Topics for Discussion

Technical (acquisition) points (Anne)

Brief follow up on images for CSF signal assessment

Brief update on QIBA – ADNI gap analysis

Other key profile points:

- Claim and Supporting paragraphs
- Blood flow impact
- Additional

QIBA – ADNI Gap analysis

GAP ANALYSIS BETWEEN QIBA AMYLOID PROFILE AND ADNI AMYLOID PET PROCEDURES

January 11, 2018, updated February 9, 2018

A review of the QIBA Amyloid imaging profile and the ADNI 2 AV-45 PET Technical Procedures Manual v1.0, 2011, shows a high level of consistency in procedures. This is expected as many of the QIBA recommendations are based upon the procedures that were developed over time by ADNI, benefitting from their experience. The data acquisition protocol for ADNI 3 has remained the same as for ADNI 2 with the exception that floretaben has been added as an amyloid tracer.

- Both documents emphasize the importance of subject positioning and motion prevention.
- The ADNI protocol is strict regarding image reconstruction parameters. (Based on the ADNI meta logs, scans have been rejected for payment and admission by ADNI QC for being found not in compliance.)
- There is an apparent inconsistency in ADNI protocol wording regarding the stringency of the 50 minutes post-injection start time in the ADNI protocol. One section appears to allow for a re-scan, which would change the time window.
- ADNI protocols do not address processing and analysis.
- Neither the QIBA profile circulated for public comment nor the ADNI protocol address the error that can be introduced into longitudinal measurement if standard axial uniformity requirements (+/-10%) are implemented and patient head position in axial field of view varies from scan to scan.

A discussion with ADNI might focus on clarifying the post-injection timing and addressing the importance of axial uniformity and consistent head placement, but in general, other acquisition guidelines are consistent with the QIBA profile.

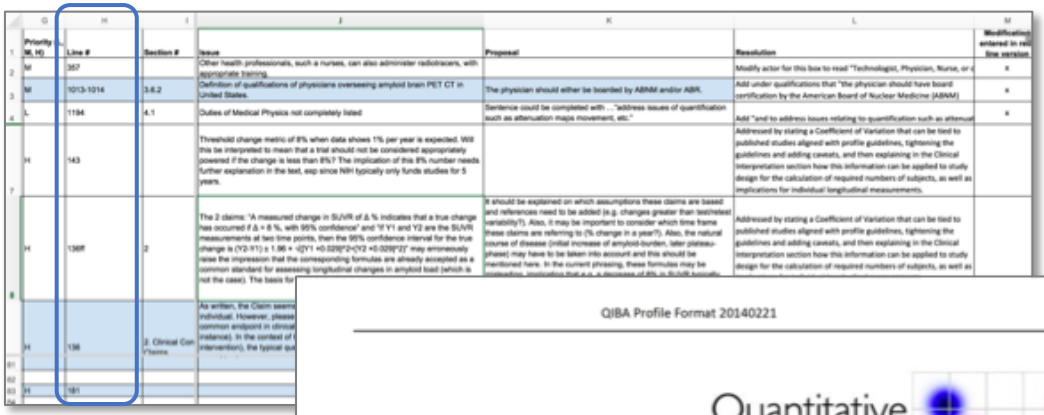
QIBA – ADNI Gap analysis (document table)

QIBA Profile		ADNI PET Technical Procedures Manual (2011)
3.1	No requirements on diet or other pre-scan activities.	No requirements on diet or other pre-scan activities.
3.1	Sedation usually avoided; indicates that effects not fully characterized.	**No sedation allowed.**
3.1.2	Subject voids prior to scan, seated comfortably.	Subject voids prior to scan, seated comfortably.
3.1.2	**Document any fluid intake**	Not addressed; may assume no intake allowed
3.1.3	Specifies mfr recommendations for 3 different tracers. **Does not provide a +/- % range. Does not specify no saline to be added.**	370 MBq (consistent with QIBA profile) **+/- 10%; no saline to be added**
3.1.3	Record any residual activity	Measure, record, and **adjust for residual activity if residual activity is 0.1 mCi or greater**
3.1.3	Record any infiltration event observed	Does not address infiltration, but notes watching for damage
3.2	CT quality checks, contains additional detail and references vs. ADNI	Less detailed but consistent wrt QIBA profile CT checks; follow mfr instructions for blood glucose monitor; typical QC for dose calibrator
App D	Scanner quality control – specific checks and frequency	Less detailed but consistent wrt daily QC/blank scan, up to date calibration, normalization on date of each imaging session.

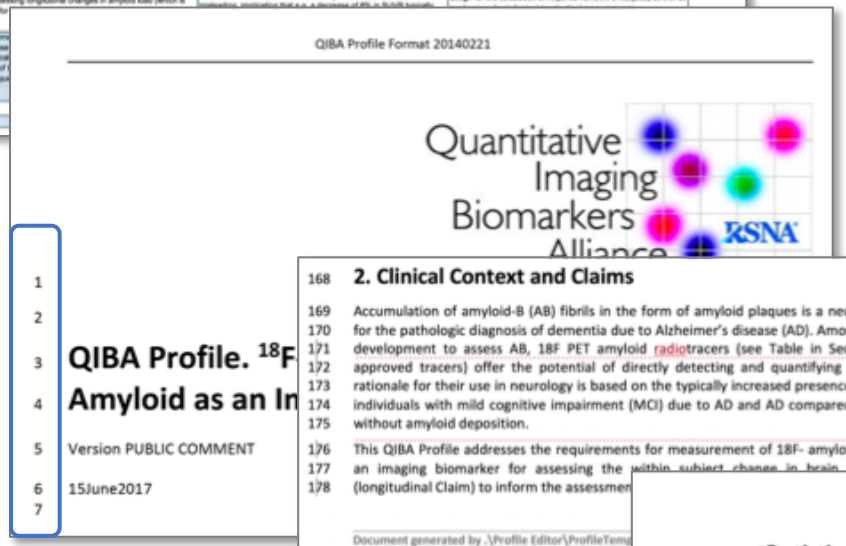
QIBA – ADNI Gap analysis (document table)

QIBA Profile		ADNI PET Technical Procedures Manual (2011)
	Profile version circulated for public comment allowed the standard +/- 10% axial variability, which is problematic for longitudinal scans.	Silent on the standard +/- 10% axial variability, which is problematic for longitudinal scans.
App F	Hoffman phantom instructions	Uses Hoffman phantom for qualification; images reviewed centrally
3.2	Use same scanner for all longitudinal scans. Does not mention changes to hardware or software within same scanner. Notify Sponsor if change to scanner.	Use same scanner for all scans in study. Do not change hardware or software. Notify ADNI if change occurs and may need to re-do phantom scan to re-qualify.
3.2	Use same acquisition parameters for all longitudinal scans	Prescribes same parameters for all scans though does not additionally stress importance for longitudinal scans.
3.2.1.1	Use same time interval from start to completion	Prescribes same time interval from start to completion for all scans but does not additionally stress importance for longitudinal scans.
3.2.1.1	Use same start time post-tracer injection.	Prescribes 50 minutes post-tracer injection. However, another section preceding says "approximately 50 minutes" and suggests a re-scan immediately following the first scan if reconstruction shows artifact or excessive motion.
3.2.1.2	Strong emphasis on subject positioning	Strong emphasis on subject positioning. Goes further in strongly recommending use of laser aligned markings.
3.2.1.2	Strong emphasis on securing subject in head holder and avoiding subject motion	Strong emphasis on securing subject and avoiding subject motion
3.2.1.3	Ensure complete anatomic coverage	Ensure complete anatomic coverage
3.2.1.4	Acquire in list mode or using multiple frames with a maximum of 5 minutes per frame	Always acquire using four frames of 5 minutes each (specific to florbetapir)
3.2.1.4	Use consistent CT acquisition; provides guidelines	Use consistent CT acquisition; provides guidelines
3.3.1	Reconstruction. Current version references tables that are not present. Reconciling.	Reconstruction specifically prescribed, always the same for a given scanner

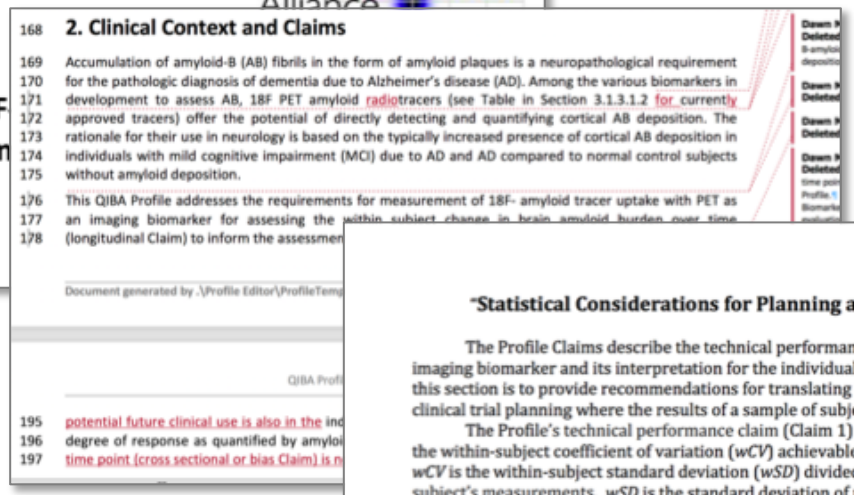
Four relevant documents



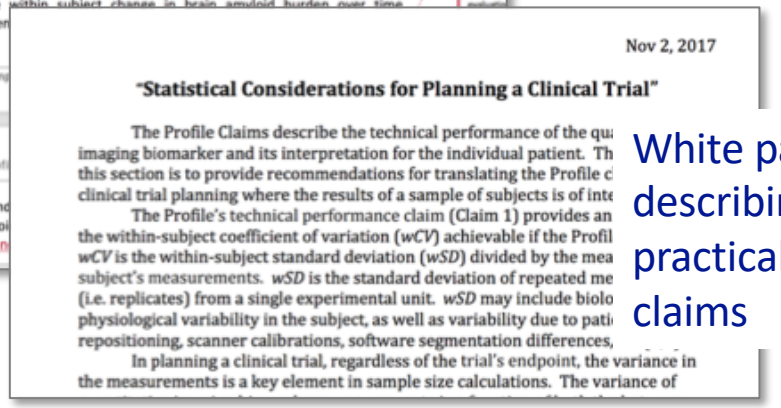
Excel spreadsheet with public comments, pdf line number references, and proposed responses



Pdf version of the profile circulated for public comment



Red-lined Word version of profile



White paper describing practical use of claims

Public comment and response worksheet

Ref. line # and section

Submitted issues or suggestions

Submitted proposed ways to address

How addressed by Profile committee in Word version*

Track

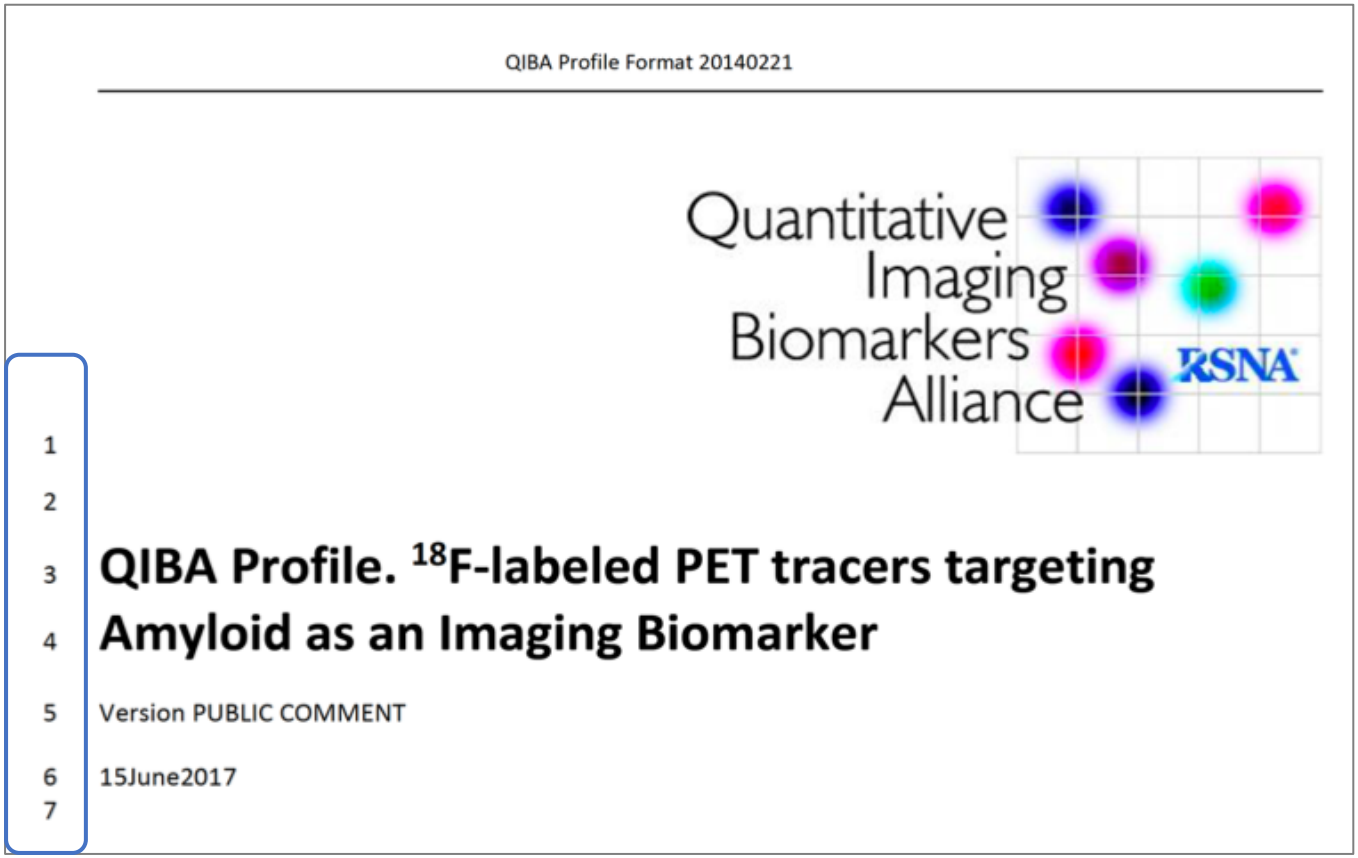
	G	H	I	J	K	L	M
1	Priority (L, M, H)	Line #	Section #	Issue	Proposal	Resolution	Modification entered in red line version
2	M	357		Other health professionals, such a nurses, can also administer radiotracers, with appropriate training.		Modify actor for this box to read "Technologist, Physician, Nurse, or c	x
3	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)	x
4	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 attenuat	x
7	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
	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 x √(Y1 x0.029^2+Y2 x0.029^2)" may erroneously	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-	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	x

*Proposed responses in Word document are provided for whole profile committee review with opportunity for suggested refinement

Status: 50 of approximately 80 updates inserted into red-line version, completing today

QIBA profile: pdf version circulated (June 2017)

Use this version to find the appropriate line(s) for each public comment



QIBA Profile Format 20140221

Quantitative Imaging Biomarkers Alliance

RSNA

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

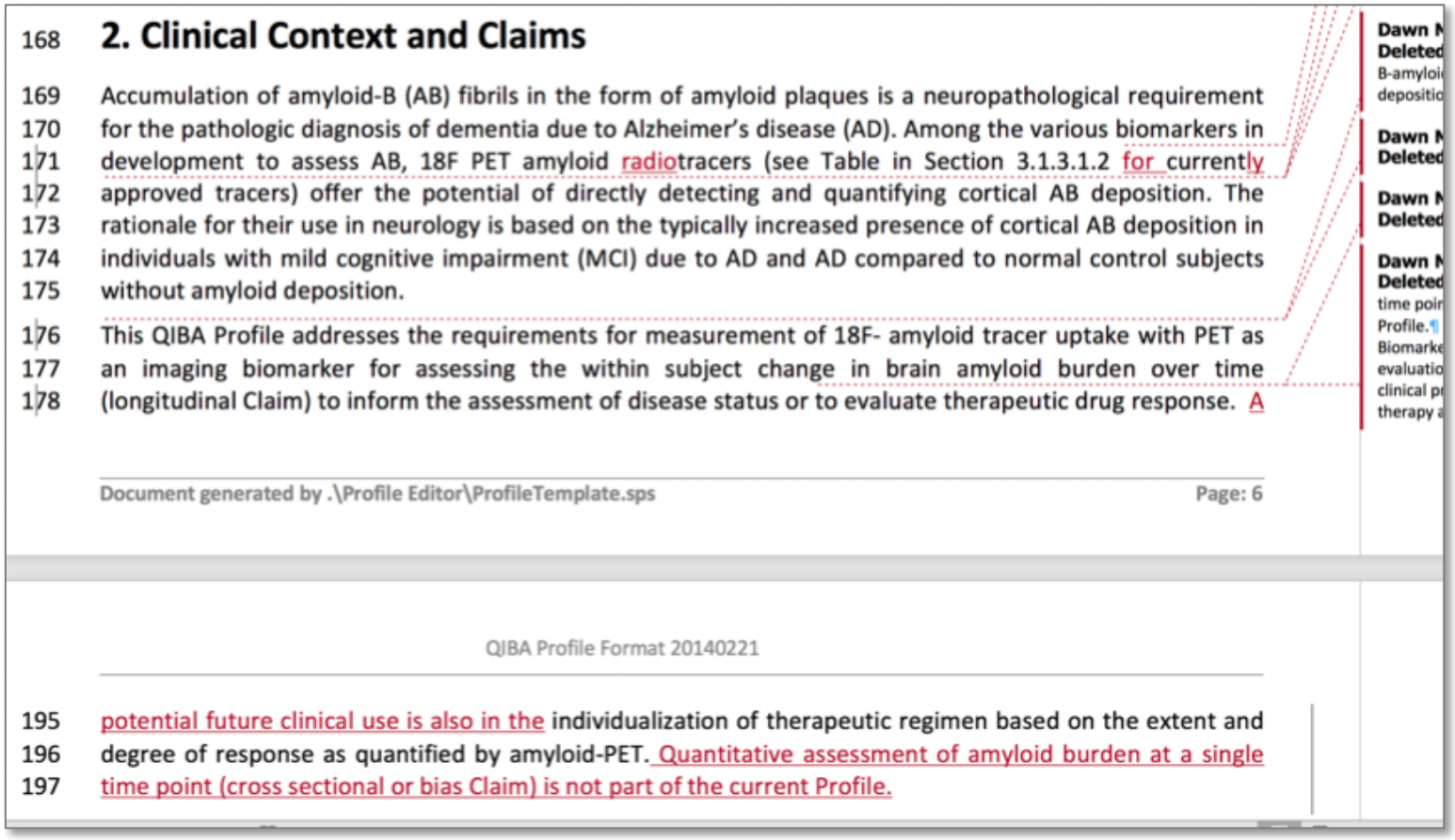
Version PUBLIC COMMENT

15June2017

Amyloid profile: Word version

Shows proposed responses, implemented

Line numbers are altered due to modifications; do not use



168 **2. Clinical Context and Claims**

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

176 This QIBA Profile addresses the requirements for measurement of 18F- amyloid tracer uptake with PET as
177 an imaging biomarker for assessing the within subject change in brain amyloid burden over time
178 (longitudinal Claim) to inform the assessment of disease status or to evaluate therapeutic drug response. A

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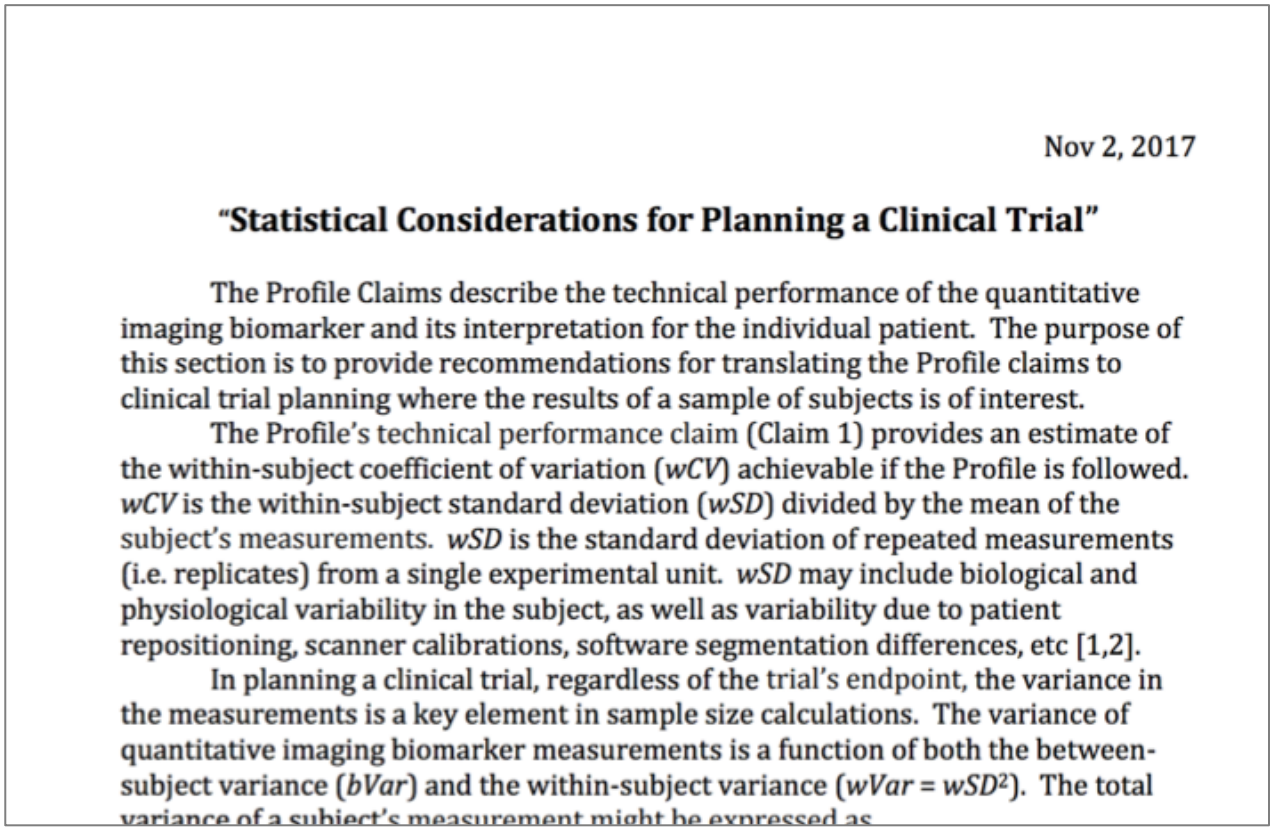
QIBA Profile Format 20140221

195 potential future clinical use is also in the individualization of therapeutic regimen based on the extent and
196 degree of response as quantified by amyloid-PET. Quantitative assessment of amyloid burden at a single
197 time point (cross sectional or bias Claim) is not part of the current Profile.

Use of claims in clinical trial planning

https://qibawiki.rsna.org/images/d/dc/StatisticalConsiderationsForClinicalTrialPlanning-2017.11.02.pdf

QIBA concepts -> Claim (definition link) -> Claim Guidance -> See also Clinical Trial Planning -> link to paper



Nov 2, 2017

"Statistical Considerations for Planning a Clinical Trial"

The Profile Claims describe the technical performance of the quantitative imaging biomarker and its interpretation for the individual patient. The purpose of this section is to provide recommendations for translating the Profile claims to clinical trial planning where the results of a sample of subjects is of interest.

The Profile's technical performance claim (Claim 1) provides an estimate of the within-subject coefficient of variation (*wCV*) achievable if the Profile is followed. *wCV* is the within-subject standard deviation (*wSD*) divided by the mean of the subject's measurements. *wSD* is the standard deviation of repeated measurements (i.e. replicates) from a single experimental unit. *wSD* may include biological and physiological variability in the subject, as well as variability due to patient repositioning, scanner calibrations, software segmentation differences, etc [1,2].

In planning a clinical trial, regardless of the trial's endpoint, the variance in the measurements is a key element in sample size calculations. The variance of quantitative imaging biomarker measurements is a function of both the between-subject variance (*bVar*) and the within-subject variance ($wVar = wSD^2$). The total variance of a subject's measurement might be expressed as

Author:
Nancy
Obuchowski

Claim: One claim, for technical performance

Claim:

If Profile criteria are met, then:

Claim 1: Brain amyloid burden as reflected by the SUVR is measurable from 18F amyloid tracer PET with a within subject coefficient of variation of 1.44%

This is a technical performance claim that applies to longitudinal measurement of change in amyloid burden rather than cross-sectional measurement of amyloid burden. The ways in which this claim can be utilized on a practical basis for the powering of longitudinal clinical trials or in determining confidence intervals around a single longitudinal measurement are described below. Important assumptions, considerations, and limitations for this claim are also summarized below.

Use of Claim:

Prior claim wording:

If Profile criteria are met, then:

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

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

Claim 3: If Y1 and Y2 are the SUVR measurements at two time points, then the 95% confidence interval for the true change is (Y2-Y1) ± 1.96 × √([Y1 ×0.029]^2+[Y2 ×0.029]^2).

Claim: Basis

Applicable references within test-retest time window:

Vandenberghe et al, 2010

Joshi et al, 2012

Additional references within a practical clinical trial time window:

Chen et al, 2015

Brendel et al, 2015

(other longitudinal papers are also cited in profile)

Use of Claim

Most relevant longitudinal applications are in powering a study to measure:

- Accumulation rates in preclinical, prodromal populations
- Reduction in accumulation rate by an interventional drug
- Amyloid removal (reduction of existing burden)

One could also apply this to evaluate an individual's change in amyloid:

- Associated with an anti-amyloid (removal) drug
- Over a duration of a few to several years whereby typical accumulation would exceed the confidence interval for measurement

Impact of blood flow changes

Changes in blood flow can cause changes in late frame SUVR that may be erroneously interpreted as amyloid change

Significant factor in some longitudinal studies, particularly in AD patients or potentially if an interventional compound alters blood flow

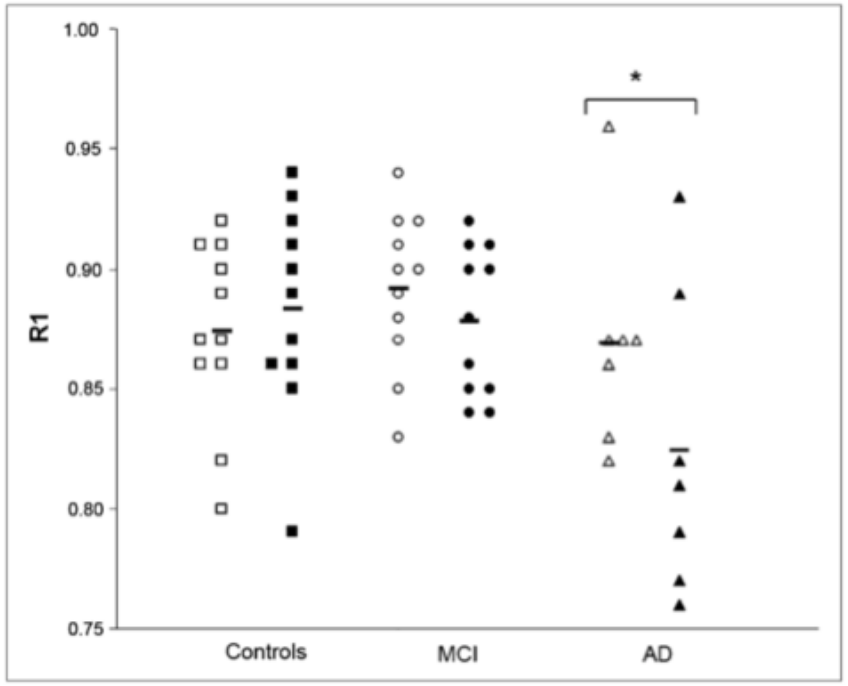


FIGURE 3. R_1 values at baseline and follow-up for AD patients (▲ and △), MCI patients (● and ○), and controls (■ and □). Significant decrease in R_1 was found in AD group only. $^*P < 0.05$.

" The flow dependence is caused by the lack of equilibrium of tracer distributions between blood and tissue and the tissue compartments "

van Berckel et al, J Nucl Med, 2013

Impact of blood flow changes

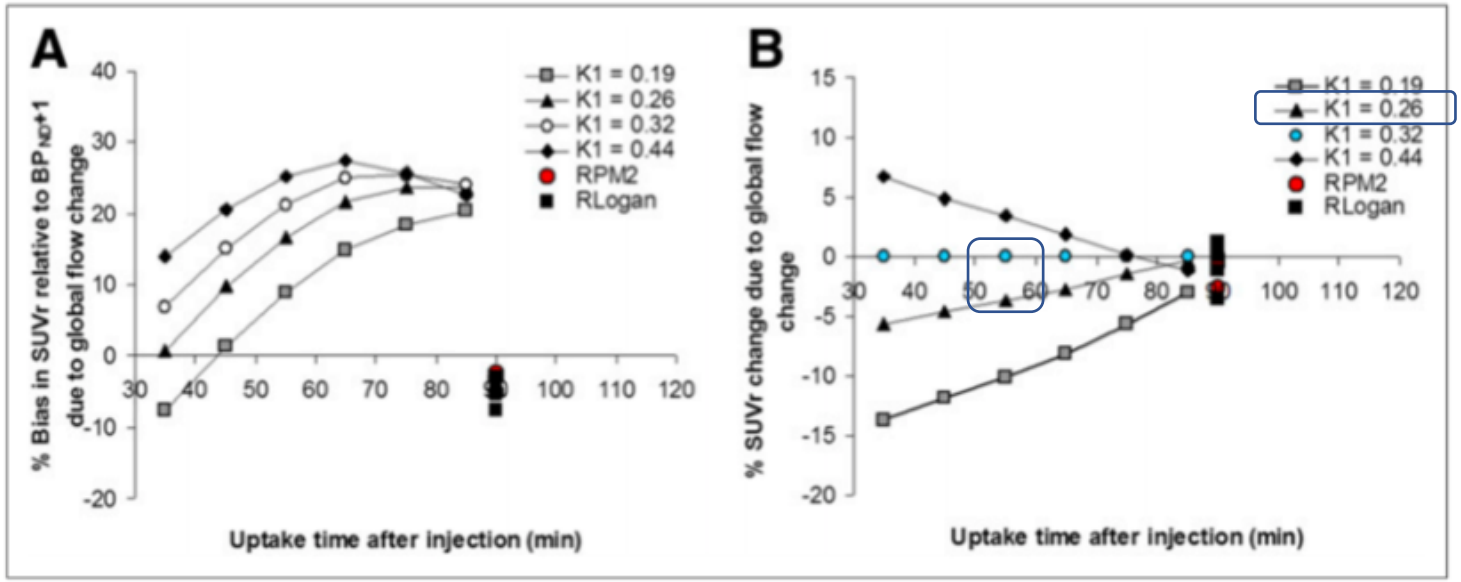


FIGURE 4. (A) Percentage bias in SUVr (relative to BP_{ND} + 1) as function of time for various K_1 values with $R_1 = 1$ (i.e., $K_1 = K_1'$). For comparison, BP_{ND} + 1 obtained with RPM2 and reference Logan are indicated at 90 min after injection. (B) Percentage bias in change in SUVr (relative to change in BP_{ND} + 1) as function of time for various follow-up K_1 values, baseline $K_1 = 0.32$ mL·cm^{-3}·min^{-1} and with $R_1 = 1$ (i.e., $K_1 = K_1'$) both at baseline and at follow-up. For comparison, BP_{ND} + 1 obtained with RPM2 and reference Logan are indicated at 90 min after injection. RPM2 and reference Logan results for all simulated K_1 values are plotted at 90 min after injection. *x*-axis represents mid-time of 10-min period for calculating SUVr measures.

van Berckel et al, J Nucl Med, 2013

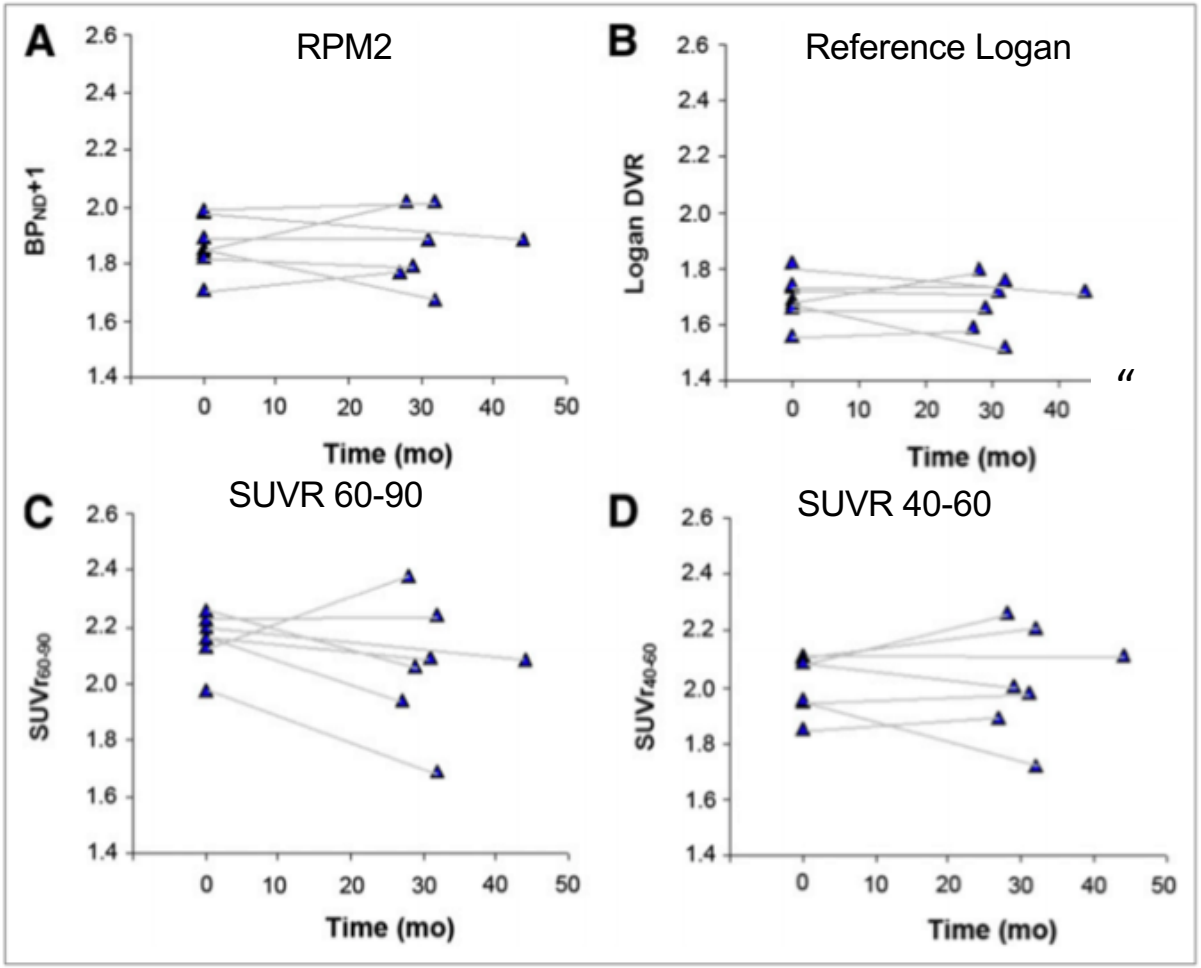
Impact of blood flow changes

Cselenyi et al, J Cerebral Blood Flow and Metabolism, 2015

Examined blood flow impact using the dual frame ADNI 2 florbetapir data

In summary, the current findings suggest that changes in rCBF can in essence produce an effect on quasi-steady-state SUVR values that are at a similar level as the previously reported annual SUVR increases, i.e., equivalent to a 2% to 5% apparent increase in amyloid burden in LMCI/AD. Therefore, future longitudinal studies, either in basic research on disease pathophysiology or in drug efficacy trials, must account for the blood flow effect by measuring amyloid changes in a way that is not sensitive to this effect. The best-suited option for this purpose is quantitative PET imaging providing DVR estimates. Finally, the hereby experimentally implicated uncertainty as to the true rate of amyloid accumulation after clinical onset highlights the challenges of using this biomarker in clinical drug trials in LMCI/AD patients.

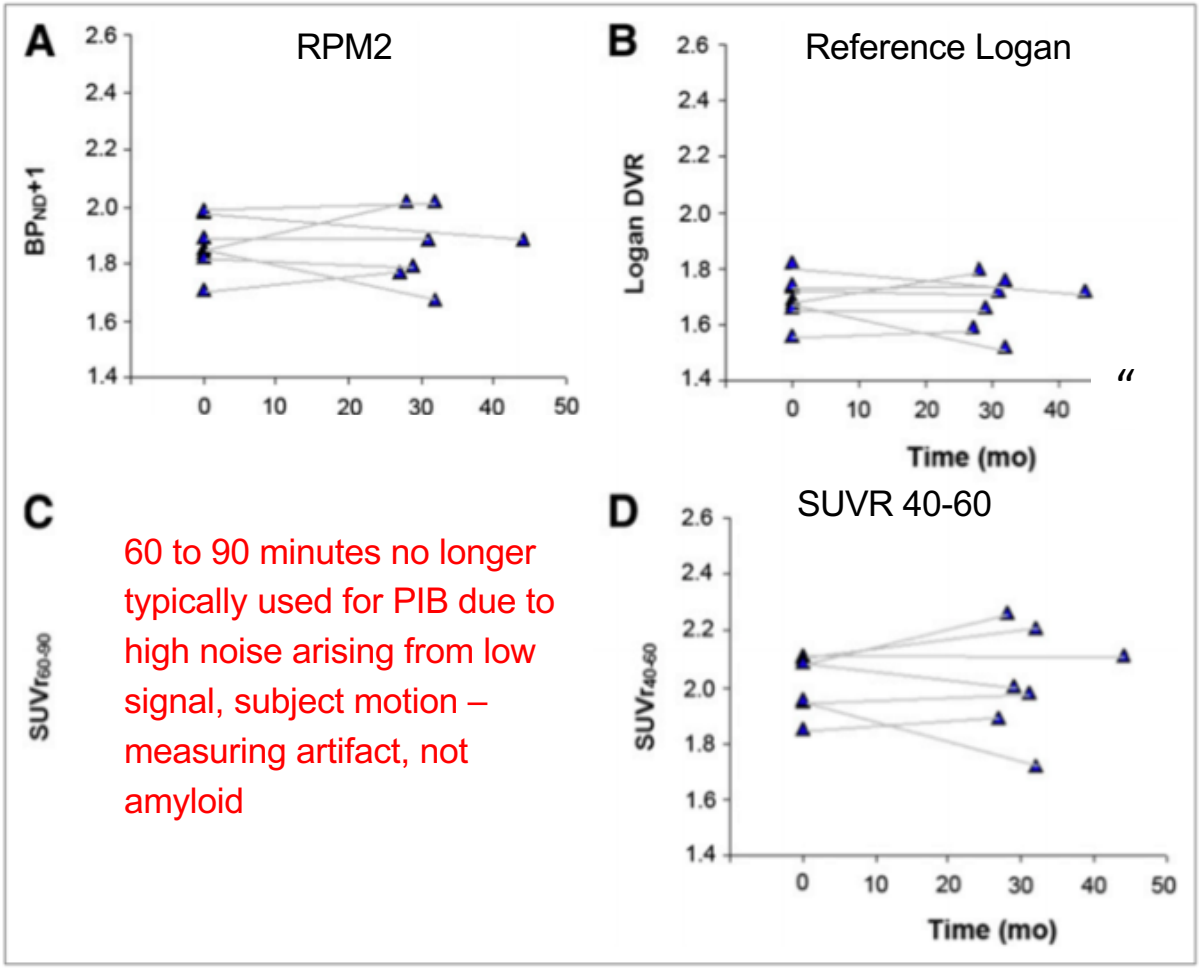
Impact of blood flow changes



Note: Dynamic models (e.g. RPM2 and reference Logan) also vary in bias and noise depending upon the model, whether blood input or reference region is used, and amyloid burden

Original figure: van Berckel et al, J Nucl Med, 2013

Impact of blood flow changes



Note: Dynamic models (e.g. RPM2 and reference Logan) also vary in bias and noise depending upon the model, whether blood input or reference region is used, and amyloid burden

Original figure: van Berckel et al, J Nucl Med, 2013

Alternatives

Exploratory full dynamic studies

Dual frame acquisition (de Santi, HAI 2018; Bullich et al, J Nucl Med, 2017)

Bolus (more difficult to implement consistently)