-regulatory agency of the United States Department of Commerce.

1585 NEMA: National Electrical Manufacturers Association is a forum for the development of technical standards
1586 by electrical equipment manufacturers.

1587 MITA: The Medical Imaging & Technology Alliance is a division NEMA that develops and promotes
1588 standards for medical imaging and radiation therapy equipment. These standards are voluntary guidelines
1589 that establish commonly accepted methods of design, production, testing and communication for imaging
1590 and cancer treatment products.

1591

1592 Appendix D: Model-specific Instructions and Parameters

1593 The presence of specific product models/versions in the following tables should not be taken to imply that
1594 those products are fully in conformance with the QIBA Profile. Conformance with a Profile involves meeting
1595 a variety of requirements of which operating by these parameters is just one. To determine if a product
1596 (and a specific model/version of that product) is conformant, please refer to the QIBA Conformance
1597 Document for that product.

1598 *D.1. Image Acquisition Parameters*

1599 The following technique tables list acquisition parameter values for specific models/versions that can be
1600 expected to produce data meeting the requirements of Section 3.6.4 ('Phantom Imaging').

1601 These technique tables may have been prepared by the submitter of this imaging protocol document, the

1602 clinical trial organizer, the vendor of the equipment, and/or some other source. (Consequently, a given
1603 model/version may appear in more than one table.) The source is listed at the top of each table.

1604 Sites using models listed here are encouraged to consider using these parameters for both simplicity and
1605 consistency. Sites using models not listed here may be able to devise their own acquisition parameters that
1606 result in data meeting the requirements of Section 3.6.4 and conform to the considerations in Section 4. In
1607 some cases, parameter sets may be available as an electronic file for direct implementation on the imaging
1608 platform.

1609 ## *D.2. Quality Assurance Procedures*

1610 Examples of recommend quality assurance procedures are shown for specific GE, Philips, and Siemens
1611 PET/CT scanners in the tables below.

1612

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

1613
1614

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

1615

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

1616

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

The list below comprises meta-information (i.e. in addition to image values of kBq/ml) that is necessary for quantitatively accurate (i.e. known and minimal uncertainties) of PET SUVs. The intent here is to list what information should be captured rather than the mechanism itself. The format and corresponding mechanism of data capture/presentation is currently unspecified, but ranges from paper notes, to scanned

forms or electronic data records, to direct entry from the measurement equipment (i.e. the PET/CT scanner or auxiliary measurement devices such as the radionuclide calibrator) into pre-specified DICOM fields. Ideally all the specified meta-data will be captured by direct electronic entry to DICOM fields, after suitable modification of the DICOM format for PET imaging.

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

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

Data fields to be recorded:

1. Site specific
   a. Site information (include name and/or other identifiers)
   b. Scanner make and model
   c. Hardware Version numbers
   d. Software Version numbers
   e. Confirmation that scanner used was previously qualified (or not)
2. Protocol specific
   a. PET
      i. Duration per bed
      ii. Acquisition mode (3D)
      iii. Reconstruction method
   b. CT technique (if PET/CT scan)
3. Scanner specific QA/QC
   a. Most recent calibration factors (scanner)
   b. Scanner daily check values
   c. most recent clock check
   d. most recent scanner QA/QC
4. Subject exam specific
   a. Weight (optional)
      b.
   c.b. Pre- and post-injection assayed activities and times of assay
   d.c. Injection time
   e.d.   Site of injection (and assessment of infiltration)
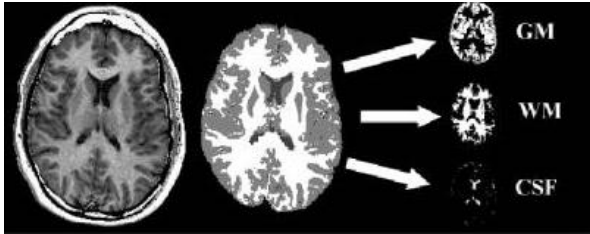   f.e. Net injected activity (calculated including decay correction)
   g.f. Uptake time

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

The University of Washington-PET QIBA PET Amyloid DRO series is a synthetically generated set of DICOM

1665 image files of known voxel values for PET. The PET data were derived from a single subject's MRI scan
1666 (provided with the DRO series). The UW-PET QIBA DRO series is intended to test the computation of
1667 standardized uptake value ratios (SUVRs) by PET amyloid image analysis workstations (IAWs). This is
1668 motivated by vendor-specific variations in PET amyloid IAWs. The development of the UW-PET QIBA DRO
1669 series is supported by the Quantitative Imaging Biomarker Alliance (QIBA) and the University of
1670 Washington.

1671 The primary goals and objectives of the UW-PET QIBA DRO series are to support the QIBA PET amyloid
1672 'Performance Assessment: Image Analysis Workstation and Software' efforts for Profile development. This
1673 will be done by (1) visual evaluation of the target and reference region placement, (2) evaluation and
1674 validation of SUVR calculations with regards to reproducibility and linearity and (3) providing a common
1675 reference standard that can be adopted and modified by IAW manufacturers.

1676 As mentioned above, the UW-PET QIBA PET Amyloid DRO series is based on a single segmented MRI scan of
1677 a patient. The MRI scan digitally had the skull and skin removed, and then was segmented into GM, WM,
1678 and CSF, which allows for different values of PET activity to be simulated in these regions.

1679
1680   Illustration of how the DRO series was created.
1681

1682 Normally, a system of measurement would have assessments and conformance levels for bias, linearity and
1683 reproducibility. However, since the claim in this Profile is a longitudinal claim (as opposed to a cross-
1684 sectional claim), the conformance assessment as detailed here will focus only on linearity and
1685 reproducibility. Please note that the implicit assumption of a longitudinal study is that same patient will be
1686 measured on the same scanner with the same acquisition and post-processing protocols.

1687 **Linearity**

1688 The linearity of the IAW will be assessed by testing a range of different subjects, as defined by varying SUVR
1689 values. The table below gives more detail about the simulated subjects and their respective SUVR values.
1690 The activity in the CSF region will be set to 0.

	0.9X	X	0.9
	1.0X	X	1.0
	1.1X	X	1.1
	1.2X	X	1.2
	1.3X	X	1.3
	1.4X	X	1.4

1691

1692 Therefore, 6 subjects were simulated in the DRO series which will be later used to test the linearity of the
1693 IAW.

1694 **Reproducibility**

1695 The reproducibility of the IAW will be assessed by making multiple realizations of the same subject. This
1696 can be thought of as simulating test-retest multiple times on the same subject. The multiple realizations
1697 will be done by adding typical levels of clinical noise five times to each subject. Please see the figure below
1698 for a pictorial representation.

1699 **The DRO Series**

1700 The simulation of six subjects and five realizations means that the DRO series will contain 30 simulated PET
1701 volumes. These volumes will be stored in DICOM format and can be downloaded from the Quantitative
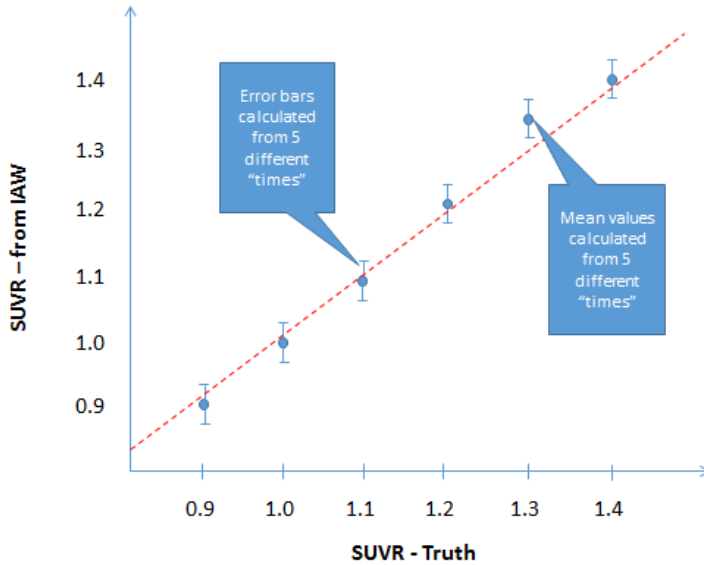1702 Imaging Data Warehouse (QIDW), with the link given below.

1703 **IAW ~~Compliance~~ Conformance Procedure**

1704   a. Download the UW-PET QIBA PET Amyloid DRO series from QIDW \<give link when ready>.

1705   b. Analyze the 30 volumes using the same procedure, target regions and reference regions as will be
1706   used with patient data.

1707   c. For each target region for a fixed reference region, the information to form the graph below should
1708   be calculated, and will be called a given target's results, e.g. (Frontal Target/Whole Cerebellum
1709   Reference Region) Results:

Example Output – For <u>Single</u> 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 – <u>Target Region 1</u>

1710

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

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

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

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

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

      • The estimate of A_0 and A_1, *along with their 95% CIs,* shall be reported as part of the assessment record (see last point below).

      • R-squared (R^2) shall be >0.90 for the IAW to be compliant for the given target and reference regions.

   c. For each of the 6 true SUVR values, calculate the mean (blue points in graph above) of the 5 measurements and the wSD (blue error bars in graph above) using the following equations

1727   where the summations are from j=1 to J=5:

1728
$$\bar{Y}_i = \sum(Y_{ij})/J \ \text{ and } \ wSD_i^2 = \sum(Y_{ij} - \bar{Y}_i)^2/(J-1).$$

1729   d. Estimate wCV using the equation, where N=6:

1730

1731
$$wCV = \sqrt{\sum_{i=1}^{N}(wSD_i^2/\bar{Y}_i^2)/N}.$$

1732

1733   f. Estimate the % Repeatability Coefficient (%RC) using the equation:

1734
$$\widehat{\%RC} = 2.77 \times wCV \times 100.$$

1735   • The %RC shall be ≤ 2.6% for the IAW to be compliant for the given target and
1736   reference regions. (Note that this conformance criterion allows 95% confidence that
1737   the %RC of the IAW meets the Profile claim.)

1738   • For future reference, the number of subjects and tests per subjects can be changed in
1739   the DRO series, which will change the RC threshold as per the table below.

6	5	2.6%
7	5	2.8%
9	5	2.9%
11	5	3.0%
6	10	3.1%

1740

1741   6. For each target's results, report the following in a format similar to the example table below.

Ref Region	Visual Placement Check	Target Region	Visual Placement Check	β_0	β_1	β_2	A_0	A_1	R^2	$R^2 > 0.90$	wCV	%RC	%RC ≤ 2.6%
1	Pass	1	Pass	0.03	0.91	0.01	0.1	0.97	0.92	Pass	7.6x10⁻³	2.1	Pass
1	Pass	2	Pass	0.05	0.9	0.02	0.07	0.95	0.91	Pass	1.05x10⁻²	2.9	Fail
1	Pass	3	Fail	-	-	-	-	-	-	-	-	-	-
1	Pass	4	Pass	0.16	0.81	0.14	0.14	1.2	0.85	Fail	-	-	-
2	Fail	-	-	-	-	-	-	-	-	-	-	-	-
3	Pass	1	Pass	0.03	0.91	0.01	0.1	0.97	0.92	Pass	7.6x10⁻³	2.1	Pass
3	Pass	2	Pass	0.04	0.95	0.04	0.03	0.92	0.93	Pass	8.0x10⁻³	2.2	Pass
...	...	...	...	...	...	...	...	...	...	...	...	...	...

1742

1743   The table report above should be saved and archived with any PET amyloid patient study that is compliant
1744   with this Profile.

1745

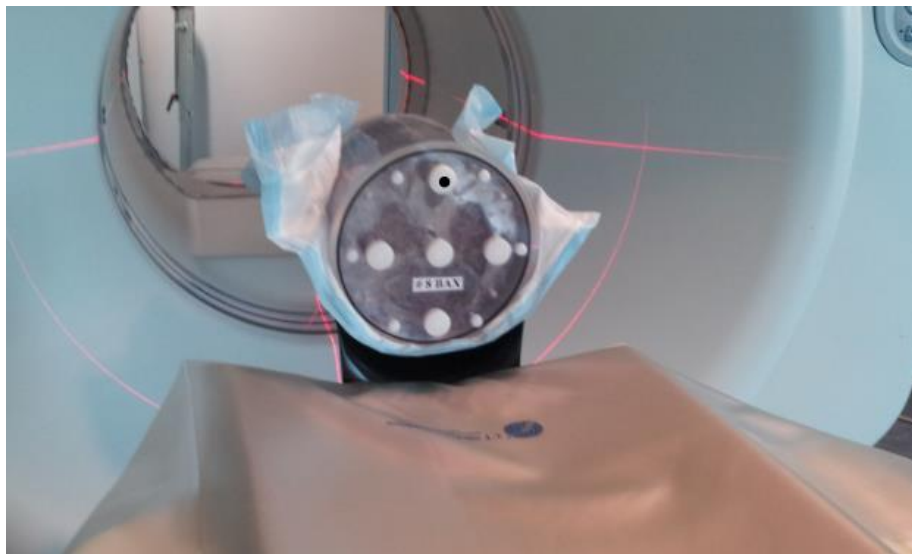## Appendix G: Best Practice Guidance for the Hoffman Brain Phantom

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

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

1765 • Once injected, replace the cap and roll back and forth vigorously for about 5min. Occasionally, pick
1766   up and tip up and down the other way.
1767 • Top off as best you can, filling through 1 or two of the ports (wherever bubbles are).
1768 • Roll a 2nd time, briefly for about 1min. this will help to get bubbles out.
1769 • Top off a 2nd time. The focus now is to remove any remaining air getting bubbles. An effective
1770   method is to hold upright (with filling ports up), and shake back and forth vigorously to make the
1771   bubbles rise. (Remember when filling to minimize spills. Wipe with a paper towel, and this goes to
1772   radioactive waste)
1773 • Roll a final 3rd time. Then top off again to remove any remaining air bubbles.
1774 • As a final check, look through the phantom at a bright light to check for bubbles. If there are some
1775   large bubbles (greater than ~3 mm), try another shaking/tapping/rolling/filling session.
1776 • Finally, if you do the CT scan and notice there are big bubbles or air spaces, take the phantom and
1777   try to top off/remove the bubbles before doing the finally CT/Pet scans
1778

1779 Generally, this process takes about 10-20min.

1780

1781

1782 Position the phantom on the scanner bed with the filling ports towards the foot of the bed, and the
1783 anterior filling port at 12 o'clock. (In this position, the cerebellar lobes should be visible at the bottom of
1784 the phantom, and should appear in the reconstructed image as if you were imaging a supine subject).

1785

1786

Appendix I: 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.
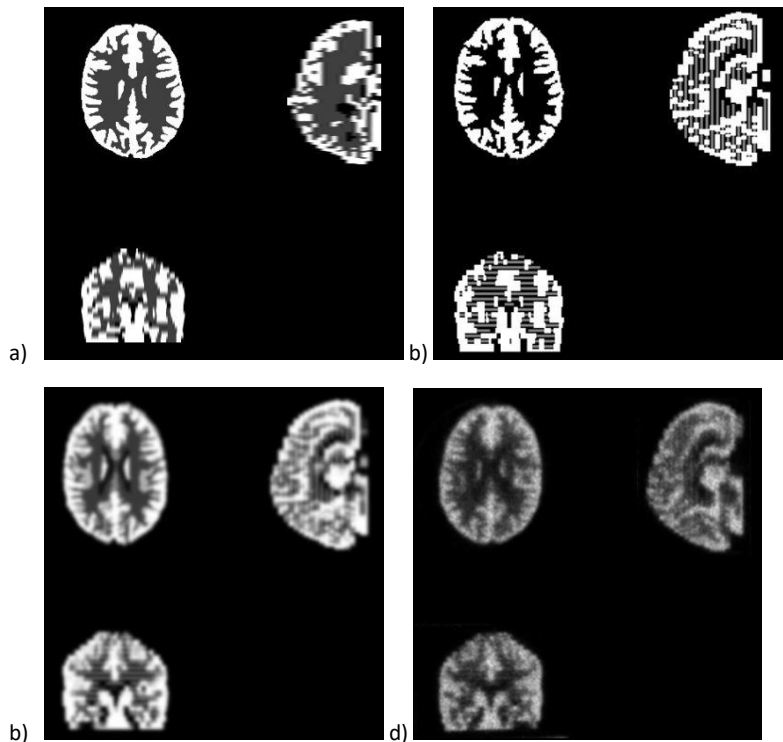

a) b)

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.

Phantom Description

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

1807

1808 Data Spectrum, who manufactures the phantom, supplies a 256x256x19 voxel digital atlas that models the
1809 phantom appearance as having one of 3 types of uniform areas in each 6.1 mm slice (gray=4, white=1,
1810 csf=0). See Figure 1a. Dr. Bob Koeppe from the University of Michigan, in collaboration with Data Spectrum
1811 and CTI (now Siemens) constructed a more accurate 160x160x90 voxel, 1.548x1.548x1.548 mm version of
1812 this phantom that models the individual layers between the slices. Each slice of this 90-slice phantom
1813 represents either a "GG" all gray layer with values either 0 or 1.0; or a "GW" layer with values either 0, 0.5
1814 or 1.0. This digital phantom (Fig 1b,c) looks much more like data obtained from a high-resolution PET
1815 scanner (Fig 1d), and can be smoothed to approximate images from lower-resolution scanners. The
1816 individual layers can actually be seen in some higher resolution scanners, such as the Siemens HRRT.

1817

1818 One important item to note is that the actual phantom size, especially the actual physical slice thickness of
1819 each phantom, can vary slightly. Therefore, when comparing data, it is important to deal with the scaling
1820 appropriately. Alternatively, if comparisons are made between two acquisitions, one must insure that the
1821 identical phantom is used in the comparison. If there are multiple phantoms in use, it is good practice to
1822 track each phantom with an appropriate identification number.

1823

1824 Regarding smoothing, it is assumed that the PET scanner resolution can be modeled by smoothing with a
1825 Gaussian kernel with the same size in the transaxial direction (i.e. x and y direction), and another size in the
1826 axial direction (i.e. z direction). This is approximate, since blurring increases transaxially away from the
1827 center, and is different in the radial and tangential directions. Also, axial resolution is degraded in the outer
1828 end planes of the scanner. However, the uniform smoothing assumption is fairly reasonable for head
1829 imaging, where the field of view is fairly close to the center of the scanner.

1830 ## Methods and Metrics

1831 ## Method Overview

1832 The method for quantitative analysis can be summarized by the following steps:

1833 1) Sum a dynamic PET test image, which we will call the "Source Image" acquisition, to produce a
1834   single average PET volume
1835 2) Register the averaged Source Image to the 90-slice digital reference using an affine transformation
1836 3) Determine Gaussian smoothing factors FHWMxy, FWHMz, to be applied to the digital phantom so
1837   that it best matches the registered Source dataset.
1838 4) Compute image metrics on differences between the matched smooth "gold standard" data, and the
1839   registered Source data.
1840 5) Create different images and graphics to augment a visual assessment of image quality.

1841 ## Relevant Data Files

1842 The following input and reference files are used in the analysis:

1843 <u>Reference Files</u>

1844 **ctiHoffman0.0_0.0.nii** – This is the 160x160x90 digital gold standard data.
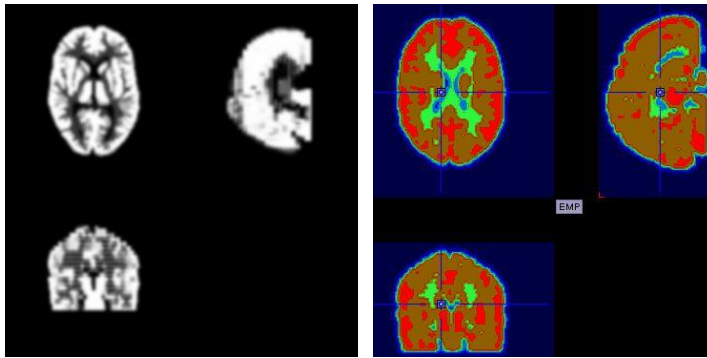
1845 **ctiHoffman5.0_5.0.nii** – This is ctiHoffman0.0_0.0.nii smoothed by a Gaussian kernel 5.0 mm FWHM in the
1846 x, y, and z dimensions. This represents an image at about the resolution of the highest-resolution scanners,
1847 such as the HRRT.

1848 **HoffmanVOI5mm6Level.25_.95BrainMask.nii** – This is a volume-of-interest (VOI) mask file with six levels
1849 created in PMOD using multi-level thresholding on the smoothed, phantom file, **ctiHoffman5.0_5.0.nii**. The
1850 resulting segmentation is seen in Figure 2. Idealized voxel intensities for CSF, white matter and gray matter
1851 are 0.0, .025, 1.0 respectively, but blurring of the digital phantom results in a partial volume effect so that
1852 voxel values vary continually between 0.0 – 1.0. Regions were defined with the following IDs and
1853 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

1854 Regions 4 and 6, which represent areas of mostly white and gray matter, respectively, are the main regions
1855 used for comparison in the analysis.

1856

1857

1858 Figure 2. Six-region Volume of Interest mask. The smoothed digital reference (left), and the volume of
1859 interest mask volume created in PMOD using multi-thresholding segmention (right). The VOI mask is used
1860 to define areas representing primarily pure gray (shown in red) and pure white matter (shown in green).
1861 These regions are used for image intensity normalization and various image quality metrics.

1862

1863 <u>Input files</u>

1864 **SourceXXX** – original dynamic PET data. Usually in DICOM format, and for this profile is recommended to
1865 be a 4 x 5 minute acquisition.

1866

1867   Intermediate Files

1868   Avg **SourceXXX.nii –** summed dynamic data.

1869   **RegSourceXXX.nii** – summed dynamic data registered to 160x160x90 voxel digital phantom template

1870   **RegSourceNorm.nii –** version of **RegSourceXXX.nii** intensity normalized to values between 0 and 1.0.

1871

1872   Output Files

1873   *Volumes*

1874   **RegSourceXXXFit.nii** – smoothed version of the Hoffman digital template , **ctiHoffman0.0_0.0.nii** , that is
1875   the best fit to **RegSourceNorm.nii.**

1876   **RegSourceXXXAbsDiff.nii –** absolute difference volume between **RegSourceFit.nii** and

1877

1878   *Text*

1879   **RegSourceXXXfit.txt** – summary output file

1880

1881   *JPG -*

1882   **RegSourceXXXXplotAbsDiffProfile**.jpg – profile of

1883   **RegSourceXXXXplotGrayWhiteProfile**.jpg -

1884   **RegSourceXXXXplotImgDiff**.jpg - central three orthogonal planes through **RegSourceXXXAbsDiff.nii**, gray
1885   scale set between -0.2 and 0.2.

1886   **RegSourceXXXXplotImgNorm**.jpg – central three orthogonal planes through **RegSourceNorm.nii**, gray scale
1887   set between 0.0 and 1.0

1888

1889   ## Method Details – Processing Steps

1890   1) Manual step: Load/visual check of image data. Add to PMOD batch file list
1891   Images need to be manually loaded to check visually that the orientation is correct. If the image loads
1892   using default parameters, it can be simply added to a PMOD file list for later batch processing. If the
1893   default settings do not work, the image must me manually loaded using the correct image reorientation
1894   switches, saved as a new dynamic file, then added to the PMOD batch file list.

1895   2) Batch step: PMOD script: Dynamic Averaging, Affine Registration to Hoffman Digital reference
1896   This step sums the dynamic PET data to obtain an averaged PET source file, and then registers the
1897   averaged PET to the Hoffman reference image. It is assumed that there is no motion between image
1898   time frames, so a motion correction step is not necessary like it would be for a patient study. As a
1899   reference image, the version of the Hoffman reference smoothed with a 5 mm isotropic Gaussian filter
1900   is used (**ctiHoffman5.0_5.0.nii**). This represents the resolution of an image that would be expected from
1901   the highest resolution PET scanners. In PMOD's registration module, Normalized Mutual Information

1902 and the "scale" option are selected to allow an affine match that will compensate for slightly different
1903 phantom actual sizes. No other pre-smoothing is used during the registration. The batch process saves
1904 the averaged and the registered dataset as two separate files. This step can be run on one or many
1905 different PET files. PMOD is not set up yet to record the reorientation matrix (I have requested this), so
1906 we do not have a full track of all operations.

1907 3) Batch step: Matlab script: Normalize PET, Fit Smoothing Model, Quantify Difference Image
1908 Once the PET source has been registered to the Hoffman reference, the following steps are carried out
1909 using a matlab script:

1910   a) *Normalize the Registered PET source intensity.* The noiseless digital phantom has values ranging
1911   between 0.0 and 1.0. Rather than normalizing to maximum intensity of the source image, the
1912   following approach is taken which adjusts for the partial volume effect and for the expected
1913   Poisson-related variability around the mean for the expected values in the areas representing
1914   gray and white matter. Using the 6-level VOI mask, we use region 6, the area representing mostly
1915   pure gray matter, as a reference region. The mean intensity of voxel values in this region is
1916   computed in both the smoothed reference volume and the registered source volume. A scale
1917   term is computed as the ratio of reference volume gray region mean intensity / source volume
1918   gray region mean intensity. This results in the mean with the area representing pure gray area to
1919   be set to a voxel intensity of 1.0 in the normalized image.

1920   b) *Fit Gaussian smoothing kernels, FWHMxy and FWHMz.*An unconstrained nonlinear estimation
1921   approach is use to find the Gaussian smoothing kernels that produce a smoothed version of the
1922   digital reference phantom best matching the normalized source volume. (using Matlab's
1923   "fminsearch" function). We investigated various image difference measures: absolute difference,
1924   squared difference, correlation, and brain-masked differences, and the simple absolute
1925   difference appeared to work well. The code is written so that any of these options can be
1926   selected, but the default is the absolute difference.

1927 2) Calculation of Quality Metrics from the Normalized Source Image and Difference Image
1928 The difference between the normalized source image and the digital reference smoothed to fit the
1929 source image is the main basis for the comparison. Additionally, some measures can also be computed
1930 from the normalized source image alone. Basic ideas to consider in this analysis include:

1931 - The ideal gray:white contrast ratio should be 4:1 in a noise free setting with perfect spatial
1932   resolution. We need to consider the partial volume effect, so most evaluations are made in
1933   comparison to global or VOI measures on the noise-free smoothed digital reference.
1934 - For evaluations using a uniform phantom, the usual figure of merit for an acceptable measurement
1935   variance is +- 10% from the mean both in-plane and axially. Therefore, an absolute difference of
1936   about 10%, i.e. +- 0.1 intensity units would ideally be a maximum difference between the
1937   normalized source and the smoothed reference image.
1938 Quality Metrics

1939 *a) Global Volume Metrics*
1940   i) **Comparison of fit smoothing parameters to published data from ADNI / Bob Koeppe's group**.
1941   This value should be consistent for a given scanner type. Differences in Z-smoothing compared
1942   to ADNI results are expected due primarily to Z-scaling during the affine registration process.
1943   Based on empirical observation, there most likely is a problem if the fit smoothing parameters
1944   differ by more than 1 mm FWHM.

1945   ii) **Average Global Absolute Difference – total image volume** : ideally, this should be less than
1946   10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
1947   iii) **Average Global Absolute Difference in the brain region only**: ideally, this should be less than
1948   10%, therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
1949   iv) **Gray:White mater ratio in the source image**. Ideally, this should be 4.0. For scanners of lower
1950   resolution we would expect the value to be less.
1951   v) **Ratio of Gray:White in the Source image compared to smoothed reference**. Ideally, this should
1952   be 1.0. <mark>Would expect at most a 10% variation</mark>.
1953   vi) **Ratio of White matter intensity standard deviation in the Source imaging compared to the
1954   smoothed reference**: This measure gives an indication of image noise. By comparing to the
1955   reference volume, variation with the white matter region due to the partial volume effect
1956   should cancel out.
1957   vii) **Ratio of Gray matter intensity standard deviation in the Source imaging compared to the
1958   smoothed reference**. : This measure gives an indication of image noise. By comparing to the
1959   reference volume, variation with the white matter region due to the partial volume effect
1960   should cancel out.
1961 b) *Slice-by-slice Metrics (computed between planes 10-80, which represent the plane with brain data in*
1962   *the Hoffman reference volume)*
1963   i) **Average Slice Absolute Difference – total slice**: ideally, this should be less than 10%, therefore
1964   less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
1965   ii) **Average Slice Absolute Difference** – brain region only: ideally, this should be less than 10%,
1966   therefore less than 0.1 for the images intensity normalized to values between 0.0 and 1.0.
1967   iii) **Average Slice Absolute Difference – gray matter only (VOI region #6)**: ideally, this should be
1968   less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0
1969   and 1.0.
1970   iv) **Average Slice Absolute Difference – white matter only (VOI region #4)**: ideally, this should be
1971   less than 10%, therefore less than 0.1 for the images intensity normalized to values between 0.0
1972   and 1.0.
1973   v) **Ratio of mean gray intensity in VOI region #6 for Source compared to smoothed reference**:
1974   ideally, this should be 1.0
1975   vi) **Ratio of mean white intensity in VOI region #6 for Source compared to smoothed reference**.
1976   Ideally, this should be 1.0.
1977   vii) **Profile Coefficient of Variation for Gray slice mean gray intensity.** This metric can be used as a
1978   sentinel for unacceptable variations in axial sensitivities.
1979
1980 3) Outputs: Graphics, Text Summary and Imaging volumes
1981   a) JPGs
1982   i) 3 orthogonal slices through the center of the difference volume – color bars set to +- 0.2 for all
1983   evaluations to highlight significant areas that differ from the reference volume. A
1984   ii) 3 orthogonal slices through the normalized, registered source volume
1985   iii) Slice-by-slice profiles of error measures between source and reference volumes
1986   iv) Slice-by-slice profiles of the ratio of mean gray and white matter region intensity regions for the
1987   source volume compared to the reference volume.
1988   b) Text file
1989   i) Numerical values for the global and plane-by-plane metrics
1990   c) Image volumes

1991   i) Difference Volume
1992   ii) Fit Smoothed Reference Volume
1993

1994 **Note: Matlab Modules Used**. In addition to the base Matlab package, the processing pipeline used the
1995 standard Matlab Image Processing Toolbox and the Optimization Toolbox. The pipeline also used the 3rd
1996 party Matlab package for reading, writing and displaying NIFTI files, "Tools for NIfTI and ANALYZE image",
1997 found at http://www.rotman-baycrest.on.ca/~jimmy/NIfTI .
1998

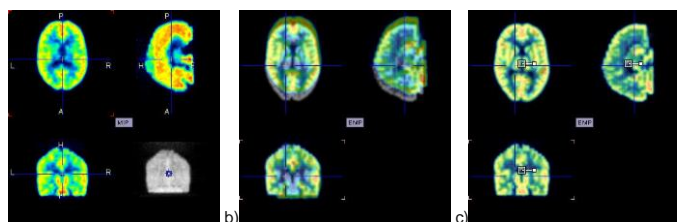

1999 a)   b)   c)
2000 Figure 3. Affine Registration Process. Source image in original orientation (a). Source image (colored grayscale, and digital gold standard
2001 (grayscale) unregistered (b), and after registration in PMOD (c).
2002

2003