Orig number	Topic	Priority (L, M, H)	Line #	Section #	Issue	Proposal	Resolution	Modification made / addressed
6	Personnel qualifications	M	357		Other health professionals, such a nurses, can also administer radiotracers, with appropriate training.		Modify actor for this box to read "Technologist, Physician, Nurse, or other qualified Health Professional"	x
53	Personnel qualifications	M	1013-1014	3.6.2	Definition of qualifications of physicians overseeing amyloid brain PET CT in United States.	The physician should either be boarded by ABNM and/or ABR.	Add under qualifications that "the physician should have board certification by the American Board of Nuclear Medicine (ABNM) and/or the American Board of Radiology (ABR)"	x
56	Responsibilities	L	1194	4.1	Duties of Medical Physics not completely listed	Sentence could be completed with …"address issues of quantification such as attenuation maps movement, etc."	Add "and to address issues relating to quantification such as attenuation maps or movement".	x
2	Claim	H	143		Threshold change metric of 8% when data shows 1% per year is expected. Will this be interpreted to mean that a trial should not be considered appropriately powered if the change is less than 8%? The implication of this 8% number needs further explanation in the text, esp since NIH typically only funds studies for 5 years.		Addressed by stating a Coefficient of Variation that can be tied to published studies aligned with profile guidelines, tightening the guidelines and adding caveats, and then explaining in the Clinical Interpretation section how this information can be applied to study design for the calculation of required numbers of subjects, as well as implications for individual longitudinal measurements.	x
20	Claim	H	136ff	2	The 2 claims: "A measured change in SUVR of Δ % indicates that a true change has occurred if Δ > 8 %, with 95% confidence" and "If Y1 and Y2 are the SUVR measurements at two time points, then the 95% confidence interval for the true change is (Y2-Y1) ± 1.96 × √([Y1 ×0.029]^2+[Y2 ×0.029]^2)" may erroneously raise the impression that the corresponding formulas are already accepted as a common standard for assessing longitudinal changes in amyloid load (which is not the case). The basis for their deduction is not explained.	It should be explained on which assumptions these claims are based and references need to be added (e.g. changes greater than test/retest variability?). Also, it may be important to consider which time frame these claims are referring to (% change in a year?). Also, the natural course of disease (initial increase of amyloid-burden, later plateau-phase) may have to be taken into account and this should be mentioned here. In the current phrasing, these formulas may be misleading, implicating that e.g. a decrease of 8% in SUVR typically equals a significant therapy response. In fact, depending on the stage of disease and the follow-up period, this number may be variable (potentially even smaller). Consequently, these two claims may require a clarification, explicitly explaining that the suggested numbers/calculations are preliminary/hypothetical, that they are in need of validation and that they may be variable depending on the question. At this position in the text it could also be mentioned that SUVR may be affected by perfusion effects and that the mentioned formulas are not suitable to correct for these effects. These claims should not be mistaken to raise a false sense of security in this context.	Addressed by stating a Coefficient of Variation that can be tied to published studies aligned with profile guidelines, tightening the guidelines and adding caveats, and then explaining in the Clinical Interpretation section how this information can be applied to study design for the calculation of required numbers of subjects, as well as implications for individual longitudinal measurements.	x
57	Claim	H	136	2. Clinical Context and Claims	As written, the Claim seems to refer to change of amyloid load in a single individual. However, please note that individual change in amyloid load is not a common endpoint in clinical trials (as opposed to the onset of dementia, for instance). In the context of this Profile (change in amyloid load following an intervention), the typical question to address is whether the intervention has significantly modified the amyloid load in a group of individuals (typically in a treatment arm as compared to a placebo group). For this alternative question, robust detection of changes in amyloid load well below the test-retest variability of the technique can be achieved, provided the study is appropriately powered (i.e., has a big enough sample size). Therefore, sample size is a necessary variable to be included in the calculation of the confidence bounds of a group analysis.	In this vein, we suggest the draft to inform on minimum sample sizes achievable, by following the recommendations in the profile, required to detect as statistically significant varying degrees of a minimum clinically important difference (MCID) in total amyloid load and/or changes in amyloid accumulation rate over a given period of time (see Chen et al. J Nucl Med 2015, as an example).	Addressed by stating a Coefficient of Variation that can be tied to published studies aligned with profile guidelines, tightening the guidelines and adding caveats, and then explaining in the Clinical Interpretation section how this information can be applied to study design for the calculation of required numbers of subjects, as well as implications for individual longitudinal measurements.	x
58	Claim	H	136	2. Clinical Context and Claims	Another problem with the Claim, as stated, is the lack of a reference time period for the computation of the changes, thus ignoring other biological sources of variability that may play a significant role in the target populations over the typical experimental period of a clinical trial (1-2.5 years). For example, changes in cerebral blood flow are well known to impact amyloid quantification using the SUVr metric and have been systematically reported in AD populations.	Specify a maximum (reference) time between scans to support the claim and acknowledge limitations of the SUVr metric as a measure of amyloid load for longer times	Addressed by stating a Coefficient of Variation that can be tied to published studies aligned with profile guidelines, tightening the guidelines and adding caveats, and then explaining in the Clinical Interpretation section how this information can be applied to study design for the calculation of required numbers of subjects, as well as implications for individual longitudinal measurements.	x
81	Claim				Verbal and email discussion: issues with claim were consistent with others raised, regarding need for time context or other way of making relevant to physiologic change and clinical trials.		Also addressed by stating a Coefficient of Variation that can be tied to published studies aligned with profile guidelines, tightening the guidelines and adding caveats, and then explaining in the Clinical Interpretation section how this information can be applied to study design for the calculation of required numbers of subjects, as well as implications for individual longitudinal measurements.	x
	Reconstruction parameters	M		3.3.1	The recommendation is made not to use Point Spread Function (PSF). The QIBA Round 6 grant project examining impact of reconstruction methods upon measured SUVR showed that differences due to use of PSF were no greater than, and in fact less than, differences introduced by other reconstruction methods or parameters. There does not appear to be a valid reason for excluding this method over other methods.	Replace the text in the box stating that PSF should not be used with the statement that it can be used. Retain language in preceding box stressing that the same reconstruction method and parameters are to be used for all longitudinal scans.	Replace the text in the box stating that PSF should not be used with the statement that it can be used. Retain language in preceding box stressing that the same reconstruction method and parameters are to be used for all longitudinal scans.	x
1	Reconstruction parameters	M	512	3.3.1	From the Profile: "The Technologist shall perform the image reconstruction such that the matrix, slice thickness, and reconstruction zoom shall yield a voxel size of < 2.5 mm in the x and y dimensions and <= 3 mm in the z dimension." The "< 3 mm in the z dimension" cannot be achieved on any but the newest GE PET/CT scanners. Most of the installed base of GE PET scanners have a 3.27 mm z dimension or slice spacing.	Consider the recently updated Vizamyl Package Insert, "…slice thickness of 2 to 4 mm, matrix size of 128 × 128 with pixel sizes of approximately 2 mm."	Modify text to read: ≤ 3.3 mm in the z dimension (or, less preferably, <4.5 mm for older scanners).	x
7	Acquisition window	H	401		These should be considered minimum durations for image acquisition. Full dynamic protocol or longer imaging window (even if not full dynamic) can significantly improve the quality of the data. This will be particularly important for trials in preclinical AD.		Added: "Note that the durations shown in the table below should be considered minimum durations for image acquisition. For example, for florbetapir, the time window used by ADNI is 20 minutes rather than 10. A full dynamic protocol or longer imaging window (even if not full dynamic) can significantly improve the quality of the data. This will be particularly important for trials in preclinical AD."	x
21	Acquisition parameter consistency	L	155ff	2	Incomplete listing	In addition to using the same scanner and protocol for follow-up studies, it may be worthwhile to explicitly mention that the same radiotracer and the same reconstruction parameters should be applied.	Modify to: "This Claim is applicable for single or multi-center studies assuming that the same 18F-amyloid PET tracer, scanner, scanner software version, image acquisition parameters, image reconstruction method and parameters, and image processing methods are used for each subject at each time point as described in the Profile."	x
24	Full dynamic modeling	H	198	2	The following paragraph appears incomplete and may be misunderstood: "Whether or not a change in SUVR is affected by changes in amyloid and/or perfusion ideally should be first demonstrated in a small cohort before SUVR is used in the larger clinical trial. At the very least these validation studies should be performed to assess the minimally required decrease in SUVR that is needed to rule out false positive findings because of (disease and/or drug related) perfusion effects"	In this context, it needs to be mentioned that performing a pilot study on a small cohort may not be suitable to reliably rule out perfusion effects, particularly if this pilot study is not performed correctly. Thus, at this position in the text it should be advocated that ideally fully dynamic pilot studies (including arterial blood sampling and tracer kinetic modelling) are required to account for perfusion effects and to validate the reliability of reference based approaches to provide quantitative information suitable for therapy monitoring (by means of comparing SUVR to BPnd values). It may also be worthwhile to define here, what a „small cohort" is supposed to mean (<20 subjects? < 100 subjects?).	Reword to the following language: "Whether or not a change in SUVR is affected by changes in perfusion and/or clearance ideally should be first demonstrated in a small (e.g. 20 subjects) cohort before SUVR is used in the larger clinical trial. At the very least these validation studies should be performed to assess the minimally required decrease in SUVR that is needed to rule out false positive findings because of disease and/or drug related perfusion effects. In the case of a new PET tracer, studies that include blood sampling should be conducted to confirm that the SUVR approach and use of a reference region are a suitable approach to measure tracer binding. For further details regarding considerations in kinetic modeling please see Appendix <>."	x
71	Acquisition window	M	467	3.2.1.4	PET should be acquired in listmode format (best) or dynamic	Provide clarification that this is not necessarily true for routine clinical patients - a 10 minute static image is acceptable as long as there is no motion		x
84	Missing table						Refer to ADNI protocol but indicate that either (a) appropriate smoothing should be performed during reconstruction, or (b) the processing sequence should provide for a uniform level of smoothing.	x
4	Centiloid	M	219		What sort of validation of the Centoilod Scale are you asking for here? Needs to be more explicit.		Text modified to: the Centiloid Scale may, after further investigation, provide a mechanism whereby a study can be performed with different amyloid PET tracers and/or different processing pipelines or measurement methods mapped to a standard range of numeric SUVR values (Klunk et al, 2015). At this time, the centiloid continues to undergo adoption and is not included in Profile requirements. Further, this Profile requires the use of a single radiotracer in a multi-center trial when pooling of data across centers is performed. For further description see section 3.4.3.3.3 of this Profile.	x
10	Centiloid	M	943/944	3.4.3.3.3 Relating SUVR values to other studies	"the values can be generated with a correlation exceeding x%" - for the correlation values we can provide the information proposed on the right (based on Klunk et al)	Using the control image set provided by the Centiloid project, it is first confirmed that by using the prescribed regions and analysis approaches, the values can be generated with a correlation with r^2 > 0.98.	Insert the following language for informational purposes: Using the control image set provided by the Centiloid project, it is first confirmed that by using the prescribed regions and analysis approaches, the values can be generated with a correlation with r^2 > 0.98.	x
11	Reference region (references)	L	873/784	3.4.3.2.2 Determine Reference Region	Some studies using florbetapir, flutemetamol and 11C-PIB have found that the pons exhibited lower longitudinal variability than a cerebellar reference region (include reference). There is not a reference yet. We propose to use Thurfjell et al, Automated Quantification of 18F-Flutemetamol PET Activity for Categorizing Scans as Negative or Positive for Brain Amyloid: Concordance with Visual Image Reads. J Nucl Med October 1, 2014 vol. 55 no. 10 1623-1628. doi: G610.2967/jnumed.114.142109	Add reference Thurfjell, 2014	Add Thurfjell reference as suggested as this is a primary one relating to flutemetamol and use of pons, but either verify that it applies longitudianlly or qualify by stating that it is relevant to cross sectional analysis.	x
12	Centiloid	L	934	3.4.3.3.3 Relating SUVR values to other studies	This section discusses the Centiloid concept. The method paper on Centiloid by Rowe at al is included. It may be beneficial for the reader to also include the references to the publications that detail the centiloid equations for the different amyloid tracers once these are published or a link to the GAAIN website where conversion data is available.	PiB, flutemetamol, fluorbetaben and NAV image, SUVR and conversion data are available on the GAAIN website: http://www.gaain.org/centiloid-project	Add the following to the suggested update to the descriptive text identified under a separate public comment: "PiB, flutemetamol, fluorbetaben and NAV image, SUVR and conversion data are available on the GAAIN website: http://www.gaain.org/centiloid-project"	x
19	Qualitative read	M	129	2	The statement:" A negative amyloid PET scan indicates sparse to no neuritic plaques and a positive amyloid scan indicates moderate to frequent amyloid neuritic plaques." has been extracted from the package insert of amyloid radiotracers using visual analysis. It is generally correct; however it falls short if the aim of the profile is to establish "requirements for measurement of 18F- amyloid tracer uptake with PET as an imaging biomarker for assessing the within subject change in brain amyloid burden over time (longitudinal Claim) to inform the assessment of disease status or possibly to evaluate therapeutic drug response „ as mentioned in lines 117-120	The statement on visual assessment may be completed with a note explaining that this only refers to qualitative „binary" visual judgement into amyloid-positive or –negative. Further comments on potential quantitative assessment are made in the profile.	As suggested, the statement on visual assessment may be completed with a note explaining that this only refers to qualitative „binary" visual judgement into amyloid-positive or –negative. Further comments on potential quantitative assessment are made in the profile.	x
		L	129	2. Clinical Context and Claims	The wording regarding the rationale for use of amyloid tracers does not quite capture the rationale for their use.	Replace wording regarding the rationale to read: "...offer the potential of directly detecting and quantifying fibrillar amyloid burden. The rationale for quantifying amyloid burden is its designation as a necessary though not definitive biomarker of Alzheimer's disease. Amyloid quantitation can be used to determine whether levels exceed a threshold for positivity (a cross sectional application) and to measure changes in amyloid burden over time, whether disease related or as modified by therapuetic intervention."	Replace wording regarding the rationale to read: "...offer the potential of directly detecting and quantifying fibrillar amyloid burden. The rationale for quantifying amyloid burden is its designation as a necessary though not definitive biomarker of Alzheimer's disease. Amyloid quantitation can be used to determine whether levels exceed a threshold for positivity (a cross sectional application) and to measure changes in amyloid burden over time, whether disease related or as modified by therapuetic intervention."	x
39	Image analysis (reference)	L	688	3.4.22	"If not reconciled, these differences can cause a few percent difference in SUVR." - That statement needs a reference.	provide reference	Add Joshi et al, 2009 reference: Joshi A, Koeppe RA, Fessler JA. Reducing between scanner differences in multi-center PET studies. Neuroimage. 2009 May 15;46(1):154-9.	x
41	Atrophy correction	M	719-730	3.4.3.1	correlation to template brain - When the subject is correlated with a template brain, the template brain often does not display similar pattern of atrophy and therefore may have reduced accuracy.	Devise a strategy to correct for correlation in atrophic brains with modifications provided for thinning of cortex.	Several updates have been made to sections 3.4.3.1, 3.4.3.1.2, and 3.4.3.1.3. The discussion of warping approaches has been reorganized into subsection 3.4.3.1.3 for better ordering. A point has been added discussing factors that can impact goodness of fit, including the use of a template that is similar to the study population (e.g. aging, atrophic). Factors impacting segmentation results when an approach such as Freesurfer is used have also been added. A point has also been added to section 3.4.3.1.2 noting that in cases of significant longitudinal atrophy, care must be taken to account for this in the VOIs used.	x

43	Image analysis	M	781	3.4.1.3	the mathematical model used for warping may be per study specification, and should be uniform across longitudinal analysis.	Provide guidance on acceptable warping models to insure uniformity across longitudinal studies.	This appears to reference section 3.4.3.1.3. Re-emphasize the current sentence that references a comparison of models (currently reads: Certain software and software versions have shown superior alignment of cerebellum, deep structures such as putamen and medial temporal regions, and ventricles as compared to older algorithms (Klein et al, 2009)) to read: "Certain software and software versions have shown superior alignment of cerebellum, deep structures such as putamen and medial temporal regions, and ventricles as compared to older algorithms (Klein et al, 2009). In addition, the template to which images are warped can impact goodness of fit and optimization for the study population may be of use."	x
44	Reference region	M	797-834	3.4.3.2.1	Structural changes in the cerebellum are relatively common in the ageing population. Focal encephalomalacia due to sequel of chronic infarct can affect accuracy as a reference region.	Provide guidance on how the cerebellum can be used as a reference in patients with history of prior infarct with obvious cerebellar encephalomalcia, if other reference regions should be used or whether such patients should be excluded in longitudinal studies	The following text has been added to section 3.4.3.2.1: "In addition, it is also noted that although not ordinarily expected, it is possible for longitudinal structural changes (abnormalities) to occur that impact the ability to use a common mapping across scans. One such example is cerebellar encephalomalcia. However, such an event is not within the scope of this profile version and it is rather recommended to exclude the subject in this case or to use target and reference regions that are unaffected by the abnormality."	x
45	Reference region	M	872-874	3.4.3.2.2	"Some studies using florbetapir, flutemetamol and 11C-PIB have found that the pons exhibited lower longitudinal variability than a cerebellar reference region (include reference). " - Unable to find references concerning "longitudinal" variability of pons reference.	Either provide a reference or delete statement. This paper shows superiority of pons reference but it is not a longitudinal study: Edison P, Hinz R, Ramlackhansingh A, Thomas J, Gelosa G, Archer HA, Turkheimer FE, Brooks DJ. Can target-to-pons ratio be used as a reliable method for the analysis of [11C]PIB brain scans? Neuroimage. 2012 Apr 15;60(3):1716-23. doi: 10.1016/j.neuroimage.2012.01.099. Epub 2012 Jan 27.	Add Thurfjell et al, 2014 and Shokouhi et al, 2016 as references. Edison paper also added as further backround and so that it is not omitted if this profile evolves to include a cross-sectional claim.	x
46	Reference region (references)	L	877	3.4.2.2	"Studies have demonstrated benefit in lower variability using subcortical white matter, and thus greater statistical power in measuring longitudinal change, relative to other reference regions (reference needed)." - references needed.	Suggested references: Blautzik J, Brendel M, Sauerbeck J, Kotz S, Scheiwein F, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Reference region selection and the association between the rate of amyloid accumulation over time and the baseline amyloid burden. Eur J Nucl Med Mol Imaging. 2017 Aug;44(8):1364-1374. Chen K, Roontiva A, Thiyyagura P, Lee W, Liu X, Ayutyanont N, Protas H, Luo JL, Bauer R, Reschke C, Bandy D, Koeppe RA, Fleisher AS, Caselli RJ, Landau S, Jagust WJ, Weiner MW, Reiman EM; Alzheimer's Disease Neuroimaging Initiative. Improved power for characterizing longitudinal amyloid-β PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region. J Nucl Med. 2015 Apr;56(4):560-6. doi: 10.2967/jnumed.114.149732. Epub 2015 Mar 5.	Add the following reference to the set already listed for reference region topic (Chen et al was already included): Blautzik J, Brendel M, Sauerbeck J, Kotz S, Scheiwein F, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Reference region selection and the association between the rate of amyloid accumulation over time and the baseline amyloid burden. Eur J Nucl Med Mol Imaging. 2017 Aug;44(8):1364-1374.	x
47	Reference region (references)	L	884	3.4.3.2.2	"add a reference to justify the composite reference region" - Reference needed.	Consider using these references: Tryputsen V, DiBernardo A, Samtani M, Novak GP, Narayan VA, Raghavan N; Alzheimer's Disease Neuroimaging Initiative. Optimizing regions-of-interest composites for capturing treatment effects on brain amyloid in clinical trials. J Alzheimers Dis. 2015;43(3):809-21. doi: 10.3233/JAD-131979. Landau SM, Fero A, Baker SL, Koeppe R, Mintun M, Chen K, Reiman EM, Jagust WJ. Measurement of longitudinal β-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. J Nucl Med. 2015 Apr;56(4):567-74. doi: 10.2967/jnumed.114.148981. Epub 2015 Mar 5.	Add references: Tryputsen V, DiBernardo A, Samtani M, Novak GP, Narayan VA, Raghavan N; Alzheimer's Disease Neuroimaging Initiative. Optimizing regions-of-interest composites for capturing treatment effects on brain amyloid in clinical trials. J Alzheimers Dis. 2015;43(3):809-21. doi: 10.3233/JAD-131979. Landau SM, Fero A, Baker SL, Koeppe R, Mintun M, Chen K, Reiman EM, Jagust WJ. Measurement of longitudinal β-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. J Nucl Med. 2015 Apr;56(4):567-74. doi: 10.2967/jnumed.114.148981. Epub 2015 Mar 5.	x
48	Reference region	M	888-889	3.4.3.2.2	Comments on using the cerebellum as a reference region may be added	avoid radiotracer contamination form surrounding structures such as the occipital cortex or the fusiform gyrus. References below described CB VOIs in relative detail: Shcherbinin S, Schwarz AJ, Joshi A, Navitsky M, Flitter M, Shankle WR, Devous MD Sr, Mintun MA. Kinetics of the Tau PET Tracer 18F-AV-1451 (T807) in Subjects with Normal Cognitive Function, Mild Cognitive Impairment, and Alzheimer Disease. J Nucl Med. 2016 Oct;57(10):1535-1542. Epub 2016 May 5. PubMed PMID: 27151986. 'The AAL-based cerebellum crus region was modified by translating it by 6 mm in the z-axis to avoid overlap with noncerebellar space. The resulting regions are shown in Figure 1.' Barret O, Alagille D, Sanabria S, Comley RA, Weimer RM, Borroni E, Mintun M, Seneca N, Papin C, Morley T, Marek K, Seibyl JP, Tamagnan GD, Jennings D. Kinetic Modeling of the Tau PET Tracer 18F-AV-1451 in Human Healthy Volunteers and Alzheimer's Disease Subjects. J Nucl Med. 2016 Dec 1. pii: jnumed.116.182881. [Epub ahead of print] PubMed PMID: 27908967. 'The cerebellar cortex region was eroded away from other regions by 8 mm to minimize spill-over, in particular from the temporal and occipital regions.' Pontecorvo MJ, Devous MD Sr, Navitsky M, Lu M, Salloway S, Schaerf FW, Jennings D, Arora AK, McGeehan A, Lim NC, Xiong H, Joshi AD, Siderowf A, Mintun MA; 18F-AV-1451-A05 investigators.. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain. 2017 Mar 1;140(3):748-763. doi: 10.1093/brain/aww334. PubMed PMID: 28077397; PubMed Central PMCID: PMC5382945. 'A cerebellar grey matter region derived from the cerebellar crustaneous (cere-crus-1 region of interest from AAL) modified by translating it inferiorly by 6 mm was chosen.' Hahn A, Schain M, Erlandsson M, Sjolin P, James GM, Strandberg OT, Hagerstrom D, Lanzenberger R, Jogi J, Olsson TG, Smith R, Hansson O. Modeling Strategies for Quantification of In Vivo (18)F-AV-1451 Binding in Patients with Tau Pathology. J Nucl Med. 2017 Apr;58(4):623-631. doi: 10.2967/jnumed.116.174508. Epub 2016 Oct 20. PubMed PMID: 27765859.	Per recommendation, add: If the reference regions includes the cerebellum, it is recommended to omit the superior portions of the cerebellum to avoid radiotracer contamination form surrounding structures such as the occipital cortex or the fusiform gyrus and to omit the lowest slices that exhibit more variability. References below described CB VOIs in relative detail: Shcherbinin S, Schwarz AJ, Joshi A, Navitsky M, Flitter M, Shankle WR, Devous MD Sr, Mintun MA. Kinetics of the Tau PET Tracer 18F-AV-1451 (T807) in Subjects with Normal Cognitive Function, Mild Cognitive Impairment, and Alzheimer Disease. J Nucl Med. 2016 Oct;57(10):1535-1542. Epub 2016 May 5. PubMed PMID: 27151986. 'The AAL-based cerebellum crus region was modified by translating it by 6 mm in the z-axis to avoid overlap with noncerebellar space. The resulting regions are shown in Figure 1.' Barret O, Alagille D, Sanabria S, Comley RA, Weimer RM, Borroni E, Mintun M, Seneca N, Papin C, Morley T, Marek K, Seibyl JP, Tamagnan GD, Jennings D. Kinetic Modeling of the Tau PET Tracer 18F-AV-1451 in Human Healthy Volunteers and Alzheimer's Disease Subjects. J Nucl Med. 2016 Dec 1. pii: jnumed.116.182881. [Epub ahead of print] PubMed PMID: 27908967. 'The cerebellar cortex region was eroded away from other regions by 8 mm to minimize spill-over, in particular from the temporal and occipital regions.' Pontecorvo MJ, Devous MD Sr, Navitsky M, Lu M, Salloway S, Schaerf FW, Jennings D, Arora AK, McGeehan A, Lim NC, Xiong H, Joshi AD, Siderowf A, Mintun MA; 18F-AV-1451-A05 investigators.. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain. 2017 Mar 1;140(3):748-763. doi: 10.1093/brain/aww334. PubMed PMID: 28077397; PubMed Central PMCID: PMC5382945. 'A cerebellar grey matter region derived from the cerebellar crustaneous (cere-crus-1 region of interest from AAL) modified by translating it inferiorly by 6 mm was chosen.' Hahn A, Schain M, Erlandsson M, Sjolin P, James GM, Strandberg OT, Hagerstrom D, Lanzenberger R, Jogi J, Olsson TG, Smith R, Hansson O. Modeling Strategies for Quantification of In Vivo (18)F-AV-1451 Binding in Patients with Tau Pathology. J Nucl Med. 2017 Apr;58(4):623-631. doi: 10.2967/jnumed.116.174508. Epub 2016 Oct 20. PubMed PMID: 27765859.	x
49	Reference region	H	889	3.4.3.2.3	The use of a "combined reference, subcortical white matter, or other "amyloid poor" regions proximal to target regions" is advised for longitudinal studies and for measurement of amyloid in subjects near the threshold of positivity. This suggestion is at least partially questionable. The use of such a composite reference region may be advantageous with regard to sensitivity in terms of differentiation between patients with and without AD. This may in part be due to the fact that amyloid-tracer binding in the white matter also reflects axonal integrity which may be affected in Alzheimer's disease resulting in a higher cortex/reference ratio. Particularly in longitudinal studies such an approach may be affected by longitudinal changes in the white matter regarding integrity and also perfusion. Finally, it is not clarified how a white matter region should be defined e.g. if only a PET/CT scan and no MRI information is available. Using standard templates will be running a high risk of including cortical regions or defining a region closely neighboring cortex and thus being affected by spill-in of cortical signal. It needs to be mentioned that no "composite reference" approach has been validated by means of fully dynamic longitudinal studies including quantitative modeling. The facts that such approaches have reduced variability or increased statistical power do not prove that they also improve quantitative accuracy. The authors of a recent longitudinal study advocating a composite reference ROI (Landau et al J Nucl Med 2015) concluded themselves that future analysis including tracer kinetic modeling may be recommended. Furthermore, it is unclear what "amyloid poor regions proximal to target regions" is supposed to mean. Using "amyloid-poor" cortical regions as a reference region in longitudinal studies may be particularly critical because they may turn amyloid-positive over time and also be affected by atrophy. Finally, regarding composite ROI's it may be mentioned that including gray and white matter regions into one reference ROI bears risks with regard to divergent changes over time, particularly in longitudinal studies	It should be clearly mentioned that none of the suggested reference region approaches has yet been demonstrated to be optimal with regard to their ability to reliably allow quantitative assessment of longitudinal changes (as compared to fully dynamic tracer kinetic modeled studies). Specific problems of the discussed reference region approaches may have to be mentioned in greater detail (as mentioned above). Currently evidence is still pending with regard to which method is superior concerning low susceptibility to atrophy, partial volume effect or perfusion effects. It may be premature to recommend one particular reference approach in the QUIBA profile.	This comment raised several points to address for clarification. Regarding the original statement describing use of white matter regions or composities: the set of manuscripts and publications listed under the resolution to comment 72 supports a finding that in the case of florbetapir SUVR, use of a white tissue containing reference results in lower longitudinal variability. There were existing comments regarding white matter considerations that included "It should be noted, however, that the signal from reference regions using subcortical white matter may be affected by vascular pathology, common in the elderly." However, additional text is added to address the points raised: 1) to address the caveat regarding longitudinal change in white matter, "There is not yet a published full dynamic modeling study of white matter as a reference. White matter axonal integrity may decline with AD progression and age, potentially increasing cross sectional differences between AD and Normal, and introducing possible variability over time: , 2) to address the point regarding white matter definition: recommend use of MRI based white matter segment with erosion of borders to prevent neighboring spillover (MRI based warping is already proposed for quantitation); 3) to address the comment rearding change in "amyloid poor" regions over time, ; 4) to address the comment regarding composites of white and gray matter, add "It is also noted that regions comprised of both gray and white matter, whether whole cerebellum or composite regions, may include divergent changes over time. These may be a suitable match for probabilistic target regions that include both gray and white matter, or given white matter spillover into gray tissue. However, for "pure" gray target regions, their longitudinal use may introduce some non-amyloid related variability. All of this must be weighed against other sources of variability arising from use of a pure cerebellar cortex reference due to low signal, scatter, subject motion, and differences in the axial placement from scan to scan.	x
50	Cortical average calculation	M	9-23-0924	3.4.3.3.1	Weighted averages - This section requires further elaboration / clarification as to how exactly a weighted average is achieved.	Provide definition of best technique (s) for this purpose. (A cortical average may be calculated as the average of multiple VOIs, or weighted by the number of voxels in each VOI.)	Text: "While the selection of which regions to include and how to combine them is dependent upon the study objectives, minimizing variation due to numerous technical factors (including subject motion, axial variability, and image alignment) is best achieved when using an average of multiple regions. The performance claim is derived from published studies in which a non-weighted average of cingulate, frontal, lateral temporal, and lateral parietal regions was applied."	x
51	Centiloid	M	929ff	3.4.3.3.3	Dr. Victor Villemagne, responsibly involved in the Centiloid project suggests minor rephrasing of this section.	Replace paragraph with the following: "Different protocols involve different tracers, target regions, and reference regions, and all of these contribute to how the SUVR can be interpreted with regard to amyloid burden. A value of 1.2, for example, can be amyloid positive using one tracer and/or set of regions for analysis, but amyloid negative using a different tracer and/or regions. In order to reconcile findings across data acquisition, processing, and analysis protocols, the concept of the Centiloid was developed (Klunk et al, 2014). The Centiloid is not intended to dictate the method for acquiring and processing data, but rather to provide a way to equate results obtained with a broad variety of protocol parameters. The basis for the Centiloid is a "gold standard" set of results derived from young healthy controls and elderly AD patients. These results have been generated using the radiotracer 11C-PiB and a defined set of target region, reference region, and image processing and analysis steps. A linear progression of values from 0 (no amyloid) to 100 (mean for amyloid positive sporadic AD patients) has been established using this approach. To establish the equivalent "Centiloid value" for a tracer and/or acquisition and analysis protocol that differ from the gold standard, two sets of relationships are required to be empirically derived. Using the control image set provided by the Centiloid project, it is first confirmed that by using the prescribed regions and analysis approaches, the Centiloid values can be replicated with a correlation exceeding 98%. Secondly, using the new tracer and/or acquisition and analysis parameters, values are generated using both the "gold standard" method and 11C-PiB, and the alternate tracer and/or methods. The regression between the two sets of results yields a transform equation that can be applied to results to convert them to "Centiloid units" for comparison to other studies. If a tracer and set of approaches are being applied that for which conversion to Centiloid units has already been established, this reference transform can be directly applied to new studies using the same conversion parameters."	As suggested, replace paragraph with the following quoted language. Also include the clarification that use and validation of the Centiloid approach are beyond the scope of this Profile as also stated for a separate public comment for line 219. "Different protocols involve different tracers, target regions, and reference regions, and all of these contribute to how the SUVR can be interpreted with regard to amyloid burden. A value of 1.2, for example, can be amyloid positive using one tracer and/or set of regions for analysis, but amyloid negative using a different tracer and/or regions. In order to reconcile findings across data acquisition, processing, and analysis protocols, the concept of the Centiloid was developed (Klunk et al, 2014). The Centiloid is not intended to dictate the method for acquiring and processing data, but rather to provide a way to equate results obtained with a broad variety of protocol parameters. The basis for the Centiloid is a "gold standard" set of results derived from young healthy controls and elderly AD patients. These results have been generated using the radiotracer 11C-PiB and a defined set of target region, reference region, and image processing and analysis steps. A linear progression of values from 0 (no amyloid) to 100 (mean for amyloid positive sporadic AD patients) has been established using this approach. To establish the equivalent "Centiloid value" for a tracer and/or acquisition and analysis protocol that differ from the gold standard, two sets of relationships are required to be empirically derived. Using the control image set provided by the Centiloid project, it is first confirmed that by using the prescribed regions and analysis approaches, the Centiloid values can be replicated with a correlation exceeding 98%. Secondly, using the new tracer and/or acquisition and analysis parameters, values are generated using both the "gold standard" method and 11C-PiB, and the alternate tracer and/or methods. The regression between the two sets of results yields a transform equation that can be applied to results to convert them to "Centiloid units" for comparison to other studies. If a tracer and set of approaches are being applied that for which conversion to Centiloid units has already been established, this reference transform can be directly applied to new studies using the same conversion parameters." See under separate public comment the additional mention of data and information available on the GAAIn website. (Note: This was implemented by inserting the specific wording differences between this paragraph and the previously existing text.)	x
60	Image analysis	M	756	3.4.3.1.2 Longitudinal PET co-registration	The optimal strategy to analyze the scans are very dependent on the actual implementation of the algoritms.	We suggest that the Profile does not make general recommendations without referrng to specific implementations of the quantification algorithms or suggesting a reference implementation. In this regard, the Centiloid reference pipeline could be of help (see: http://www.gaain.org/centiloid-project)	Consistent with the suggestion, the Profile allows for multiple technical approaches to VOI definition, fitting, and measurement. However, it also notes where certain VOI approaches and in particular, certain reference region definitions, have resulted in lower variability that may increase the ability to meet the Claim. The Centiloid is discussed within the Profile (though not mandated as it is continuing to evolve) for its usefulness in reconciling the general values obtained from different tracers and measurement approaches, but as noted by Su et al (2018), it does not reduce within method variability. This is noted in the discussion of the Centiloid, and the Su reference has been added to the Centiloid reference section.	x

72	Reference region (references)	M	888	3.4.3.2.2	Just noting the need for multiple references in this section		Add the following references: Reference regarding pons vs. cerebellum: Shokouhi et al, 2016; Chen et al, 2015; Reference regions incorporating subcortical white matter: Schwarz et al, 2016; Landau et al, 2015; Joshi et al, 2014; Brendel et al, 2015; Chen et al, 2015; Matthews et al, 2014; Blautzik et al, 2017; References regarding composite regions: Fleisher et al, 2014; Koeppe et al, 2012; Klein et al, 2015. Full references: Brendel M, Högenauer M, Delker A, Sauerbeck J, Bartenstein P, Seibyl J, Rominger A; Alzheimer's Disease Neuroimaging Initiative. Improved longitudinal [(18)F]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction. Neuroimage. 2015 Mar;108:450-9. Chen K, Roontiva A, Thiyyagura P, Lee W, Liu X, Ayutyanont N, Protas H, Luo JL, Bauer R, Reschke C, Bandy D, Koeppe RA, Fleisher AS, Caselli RJ, Landau S, Jagust WJ, Weiner MW, Reiman EM; Alzheimer's Disease Neuroimaging Initiative. Improved power for characterizing longitudinal amyloid-β PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region. J Nucl Med. 2015 Apr;56(4):560-6. Landau SM, Breault C, Joshi AD, Pontecorvo M, Mathis CA, Jagust WJ, Mintun MA; Alzheimer's Disease Neuroimaging Initiative. Amyloid-β imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med. 2013 Jan;54(1):70-7. Landau, S.M., Fero, A., Baker, S.L., Koeppe, R., Mintun, M., Chen, K., Reiman, E.M., Jagust, W.J. Measurement of Longitudinal B Amyloid Change with 18F Florbetapir PET and Standardized Uptake Value Ratios. J. Nucl. Med. 2015:56, 567–574. Schwarz CG, Senjem ML, Gunter JL, Tosakulwong N, Weigand SD, Kemp BJ, Spychalla AJ, Vemuri P, Petersen RC, Lowe VJ, Jack CR Jr. Optimizing PiB-PET SUVR Change-Over-Time Measurement by a large-scale analysis of Longitudinal Reliability, Plausibility, Separability, and Correlation with MMSE. Neuroimage. 2016 Aug 27. pii: S1053-8119(16)30448-7. Shokouhi S, Mckay JW, Baker SL, Kang H, Brill AB, Gwirtsman HE, Riddle WR, Claassen DO, Rogers BP; Alzheimer's Disease Neuroimaging Initiative. Reference tissue normalization in longitudinal (18)F-florbetapir positron emission tomography of late mild cognitive impairment. Alzheimers Res Ther. 2016 Abstracts and Presentations Fleisher, A.S., Roontiva, A., Reschke, C., Bandy, D., Reiman, E.M., Protas, H., Luo, J., Chen, K., Weiner, M.W., Ayutyanont, N., Thiyyagura, P., Caselli, R.J., Baur, R.I., Koeppe, R., Landau, S., Lee, W., Jagust, W., Liu, X. Improving the Power to Track Fibrillar Amyloid PET Measurements and Evaluate Amyloid Modifying Treatments using a Cerebral White Matter Reference Region of Interest, in: Alzheimer's Association International Conference (AAIC). Elsevier, Copenhagen, Denmark, 2014. Joshi, A., Kennedy, I.A., Mintun, M., Pontecorvo, M., Navitsky, M.A., Devous, M.D. Measuring change in beta amyloid burden over time using florbetapir PET and a subcortical white matter reference region, in: Alzheimer's Association International Conference (AAIC). Elsevier, Copenhagen, Denmark, 2014. Klein G, Sampat M, Staewen D, Scott D, Suhy J. Comparative Assessment of SUVR Methods and Reference Regions in Amyloid PET Studies. Alzheimer's Association International Conference (AAIC), July 18-23, 2015, Washington, DC, USA. Koeppe R. Basic Principles and Controversies in PET Amyloid Imaging. Human Amyloid Imaging Meeting, Miami Beach, Florida, USA, 2012. On-line at:	x
8	Radiotracer administration	M	349/350	3.1.3.1.3 Radiotracer Administration Route	For the injection of the radiotracer, optional use of power injectors is mentioned. This is generally possible, however, it should be ensured that there is no pre-dilution step with saline before the injection. Some automatic injectors increase the injected volume by diluting with saline before the tracer is injected. As amyloid imaging agents contain a surfactant to reduce stickiness to tubing etc, a pre-dilution step decreases the surfactant concentration and leads to stickiness, resulting in possibly too low a dose delivered to the patient and sub-optimal images. On the other hand a post-injection saline flush is recommended when using injection lines to ensure that the entire radiotracer volume is administered to the patient and not remaining in the injection line.	add a clarification saying "It should be ensured, for both automated and manual injection, that the radiotracer is not being diluted with saline before or during the injection process. Flushing with saline should only occur after the injection and is recommended when using injection lines."	As suggested, add a clarification saying "It should be ensured, for both automated and manual injection, that the radiotracer is not being diluted with saline before or during the injection process. Flushing with saline should only occur after the injection and is recommended when using injection lines."	x
9	Radiotracer label	L	401/402	3.2.1.1 Timing of Image Data Acquisition	The table mentions an outdated uptake time and scan window for Vizamyl in column 3. The US label for Vizamyl has been updated in February 2017 to reflect an update/clarification to the uptake times to 60-90 minutes post injection and scan duration to 10-20 minutes. See https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203137s008lbl.pdf for the full PI	update Vizamyl information to 60-90 mpi for the Tracer Uptake Time and 10-20 min for the Scan Duration in the table	Modify to be consistent with the update of February 2017 to reflect uptake times to 60-120 minutes post injection and scan duration to 10-20 minutes. In addition, add the following qualifier: "The table below lists recommended tracer administration parameters at the time of this Profile, for tracers that have been approved by the FDA in the U.S. However, in all cases, the manufacturer's current labeling parameters should be consulted and followed, as these may change over time." Reference source updated to: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203137s008lbl.pdf for the full Prescribing Information (PI).	x
13	NAV4694	M	344/345 and 401/402	3.1.3.1.2 Radiotracer Activity Calculation and/or Schedule 3.2.1.1 Timing of Image Data Acquisition	These sections mention injection and image acquisition details for the tracer NAV4694. This tracer has not completed validation in phase III clinical trials and we would therefore challenge the validity of including this tracer with dose and acquisition details in a similar fashion to tracers that have completed their clinical development program, including autopsy validation, and have been approved by the regulatory authorities		Following the table, add: Another amyloid tracer, AV4694, has not yet completed validation in phase III clinical trials and therefore dose and the following acquisition details are preliminary: <acquisition data> Further state that while the principles of this profile are fairly generalizable, the specifics apply to the tracers that have already been approved and for which data is available.	x
36	Radiotracer administration	L	1259	4.2	Administered Radiotracer radioactivity and Acquisition device may be complemented	It should be documented when the 18F Radioactivity dose was received relative to the production time and the allowed expiration time in hours, since most of these tracers are sent from regional radiopharmacies.	As long as the use of the radioactive tracer is within the limits of the package insert, the additional documentation related to the time of production is likely to minimally impact the quantification. Proposed resolution is to not modify.	x
67	Radiotracer label	M	344	3.1.3.1.2	There is no notation that all of the tracers have a maximum of 10 ml	Consider noting that all tracers have a maximum of 10 ml	Note that all tracers have a maximum of 10 ml	x
68	Radiotracer label	M	401	3.2.1.1	Values on Vizamyl may be wrong	Please confirm as of February 2017, the new parameter is 60-120 mpi	As noted in previous comment regarding line 401, it will be noted that as of February 2017, the new parameter is 60-120 mpi.	x
77	Radiotracer label	M	1413	REFERENCES (below 4.5)	References - Package Inserts	If this is a global recommendation, should the EU product labels be in there	Modify section to say: "Note that U.S. prescribing information is listed below for approved tracers. However, this profile is not limited to the U.S. and prescribing information for the relevant country should be consulted for studies outside of the U.S."	x
78	Radiotracer label	L	1416	REFERENCES (below 4.5)	Change date for Vizamyl	Updated February 2017	Change date for Vizamyl to Updated February 2017.	x
82	Radiotracer label parameters	M	1420	REFERENCES (below 4.5)	Neuraceq [package insert]. Change 2014 to 2017.			x
		L	1341	REFERENCES (below 4.5)	The Centiloid Scale paper from Chris Rowe is sited but you might also want to include this attached paper by Chris Rowe on the Centiloid for Neuraceq.		Add reference: Rowe CC, Doré V, Jones G, Baxendale D, Mulligan RS, Bullich S, Stephens AW, De Santi S, Masters CL, Dinkelborg L, Villemagne VL. 18F-Florbetaben PET beta-amyloid binding expressed in Centiloids. Eur J Nucl Med Mol Imaging. 2017 Nov;44(12):2053-2059.	x
52	Reporting	M	968-974	3.5	In this section that use of structured reporting is mandated. This is an often-debated topic. Many institutions have not adopted the concept of structured reporting, and are, in fact, opposed to its use in image interpretation.	Resolve how reporting will be done with quantitative/and or qualitative values.	Remove: "In other words, how quantitative response is measured should be specified a priori by the trial itself. This also applies to target lesion selection." In addition, modify language in box to read "Imaging reports shall be populated from DICOM header information and shall conform to the requirements of the study protocol" rather than to refer to structured reporting.	x
14	PET/MR	H	59	1	The statement "PET/MR scanners are excluded because of their novelty und unknown quantification differences as compared to PET/CT and dedicated PET scanners" raises the following concerns: It may not be reasonable to categorically exclude PET/MR scanners. In fact, modern PET/MR scanners are no experimental tools but they are approved for clinical application. A number of studies have been published on successful PET/MR application in the brain, including amyloid-imaging. Although some differences have been reported, it cannot be concluded that PET/MR scanners are generally unsuitable for amyloid-PET studies. Particularly, in several recent studies optimized attenuation correction algorithms for PET/MR (now also taking bone into account) have been introduced. For these approaches, comparable performance to PET/CT has been demonstrated. If patients are scanned twice on the same PET/MR scanner, variance introduced by the scanner type cannot be reasonably expected to result in errors greater than those potentially evoked by the suggested semi-quantitative assessment of longitudinal amyloid-PET data itself. Additionally, CT-based attenuation correction using a separately acquired head CT can be used for attenuation correction of emission data from PET/MR studies. It may also be strategically inopportune to exclude validity of the QIBA profile for an entire instrumentation class (which is considered a tool particularly well-suited for brain imaging).	Consequently, it may be suggested to include a statement that the conclusions of the QIBA profile may also be considered to be valid for PET/MR - depending on status of validation of the respective scanner and the employed data processing approaches. Please also see references enclosed see additional reference as a comment: References: 1: Cecchin D, Barthel H, Poggiali D, Cagnin A, Tiepolt S, Zucchetta P, Turco P,Gallo P, Frigo AC, Sabri O, Bui F. A new integrated dual time-point amyloid PET/MRI data analysis method. Eur J Nucl Med Mol Imaging. 2017 Jul 4. doi: 10.1007/s00259-017-3750-0. [Epub ahead of print] PubMed PMID: 28674847. 2: Werner P, Rullmann M, Bresch A, Tiepolt S, Jochimsen T, Lobsien D, Schroeter ML, Sabri O, Barthel H. Impact of attenuation correction on clinical [(18)F]FDG brain PET in combined PET/MRI. EJNMMI Res. 2016 Dec;6(1):47. doi: 10.1186/s13550-016-0200-0. Epub 2016 Jun 3. PubMed PMID: 27255510; PubMed Central PMCID: PMC4891306. 3: Hitz S, Habekost C, Fürst S, Delso G, Förster S, Ziegler S, Nekolla SG, Souvatzoglou M, Beer AJ, Grimmer T, Eiber M, Schwaiger	Based upon group discussion have modified language to allow for PET-MR scanners as long as they meet the performance criteria stated by the guidelines. In particular, because the profile requires use of the same scanner and software from scan to scan, longitudinal differences arising from PET-MR vs. PET-CT are avoided. The following language has been added to section 3.2" "PET/MR scanners are not strictly excluded in this version as long as the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the Claims. This work was not yet published when this Profile was released. Since the claims of this profile are only valid for the same patient being scanned on the same scanner with the same protocols and analysis, only the repeatability of the PET/MR SUVRs needs to be validated in the context of the Claims, and not the difference in SUVRs as compared to PET/CT scanners. Going forward in this document, PET scanner can mean either a PET/CT or a dedicated PET scanner (or as stated above, PET/MR). " The following language has been added to section 3.6.3: "PET/MR scanners may be added in future versions of this Profile or may already be included in this Profile if the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the claims." In addition, a section has been added to the References for PET-MR, listing the references suggested at left.	x
18	Scanner QC	L	86ff	1	Incomplete discussion on quality control	It may be mentioned here that for longitudinal studies a precise quality control of the scanner both daily and after some months for stability purposes is of paramount relevance. In addition, a process of harmonization is also of high relevance to make results comparable between centers.	Add suggested comments.	x
28	CT parameters	M	475-486	3.2.1.4	The statement Thus higher kVp (greater than or equal to 80 kVp) CT acquisitions are recommended in general (Abella et al). This statement is inconsistent with a later stagement in table on page 19" CT acquisition mode: 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."	There should be resolution between these two values and decision made to follow one or the other values.	In section 3.2.1.4 , the value of 100 has been changed to 80 in the appropriate box to match the text below that (and the Abella citation).	x
34	Phantom	M	1208-1209	4.1	"The technologist shall perform a 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" - How widely available and feasible is the Ge-68-cylinder constancy phantom for technologists?	This pertains to PET only scanners. Clarify that is this only applies to those scanners	The constancy check actually does not just apply to PET only scanners but the method may vary, and this section is "grayed", i.e. listed as a future item.	x
75	Terminology	M	1080	3.6.4.1	Under Uniformity QC should 3D be included under standard deviation and mean values?	Consider stating 3D	The term 2D has been used because it refers to drawing (or applying) a 2D region on all relevant slices. It has been clarified with additional text in parentheses that a 2D ROI drawn on multiple slices results in a 3D VOI.	x
55	Software availability	M	1065	3.6.4.1	General availability of software required for these analyses (for example Hoffman equivalent FWHM and gray/white ratio)	If such soft ware is required, suggest how it might be made generally available or propose to establish a centralised performance of complex analyses (like the Hoffman equivalent FWHM and gray/white ratio) at one central accreditation point using DICOM transferred files (as performed in ADNI, ACR or ACRIN trials). For other analyses, consider using SUVr software tools like, GE , Siemens, PMOD, MIM, etc. There are two groups of SUVr software approaches, first which are PET template based and depend on the tracer, and second, which are based on MRI templates and are not tracer dependant.	The Appendix H contains a detailed description of a process used to make use of the Hoffman phantom, and to evalute scans. The MATLAB script has not yet been provided but will be sought.	x
35	Patient specs	L	1234	4.2	List of required Metadata is not complete	The metadata list should also include information such as Body Mass Index (BMI), and any events that occur during the scan such as subject happened to leave the scanner to void or any unusual head movements that may have happened even during one scan frame duration.	List has been updated to indicte that the metadata list should also include information such as Body Mass Index (BMI - depending upon study requirements, in a grayed box), and any events that occur during the scan, such as subject needed to leave the scanner to void or any excessive head motion (in a grayed box). (BMI was previously omitted because this is a ratiometric calculation, but a BMI or weight measure can be useful in determining whether an out of range dose was actually administered.)	x
69	Subject positioning	M	435	3.2.1.2	There is no statement regarding centering	Consider including a statement about using lasers for horizontal and vertical centering	Insert "Lasers are recommended to aid in horizontal and vertical centering."	x
70	Subject positioning	M	438	3.2.1.2	There is no mentioning of centering	Perhaps revise to say Special attention must be paid to include the entire cerebellum "centered" in the image...	Revise to say Special attention must be paid to include the entire cerebellum centered along the x-axis (Anne verify), distanced if possible from the edge of the axial field of view (FOV) while also keeping the top of the brain within the FOV.	
16	Terminology	L	57	1	Using the term "neurology" could be misunderstood by other clinicians (no neurologists) that are also involved in the prescription and use of amyloid PET (regarding context and claims).	It might be considered to substitute the term "neurology" by "neurological conditions" or" neurodegenerative disorders".	Change "which target amyloid across scanners in neurology" to "that bind to fibrillar amyloid in the brain".	x
22	Terminology	H	170	2	The abbreviation "wCV" is not specified anywhere in the document	Explain abbreviation "wCV"	Prior to "wCV" spell out within subject Coefficient of Variation	x

23	Terminology	L	172	2	The text for point 7 is excessively long.	The text could potentially be somewhat shortened or focused stronger on the issue of a potential bias induced by longitudinal perfusion changes.	lines 115 through 208 have been reorganized for clarity, and the discussion of perfusion and clearance impact has been separated from text defining SUVR. A more detailed appendix is also being added for further information. The full paragraph in the Claim Considerations section now reads: "The SUVR, based on late timeframes, has been selected due to its logistical feasibility in multi-site trials, and its use to date in large reference studies such as ADNI. However, from the fundamental kinetic properties of radiotracers it can be understood that changes in SUVR may not represent only a change in specific signal (amyloid) but could, at least in part, be the result of changes or variability in perfusion (van Berckel et al, J Nucl Med. 2013) and/or tissue clearance (Carson RE et al, 1993). This impact, when random, is another source of variability included that contributes to the wCV. However, changes in perfusion and/or clearance can be systematic due to the action of certain pharmacological agents or due to disease progression (for example, in dementia stages of AD), creating artificial change in amyloid SUVR. Changes to SUVR can be on the order of 2% to 5% or greater, becoming significant in studies of amyloid accumulation, prevention, or modest removal. Whether or not a change in SUVR is affected by changes in perfusion and/or clearance ideally should be first demonstrated in a small (e.g. 20 subjects) cohort before SUVR is used in the larger clinical trial. At the very least these validation studies should be performed to assess the minimally required decrease in SUVR that is needed to rule out false positive findings because of disease and/or drug related perfusion effects. In the case of a new PET tracer, studies that include blood sampling should be conducted to confirm that the SUVR approach and use of a reference region are a suitable approach to measure tracer binding. For further details regarding considerations in kinetic modeling please see Appendix <>."	x
25	Terminology	L	208	3	Figure 3. Profile Activities - the figure includes "Image interpretation" on the right. For longitudinal assessment it could possibly include "image quantification"?	Possibly add "image quantification"	Figure 3 has been updated to show that the Analysis blocks result in SUVR (or DVR) measurements that can be compared for longitudinal assessment. A sentence has also been added indicating that the measures are then interpreted per the thresholds or criteria of the study (different from visual interpretation).	x
26	Terminology	M	241	3, point 3.4	Image Analysis: The term "Imaging physician" is not clear. Besides, in this scheme it does not become clear who is in charge of the PET study.	It may be recommended to follow the definition included in the EANM-SNMMI joint guidelines on amyloid-imaging: "Amyloid PET examinations should be performed by, or under supervision of, a physician specialized in nuclear medicine and certified by accrediting boards. Physicians who interpret amyloid PET should also complete appropriate training programs provided by the manufacturers of approved radiotracers."	Change Imaging Physician in 3.4 to Radiologist, Nuclear Medicine Physician or other qualified person with the necessary training to operate the image processing and analysis software. Change Imaging Physician in 3.5 to Radiologist, Nuclear Medicine Physician, or an individual meeting requirements designated for the study; note that qualitative image interpretation is not within the scope of this Profile.	x
27	Terminology	M	419	3.2.1.2	Regarding head positioning more detailed instruction may be expedient	Regarding hear positioning, it may be added: "Head should ideally be flexed to have axial slices passing through the cerebellum without intersection with the posterior occipital lobe. This avoids contamination of the posterior cerebellar region by the occipital lobe and the tentorium.	Add "Head should ideally be positioned to have axial slices passing through the cerebellum without intersection with the posterior occipital lobe. This avoids contamination of the posterior cerebellar region by the occipital lobe and the tentorium." (The word "flexed" suggests a potentially uncomfortable position)	x
29	Terminology	M	630	3.4	"specified measurements on the images" - this statement intrinsically implies a quantitative task.	Substitute "specified analysis of the images" to encompass qualitative and quantitative interpretation in this sentence.	Change to "specified measurements and analyses"	x
30	Terminology	L	638	3.4.1	"as received, without modification" - This statement is redundant.	One term or the other should be used.	Change to "The original (deidentified when applicable) data, without modification"	x
31	Terminology	L	640	3.4.1	" measurement" - Many different quantitative analyses may be acquired.	Use the term "measurements"	Change "measurement" to "measurements".	x
32	Terminology	L	661	3.4.2.1		Provide definition	Use PVEc, which was used repeatedly in prior sentences, and defined in the first sentence of this section.	x
33	Terminology	L	679	3.4.2.1	" PVE" - this is not an abbreviation not previously defined in this document.	Provide definition	State "Partial Volume Effects (PVE) when first used (see line 661)	x
37	Terminology	L	664	3.4.2.1	"FDG" - FDG not previously defined in this document	Substitute Fluorine 18 deoxyglucose for FDG as this is first usage of the term.	State "[18F]2-fluoro-D-2-deoxyglucose (FDG)".	x
38	Terminology	L	665	3.4.2.1	" amyloid deposits" - Use of the word deposit	consider " amyloid deposition …" as more appropriate phrasing	Replace deposits in that case with deposition. However, also separate that sentence into two, rather than using a semi-colon, as the current syntax is a little confusing.	x
40	Terminology	L	716	3.4.3	"These are discussed below and guidance provided to achieve accuracy and reproducibility." - Not grammatically correct.	Change to "These factors are discussed below and guidance is provided to achieve accuracy and reproducibility"	Change to "These factors are discussed below and guidance is provided to achieve accuracy and reproducibility"	x
42	Terminology	M	750-767	3.3.4	reporting characteristics - Are these required characteristic strictly for scientific data reporting, or are recommended for inclusion into the clinical report / scan interpretation.	Provide definition of reporting for scientific data (study) versus clinical reporting	The relationship between this comment and the section and lines cited were not quite understood. However, for reporting and scan interpretation, text has been added regarding the way "interpretation" applies to quantitative imaging - - i.e. not visual interpretation, but the subsequent application of, for example, comparison of longitudinal change across groups, or determination of whether the change meets criteria for an amyloid reducing therapy. Text in the interpretation section begins now with "In the context of this quantitative Profile, interpretation refers to the way in which the quantitative SUVR or DVR measurements are used, rather than to a visual interpretation of the scan. Reporting of SUVR or DVR values is subject to the requirements of the study."	x
54	Terminology	L	1031	3.6.3	Typographical error- quotation marks at end of the line	Remove quotation marks	Remove quotation marks as suggested.	x
59	Terminology	L	70	1. Executive Summary	Bias might be more important than precision for cross-sectional selection of subjects for trials. Precision is more important than bias for longitudinal measurements.	Change "precision" in line 70 and insert "bias" instead	Indicate that characterization of bias is important. Consult Nancy O for wording; current modified wording is: "Characterization of measurement bias is important for a cross-sectional Claim wherein the amyloid tracer is used primarily to select amyloid positive subjects. For the current Profile, which is a longitudinal Claim, the primary purpose is to assess for change in amyloid load following an intervention; in this case, precision is most important as long as bias remains constant over time."	x
61	Terminology	M	129		Does this line need the full PI Statement?	Include full PI statement regarding "inconsistent with pathological finding, etc.	The Profile text has been changed to exclude statements regarding the labeling implications of the amyloid tracer(s).	x
62	Terminology	M	237		Some tracers are approved in the EU.	Clarify to say "not approved in the US.	Clarify to say "not approved for clinical practice in the U.S. However, quantitation is available as part of various scanner and workstation software packages and is used extensively in clinical trials."	x
63	Relevance	M	304	3.1.2.3	No impact on data	Note this is a comfort measure with no impact on data	In parentheses note that (This is for comfort purposes and does not directly impact tracer uptake.)	x
64	Relevance	M	305	3.1.2.3	No impact on data	Note this is a comfort measure with no impact on data	In parentheses note that (This is for comfort purposes and does not directly impact tracer uptake.)	x
65	Relevance	M	306	3.1.2.3	May not apply to all tracers	May only be a comfort measure for some, but a "must do" for others	Changed to include "(and if not a full dynamic scan or early frame scan whereby acquisition begins immediately after injection, and if verified with tracer manufacturer's recommendations)"	x
66	Relevance	M	315	3.1.2.3	May not be necessary for all clinical exams	Please clarify if this is necessary for all clinical exams	Change to "use of all medications for the scan session (e.g. diuretic, sedative)"	x
73	Terminology	L	1013	3.6.2	Clarification on name of Society	Society of Nuclear Medicine and Molecular Imaging	Change to Society of Nuclear Medicine and Molecular Imaging	x
74	Terminology	L	1013	3.6.2	Clarification on SNMMI Tech Section	(SNMMI-TS)	Change abbreviation to (SNMMI-TS)	x
76	Terminology	L	1114	3.6.4.3	typo	"measured"	This actualy was likely intended to be "measurand" but has been changed to "measurement".	x
5	Appropriate Use	M	266		The Appropriate Use Criteria does not apply for clinical trials of asymptomatic AD.		Substitute the following text: "Guidance for the use of amyloid to support diagnosis of symptomatic patients has been published in "Appropriate Use Criteria for Amyloid PET: A Report of the Amyloid Imaging Task Force". Asymptomatic or other clinical trials are guided by study objectives. See tracer manufacturer guidance for additional information regarding patient exclusions."	x
83	Radiotracer label use						(no action as comment was not present)	x
3	undefined	H	181				Have sent inquiry as to intended comment.	x
				3.6.6.	This section refers to inter-rater reliability, and visual reads are not within the scope of this Profile.	Remove section 3.6.6.	Remove section 3.6.6.	x
				3.6.5.3.	No content. Title referred to subjects for exclusion, but already addressed previously.	Remove section 3.6.5.3.	Remove section 3.6.5.3.	x
				References	Need to be updated to include those added, and to exclude references that are not relevant. In addition, may be difficult to find references as ordered by title when they are referred to in text body by first author last name.	Update Reference list. Begin each entry with the last name of the first author, and order within each section alphabetically to facilitate locating.	Update Reference list. Begin each entry with the last name of the first author, and order within each section alphabetically to facilitate locating.	x
				3.6.4.4	Major issue in that axial uniformity allowed for a 10% tolerance. This can introduce similar error into the longitudinal SUVR change if the subject is not positioned in the same axial place from scan to scan.	Add text regarding the axial uniformity implications and reduce uniformity requirement to 1%. Indicate that if this cannot be achieved, then reference and target regions must be in same axial slices to cancel out the error.	The following text has been added: Note that the historical axial uniformity tolerance of 10% has the implication that if a subject is imaged in one axial location for one scan, and in a different axial location (e.g. a few cm different) for the next scan, then the slices used to calculate each reference or target region value may change DIFFERENTLY. This can introduce error of a few percent to many percent into the longitudinal SUVR change. Selection of reference region and target region in the same axial slices can help to mitigate this potential source of noise, as the differences cancel out.	x
				3.6.4.3	Section numbers are repeated.	Increase last number so that section numbers are not redundant (3.6.4.4, 3.6.4.5)	Adjust section numbers	x