

Quantitative
Imaging
Biomarkers
Alliance



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QIBA Profile. FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy

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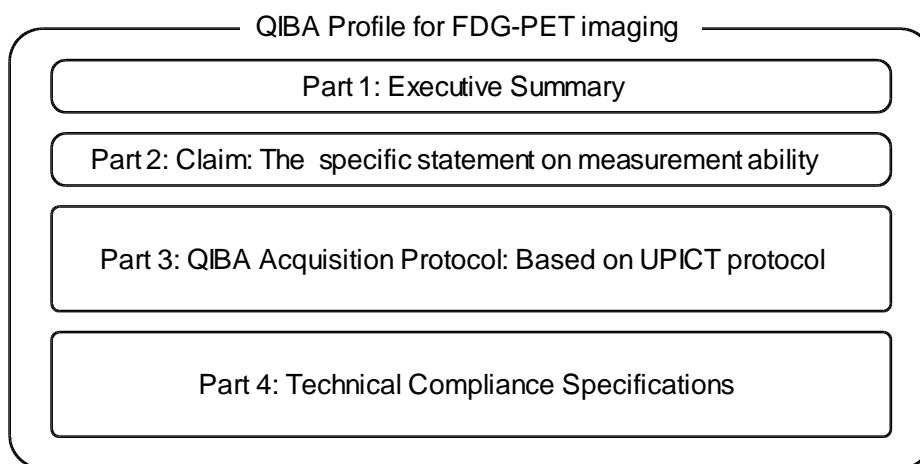
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40 1. Executive Summary

41 This QIBA Profile documents specifications and requirements to provide comparability and consistency for
42 quantitative FDG-PET across scanners in oncology. It can be applied to both clinical trial use as well as
43 individual patient management. This document organizes acquisition, reconstruction and post-processing,
44 analysis and interpretation as steps in a pipeline that transforms data to information to knowledge.

45 The document, developed through the efforts of the QIBA FDG-PET Technical Subcommittee, has shared
46 content with the FDG-PET UPICT protocol, as well as additional material focused on the devices used to
47 acquire and analyze the FDG-PET data.



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Figure 1: Illustration of the Profile components

50 The Profile Part 3 is largely derived from the FDG-PET UPICT protocol for FDG PET imaging in clinical trials.
51 In the UPICT protocol, there is a carefully developed hierarchy with tiered levels of protocol compliance.
52 This reflects the recognition that there are valid reasons to perform trials using different levels of rigor,
53 even for the same disease/intervention combination. For example, a high level of image measurement
54 precision may be needed in small, early-phase trials whereas a less rigorous level of precision may be
55 acceptable in large, late-phase trials of the same drug in the same disease setting.

56 The three levels of compliance for UPICT protocols are defined as:

57 ACCEPTABLE: failing to meet this specification will result in data that is likely unacceptable for the intended
58 use of this protocol.

59 TARGET: meeting this specification is considered to be achievable with reasonable effort and equipment
60 and is expected to provide better results than meeting the ACCEPTABLE specification.

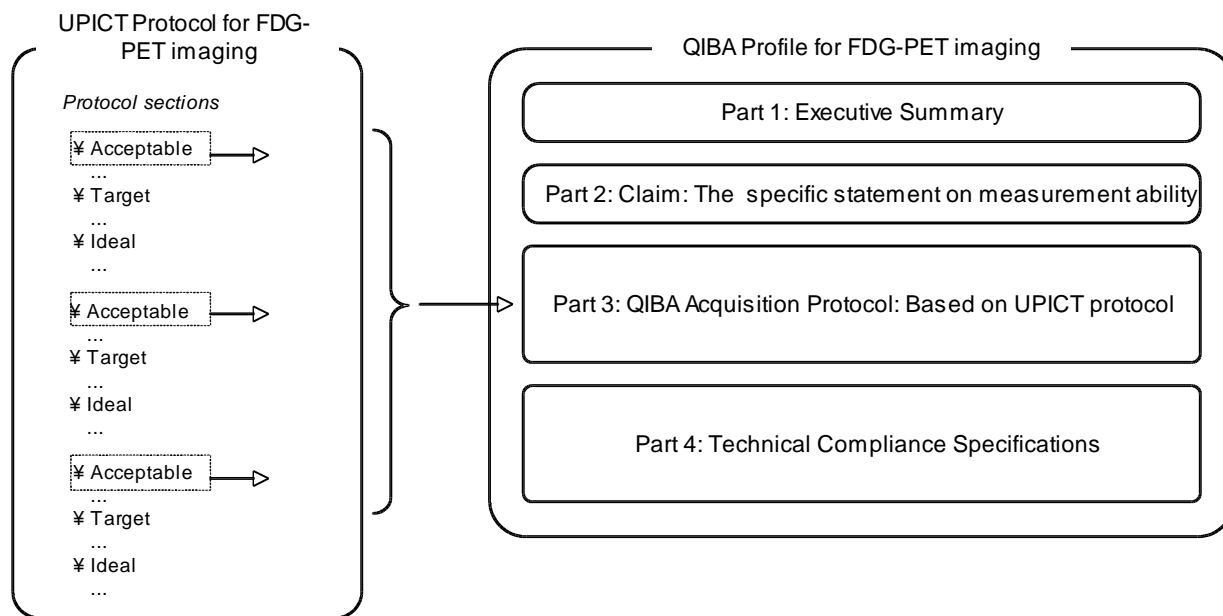
61 IDEAL: meeting this specification may require unusual effort or equipment, but is expected to provide
62 better results than meeting the TARGET.

63 ACCEPTABLE values are always provided for each parameter in a UPICT Protocol. When there is no reason
64 to expect better results (e.g. in terms of higher image quality, greater consistency, lower radiation dose,
65 etc.), TARGET and IDEAL values are not provided.

66 This Profile draws on the ACCEPTABLE components of the UPICT Protocol. Later revisions of this Profile are
67 expected to draw on the Target and then Ideal categories of the UPICT Protocol. The Target and Ideal

68 categories are intended to account for advances in the field and the evolving state-of-the-art of FDG-
 69 PET/CT imaging. These concepts are illustrated in Figure 2 below.

70



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Figure 2. Relationship between the UPICT Protocol and the Profile.

73 Summary for Clinical Trial Use

74 The QIBA FDG-PET/CT Profile defines the technical and behavioral performance levels and quality control
 75 specifications for whole-body FDG-PET/CT scans used in single- and multi-center clinical trials of oncologic
 76 therapies. While the emphasis is on clinical trials, this process is also intended to apply for clinical practice.
 77 The specific claims for accuracy are detailed below in the Claims.

78 The specifications that must be met to achieve compliance with this Profile correspond to acceptable levels
 79 specified in the FDG-PET UPICT Protocol. The aim of the QIBA Profile specifications is to minimize intra- and
 80 inter-subject, intra- and inter-platform, and inter-institutional variability of quantitative scan data due to
 81 factors other than the intervention under investigation. FDG-PET/CT study(ies) performed according to the
 82 technical specifications of this QIBA Profile in clinical trials can provide qualitative and/or quantitative data
 83 for single time point assessments (e.g., diagnosis, staging, eligibility assessment, investigation of predictive
 84 and/or prognostic biomarker(s)) and/or for multi-time point comparative assessments (e.g., response
 85 assessment, investigation of predictive and/or prognostic biomarkers of treatment efficacy).

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

90 The intended audiences of this document include:

- 91 • Technical staff of software and device manufacturers who create products for this purpose .

- 92 • Biopharmaceutical companies, oncologists, and clinical trial scientists designing trials with imaging
93 endpoints.
- 94 • Clinical research professionals.
- 95 • Radiologists, nuclear medicine physicians, technologists, physicists and administrators at healthcare
96 institutions considering specifications for procuring new PET/CT equipment.
- 97 • Radiologists, nuclear medicine physicians, technologists, and physicists designing PET/CT acquisition
98 protocols.
- 99 • Radiologists, nuclear medicine physicians, and other physicians making quantitative measurements
100 from PET/CT images.
- 101 • Regulators, nuclear medicine physicians, oncologists, and others making decisions based on
102 quantitative image measurements.

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

106 2. Clinical Context and Claims

107 FDG is a glucose analogue. The rationale for its use in oncology is based on the typically increased rate of
108 glycolysis in tumors compared to normal tissue. FDG is transported into tumor cells via glucose transport
109 proteins, usually up-regulated in tumor cells. Once internalized FDG is phosphorylated to FDG-6-phosphate;
110 it does not progress any further along the glycolytic pathway and becomes substantially metabolically
111 trapped. FDG uptake is not specific for tumor cells and there are some normal tissues and other processes
112 with increased glucose turnover, e.g. infection and inflammation, that show elevated uptake or
113 accumulation of FDG.

114 Applications and Endpoints for Clinical Trials

115 FDG-PET/CT imaging can be used for a wide range of clinical indications and research questions. These are
116 addressed more completely in the FDG-PET/CT UPICT Protocol (UPICT section 1.1). This QIBA Profile
117 specifically addresses the requirements for measurement of tumor FDG uptake with PET/CT as an imaging
118 biomarker for evaluating therapeutic response.

119 Biomarkers useful in clinical research for patient stratification or evaluation of therapeutic response would
120 be useful subsequently in clinical practice for the analogous purposes of initial choice of therapy and then
121 individualization of therapeutic regimen based on the extent and degree of response as quantified by FDG-
122 PET/CT.

123 The technical specifications described in the Profile are appropriate for quantification of tumor FDG uptake
124 and measuring longitudinal changes within subjects. However, many of the Profile details are generally
125 applicable to quantitative FDG-PET/CT imaging in other applications.

126 FDG-PET scans are sensitive and specific for detection of most malignant tumors [Fletcher 2008]. Coverage
127 for oncology imaging procedures in the US by the Centers for Medicare and Medicaid Services are explicitly
128 listed in the National Coverage Determination (NCD) for Positron Emission Tomography (PET) Scans (220.6).
129 FDG-PET scans reliably reflect glucose metabolic activity of cancers and this metabolic activity can be
130 measured with high reproducibility over time. Longitudinal changes in tumor 18F-FDG accumulation during
131 therapy often can predict clinical outcomes earlier than changes in standard anatomic measurements

[Weber 2009]. Therefore, tumor metabolic response or progression as determined by tumor FDG uptake can serve as a pharmacodynamic endpoint in well-controlled Phase I and Phase IIA studies as well as an efficacy endpoint in Phase II and III studies. In tumor/drug settings where the preceding phase II trials have shown a statistically significant relationship between FDG-PET response and an independent measure of outcome, changes in tumor FDG activity may serve as the primary efficacy endpoint for regulatory drug approval in registration trials.

Claim: Measure Change in SUV

If Profile criteria are met, then tumor glycolytic activity as reflected by the maximum standardized uptake value (SUV_{max}) should be measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%.

The following important considerations are noted:

1. This Claim applies only to tumors that are considered evaluable with PET. In practice this means tumors of a minimum size and baseline SUV_{max} (e.g. [Wahl 2009, de Langen 2012]). More details on what tumors are evaluable (minimum size and SUV_{max}) are described in section 3.6.5.3.

2. Details of the claim were derived from a review of the literature and are summarized in Appendix B. In these reports [Nakamoto 2002, Krak 2004, Velasquez 2009, Hatt 2010], it was assumed that the repeatability of SUV_{max} could be described by a fixed percentage of the baseline measurement. This assumption may not be applicable over the full range of clinically relevant SUVs and combinations of relative and absolute SUV changes have been proposed [de Langen 2012].

3. A within-subject coefficient of variation of 12% implies a limit of repeatability of $\pm 33\%$, that is, separate SUV_{max} measurements derived from test-retest PET/CT studies will differ by less than 33% for 95% of the observations. Note that asymmetric limits of repeatability have also been reported, e.g. -27 % to +37 % [Velasquez 2009].

4. This Claim is applicable for single-center studies using the same scanner. For multi-center studies, if FDG-PET/CT imaging is performed using the same scanner and protocol for each patient at each time point (as described in the Profile), then it is anticipated that this Claim will be met.

5. This Claim is based on SUV_{max} due to the evidence provided in the scientific literature. However, the use of SUV metrics derived from larger regions-of-interest (e.g. SUV_{peak}) are to be encouraged, as they may provide improved repeatability. In addition the use of automated and/or centralized analysis methods will further improve SUV repeatability. Note that while relative limits appear to be appropriate for SUV_{max} measures, it may be that absolute limits may be more appropriate for SUVs based on mean values for volumetric ROIs [Nahmias and Wahl 2008].

While the claim has been informed by an extensive review of the literature, it is currently a consensus claim that has not yet been substantiated by studies that strictly conform to the specifications given here. In addition we note that this claim should be re-assessed for technology changes, such as PSF (point spread function) based reconstruction or TOF (time of flight) imaging that were not utilized in published test-retest studies. A standard utilized by a sufficient number of studies does not exist to date. The expectation is that from future studies and/or field testing, data will be collected and changes made to this Claim or the Profile specifications accordingly.

3. Profile Details

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

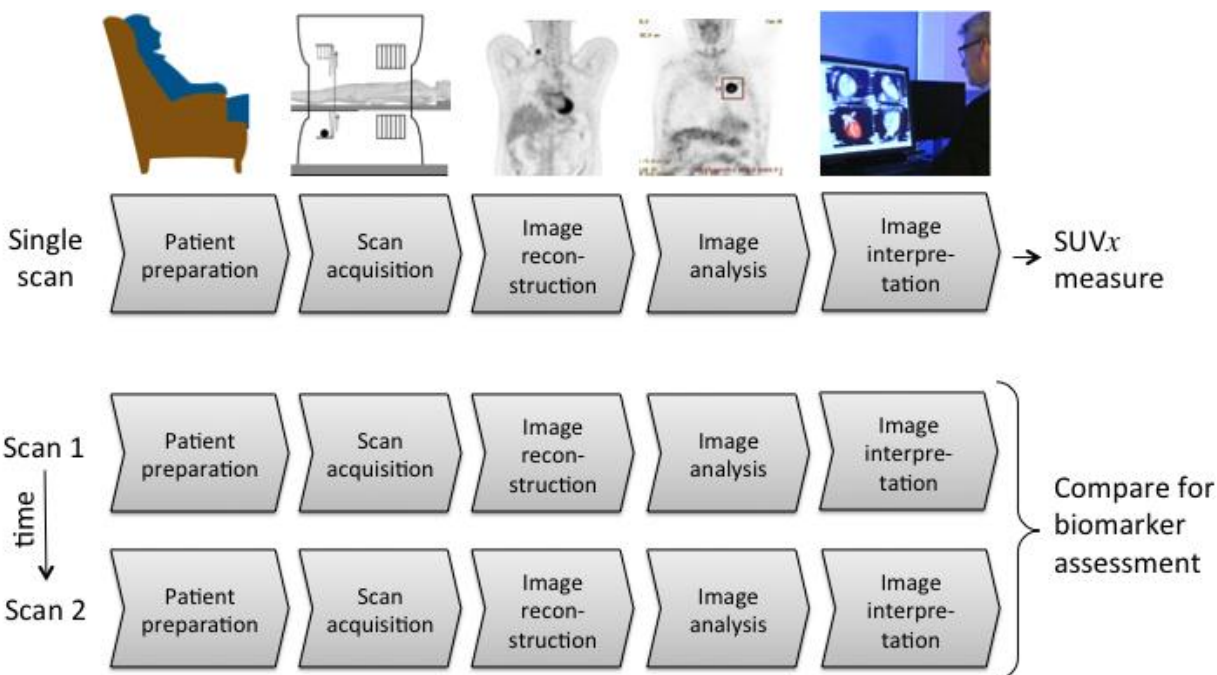


Figure 3: The assay method for computing and interpreting glycolytic metabolic activity using PET/CT may be viewed as a pipeline using either one or two or more scan sequences. The measure SUV_x refers to one of several possible SUV measures, such as SUV_{max}, SUV_{mean} or SUV_{peak}, with normalization by body weight or lean body mass.

Patients may be selected or referred for FDG-PET/CT imaging through a variety of mechanisms. In addition, patients are often required to undergo screening according to pre-scan requirements such as fasting levels and/or serum glucose levels as described below.

The imaging steps corresponding to Figure 1 are:

- 1) Patients or subjects are prepared for scanning (e.g. 6 hr fasting). FDG is administered. Patient waits quietly for bio-distribution and uptake of FDG (typically 60 min)
- 2) Scan data from the PET and CT exams is acquired.
- 3) Data correction terms are estimated and PET (and CT) images are reconstructed.
- 4) Quantitative measurements are performed.
- 5) Images are reviewed for qualitative interpretation.

Note that steps 4 and 5 may occur in either order or at the same time. More details on the requirements are given below.

Images may be obtained at multiple time points over days or weeks, notably at a minimum of two time points before and after therapeutic intervention for a response assessment as is considered by this document. The change in FDG uptake is typically assessed as a percentage according to the formula:

$$\left[\frac{\text{(post-treatment metabolic activity - pre-treatment metabolic activity)}}{\text{pre-treatment metabolic activity}} \right] \times 100$$
 Response criteria are then applied to categorize the response assessment. These response criteria

196 are beyond the scope of this document, but are discussed in the PERCIST proposal [Wahl 2009].

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

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

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

202 **3.1. Subject Handling**

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

205 ***3.1.1 Subject Selection, Timing, and Blood Glucose Levels***

206 The study protocol should include specific directions as to the management of subjects with abnormal
 207 fasting blood glucose measurements whether known to be diabetic or not. While it is known that high
 208 levels of circulating blood glucose reduce FDG uptake, there is a paucity of scientific data to suggest a
 209 specific cutoff for abnormally high blood glucose measurements or if these subjects should be excluded
 210 from clinical trials that use FDG-PET/CT scan data. It is important to define how such subjects and the data
 211 from their imaging studies will be managed to ensure comparability of imaging data within and among
 212 clinical trials. Specifically, consideration should be given to the exclusion of subjects with abnormal fasting
 213 blood glucose when quantitative FDG-PET/CT is being used as the study's primary endpoint. Refer to the
 214 FDG-PET/CT UPICT Protocol for Diabetic Scheduling and Management discussion (UPICT Section 4.2.2). It is
 215 also recommended that the study specifies what level of within subject variability in serum glucose levels is
 216 acceptable across time points and how subjects that fall outside that range will be interpreted.

217 **3.1.1.1 Timing of Imaging Test Relative to Intervention Activity (UPICT Section 1.2)**

218 The study protocol should specifically define an acceptable time interval that should separate the
 219 performance of the FDG-PET/CT scan from both (1) the index intervention and (2) other interventions (e.g.
 220 chemotherapy, radiotherapy or prior treatment). This initial scan (or time point) is referred to as the
 221 "baseline" scan (or time point). The time interval between the baseline scan and the initiation of treatment
 222 should be specified as well as the time intervals between subsequent FDG-PET studies and cycles of
 223 treatment. Additionally, the study protocol should specifically define an acceptable timing variance for

performance of FDG-PET/CT around each time point at which imaging is specified (i.e., the acceptable window of time during which the imaging may be obtained “on schedule”). The timing interval and window are dependent upon 1) the utility for the FDG-PET/CT imaging within the clinical trial, 2) the clinical question that is being investigated and 3) the specific intervention under investigation. Suggested parameters for timing of FDG-PET/CT within oncologic trials are more completely addressed in the FDG-PET/CT UPICT Protocol section 1.2.

3.1.1.2. Timing Relative to Confounding Activities (UPICT Section 3.2)

Activities, tests and interventions that might increase the chance for false positive and/or false negative FDG-PET/CT studies should be avoided prior to scanning. The allowable interval between the potentially confounding event and the FDG-PET/CT exam will be dependent on the nature of the confounding variable. For example, inflammation may cause focally increased FDG-PET activity (e.g. from a percutaneous or excisional biopsy of a suspicious mass) or might lead to the appearance of a non-malignant mass (e.g., hematoma) on the CT portion of the study. A percutaneous ablation procedure of a known malignant focus may cause focally increased FDG-PET activity and/or an immediate post-ablation increase in the apparent volume of the ablated target lesion. The time of onset and the duration of the increased FDG-PET activity and/or the change in lesion volume might be different for these two confounding factors.

If iodinated contrast is to be used for the CT portion of the PET/CT study, conflict with other tests and treatments should be avoided congruent with community standards of care (e.g., thyroid scan).

3.1.1.3. Timing Relative to Ancillary Testing (UPICT Section 3.3)

Avoid scheduling tests that might confound the qualitative or quantitative results of the FDG-PET/CT study within the time period prior to the scan. For example, a glucose tolerance test should not be scheduled during the 24 hours prior to the performance of FDG-PET/CT. Similarly, other tests that might involve increasing plasma glucose, insulin, or corticosteroid levels should also be avoided. Exercise cardiac stress testing should be avoided during the twenty-four (24) hours prior to the performance of FDG-PET/CT. Similarly, other tests that might involve vigorous exercise and thereby increase muscle metabolic function should also be avoided.

3.1.2 Subject Preparation (UPICT Section 4)

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

3.1.2.1. Prior to Arrival (UPICT Section 4.1)

The main purpose of subject preparation is to reduce tracer uptake in normal tissue (kidneys, bladder, skeletal muscle, myocardium, brown fat) while maintaining and optimizing tracer uptake in the target structures (tumor tissue). For more detail, refer to the FDG PET UPICT Protocol (Section 4.1) that addresses (1) Dietary, (2) Fluid Intake, and (3) Other activities that may affect tissue FDG uptake.

(1) Dietary

- a. Diabetic management – Refer to FDG-PET/CT UPICT Protocol sections 1.7.2 and 4.2.2
- b. Fasting status - Subjects should not eat any food (either oral or parenteral) for at least six hours prior to the anticipated time of FDG administration.

264 (2) Fluid Intake: Adequate hydration (before and after FDG administration) is important both to ensure
265 a sufficiently low FDG concentration in urine (fewer artifacts) and to reduce radiation exposure to
266 the bladder. Adequate hydration is especially important when contrast CT imaging will be used.
267 Whichever hydration strategy is used (how much and when to administer), the protocol should be
268 uniform among sites during a trial. Specific hydration recommendations are presented in the FDG-
269 PET/CT UPICT Protocol (reference Section 4.2.1). The fluid administered should not contain glucose
270 or caffeine.

271 (3) Other Activities: To minimize FDG uptake in muscle, the subject should avoid strenuous or extreme
272 exercise before the PET exam for a minimum of at least 6 hours (preferably for a time period of 24
273 hours).

274 The compliance issues around these parameters are dependent upon adequate communication and
275 oversight of the Scheduler or Technologist at the Image Acquisition Facility with the subject.
276 Communication with the subject and confirmation of compliance should be documented.

277 3.1.2.2. Upon Arrival (UPICT Section 4.2)

278 Upon arrival 1) confirmation of subject compliance with pre-procedure instructions and 2) the occurrence
279 of potentially confounding events (see listing in Section 4.2.1 of FDG-PET/CT UPICT Protocol) should be
280 documented on the appropriate case report forms.

281 There should be documentation of subject-specific risk factors including, but not limited to, previous
282 contrast reactions (if iodinated contrast is to be used).

283 3.1.2.3 Preparation for Exam (UPICT Section 4.2.3)

284 In order to avoid heterogeneous physiological distribution of the FDG, it is critical that subject preparation
285 after arrival and prior to imaging is standardized among all sites and subjects throughout the conduct of the
286 clinical trial.

- 287 • The waiting and preparation rooms should be relaxing and warm (> 75° F or 22° C) during the entire
288 uptake period (and for as long as reasonably practicable prior to injection, at least 15 minutes is
289 suggested as acceptable). Blankets should be provided if necessary.
- 290 • The subject should remain recumbent or may be comfortably seated; activity and conversation
291 should be kept to an absolute minimum. For example, the subject should be asked to refrain from
292 speaking, chewing, or reading during the uptake period. For brain imaging the subject should be in a
293 room that is dimly lit and quiet for FDG administration and subsequent uptake period.
- 294 • The subject may use the toilet, but if possible not for the 30 minutes immediately after injection of
295 FDG. The subject should void immediately (within 5 – 10 minutes) prior to the FDG-PET/CT image
296 acquisition phase of the examination.
- 297 • Bladder catheterization is not routinely necessary; but if necessary the catheter should be placed
298 prior to injection of FDG. Bladder catheterization may be important for the evaluation of pelvic
299 tumors (e.g., cervix or prostate cancer).
- 300 • Following the administration of FDG, the subject should drink 500 ml of water (or receive by
301 intravenous administration 250 - 500 ml of non-glucose containing fluid). Fluid intake may need to
302 be modified for those subjects on fluid restriction.
- 303 • For specific areas of anatomic interest (e.g., tumors located in the lower abdomen, pelvis or kidney)

304 intravenous diuretic agents may be used (e.g., 20 – 40 mg of furosemide given 15 minutes after the
 305 administration of FDG). If bladder catheterization is performed, IV diuretics should be administered
 306 as described here so as to ensure that the concentration of activity in the renal collecting systems
 307 and bladder is relatively dilute.

- 308 • Sedation is not routinely required, but is not contraindicated provided that the sedative used does
 309 not interfere with the uptake of FDG. Sedation may have utility in specific clinical circumstances
 310 such as brain or head and neck tumors, claustrophobic subjects, or children.
- 311 • The amount of fluid intake and use of all medications (e.g., diuretic, sedative) must be documented
 312 on the appropriate case report form.
- 313 • Subjects undergoing a CT scan should empty their pockets and remove any clothing containing
 314 metal and any metallic jewelry from the body parts to be scanned, changing into a hospital gown if
 315 necessary.

Parameter	Entity/Actor	Specification
Height and Weight	Imaging Technologist	The Technologist shall measure and document subject height and weight and enter this information into the scanner during the PET/CT acquisition. Subject height and body weight shall be measured at the time of each PET/CT scan with standardized measurement devices and with the subject in an examination gown or light clothing. If subject cannot be moved from the bed, the date and source of information should be documented.
		The Technologist shall measure subject height and weight and enter this information into a common data format mechanism used for recording all needed information (Appendix E).

- 316 • Diabetic Monitoring and Management (UPICT Section 4.2.2)

317 The subject's blood glucose level should be measured [using CLIA-approved, CLIA cleared, or equivalent
 318 (outside US) glucose measurement device or laboratory] within the preceding 2 hours (ideally within 1
 319 hour, especially in subjects with diabetes) of FDG administration and documented.

Parameter	Entity/Actor	Specification
Blood glucose level measurement	Imaging Technologist or Lab Technologist	Within 2 hours preceding FDG administration, shall measure and document time of subject blood glucose collection. Glucose measurement should be performed using a CLIA approved, CLIA cleared, or equivalent (outside US) glucose measurement device. Deviations from this process shall be documented.
Blood glucose level documentation	Imaging Technologist or Lab	Shall enter the results of the blood glucose assay and the time of blood draw on a case report form or similar subject information sheet.

Parameter	Entity/Actor	Specification
	Technologist	Shall enter the results of the blood glucose assay into a common format mechanism used for recording all needed information (Appendix E).
Blood glucose level Threshold	Imaging Technologist	Shall enforce the glucose thresholds for imaging as defined in the Protocol; if not, then reason for non-compliance shall be provided and documented on case report form or similar subject information sheet.
		Shall document any information on non-compliance with the protocol into a common format mechanism used for recording all needed information (Appendix E).

3.1.3. Imaging-related Substance Preparation and Administration (UPICT Section 5)

3.1.3.1. Radiotracer Preparation and Administration

3.1.3.1.1 Radiotracer Description and Purpose

The FDG radiopharmaceutical must meet USP United States Pharmacopeia or comparable International equivalent specifications or meet other current specifications as defined by the FDA, EMEA or other appropriate regulatory agency approval.

3.1.3.1.2 Radiotracer Activity Calculation and/or Schedule (UPICT Section 5.2)

The ¹⁸F-FDG activity administered ranges between about 185 – 740MBq (5 – 20 mCi). The administered activity typically depends upon the local imaging protocol. The local protocol may require fixed activity, or the activity may vary as a function of various parameters including but not limited to subject size or age, scanning mode, or percentage of scan bed (slice) overlap. To date there are no data providing evidence of superiority of parameter-dependent administered activity protocols. The exact activity and the time at which activity is calibrated should be recorded. Residual activity remaining in the tubing, syringe or automated administration system or any activity spilled during injection should be recorded. The objective is to record the net amount of FDG radiotracer injected into the subject to provide accurate factors for the calculation of the net SUV.

Parameter	Entity/Actor	Specification
Administered FDG Radiotracer Activity	Imaging Technologist	<p>The Technologist shall</p> <ol style="list-style-type: none"> 1. Assay the pre-injection FDG activity (i.e. radioactivity) and time of measurement, 2. Record the time that FDG was injected into the subject, 3. Assay the residual activity in the syringe (and readily available tubing and components) after injection and record the time of measurement. <p>These values shall be entered into the scanner during the PET/CT</p>

Parameter	Entity/Actor	Specification
		<p>acquisition.</p> <p>For scanners that do not provide for entry of residual activity information, the net injected radioactivity should be manually calculated by decay correcting all measurements to the time of injection and then subtracting the residual radioactivity from the pre-injection radioactivity. The net injected radioactivity is then entered into the scanner during the PET/CT acquisition.</p> <p>All data described herein on activity administration shall be documented.</p>
		All data should be entered into the common data format mechanism (Appendix E).

336 3.1.3.1.3 Radiotracer Administration Route (UPICT Section 5.4)

337 FDG should be administered intravenously through a large bore (21 gauge) indwelling catheter placed
338 anatomically remote (e.g., contralateral extremity to site of disease if at all possible) to any site(s) of
339 suspected pathology, preferably in an antecubital vein. Intravenous ports should not be used, unless no
340 other venous access is available. If a port is used, an additional flush volume should be used. As
341 reproducible and correct administration of FDG is required for quantification purposes, extravasation or
342 paravenous administration should be avoided. If an infiltration is suspected, the event and expected
343 quantity should be recorded and the infiltration site should be imaged. The approximate amount of
344 infiltration should be estimated from the images where possible. If the infiltration is greater than 5% of the
345 administered activity and the quantitative result from the FDG-PET/CT study is a primary or secondary
346 endpoint, the data point might be censored from review or the subject might not be included in the study.
347 The anatomical location of the injection site should be documented on the appropriate case report form or
348 in the Common Data Format Mechanism (Appendix E).

349 Presuming that the IV access is properly functioning, the same route of administration may be used for
350 iodinated contrast as is used for FDG.

Parameter	Entity/Actor	Specification
FDG Administration	Technologist	<p>Technologist shall administer FDG intravenously through a large bore (21 gauge) indwelling catheter placed anatomically remote to any sites of suspected pathology, preferably in an antecubital vein. Intravenous ports should not be used, unless no other venous access is available.</p> <p>In the case of manual administration, a three-way valve system should be attached to the intravenous cannula so as to allow at least a 10 cc normal (0.9% NaCl) saline flush following FDG injection.</p>
Suspected infiltration	Technologist	<p>Technologist shall</p> <ol style="list-style-type: none"> 1. Record the event and expected amount of FDG: [Minor (estimated less than 5%), Moderate (estimated more than 5% and less than 20%), Severe (estimated more than 20%)]. Estimation will be done based on

Parameter	Entity/Actor	Specification
		images and/or known injected volumes. 2. Image the infiltration site.
		Record the event and expected amount of FDG into the common data format mechanism (Appendix E).

3.1.3.2 CT Contrast Material Preparation and Administration

The use of CT contrast material during FDG-PET/CT imaging is complex and analyzed in detail in the UPICT FDG-PET Protocol (Section 3.2). In summary, the presence of IV and/or oral contrast material improves the detection of lesions with CT and may improve the anatomic localization, interpretation, and analysis of the FDG-PET/CT exam. However, the presence of contrast material may affect the attenuation correction of the PET scan with consequent bias in measured SUVs.

Parameter	Entity/Actor	Specification
CT Contrast Agent	Technologist	Technologist shall record the type and amount of CT Contrast Agent. 1. Was oral contrast used: Type [Positive, Negative], amount (volume in cc). 2. Was IV contrast used?, amount (volume in cc), time of injection.
		Record the event and expected amount of CT Contrast Agent into the common data format mechanism (Appendix E).

3.2. Image Data Acquisition

This section summarizes the imaging protocols and procedures that shall be performed for an FDG-PET/CT exam. Detailed descriptions are included in the referenced FDG-PET/CT UPICT protocol sections.

The motivation for controlling the image acquisition as tightly as described here is that over the course of a trial, hardware and software updates will occur. The intent of the Profile is to ensure that the instrument gives the same results over the duration of the trial.

It is recommended that all FDG-PET/CT scans for an individual subject be performed on the same PET/CT scanner hardware and software throughout the trial. In the event of equipment malfunction, follow-up scans on an individual participant can be performed on a different scanner of the same model and software version provided it has met the scanner qualification requirements. The follow up scans should be performed with identical acquisition parameters as the first (baseline), inclusive of all the parameters required for both the CT and PET acquisitions.

The FDG-PET/CT UPICT Protocol (Section 7.1.1) describes scanning strategies that can be used in a clinical trial. For strategy 1, there is no intent to obtain a diagnostic CT scan at the FDG-PET imaging session, however a low-dose CT scan is needed for attenuation correction. For strategy 2, a diagnostic CT scan is obtained. There are further considerations that must be followed for each of the two strategies. The workflow chosen for a given protocol should be described in the protocol and should be tailored commensurate to the level of expectation of the obtained data (e.g. qualitative or quantitative SUV analysis).

376 Strategy 1: For FDG-PET/CT in which the CT is used for attenuation correction and localization only (no
377 diagnostic CT intent):

- 378 • CT Scout (i.e. topogram or scanogram etc.), followed by
- 379 • CT for anatomic localization and attenuation correction, followed by
- 380 • PET Emission scan acquisition

381 Strategy 2a

- 382 • Follow Strategy 1 (above)
- 383 • Acquire an additional IV contrast-enhanced diagnostic CT scan

384 Strategy 2b

- 385 • Perform an IV contrast-enhanced diagnostic CT scan
- 386 • Follow Strategy 1 (above)

387

Parameter	Entity/Actor	Specification
Scanning Strategy (Workflow)	Technologist	Technologist shall follow Profile compliant workflow strategy, which will be compatible with Acquisition Device capability. The same workflow used at baseline shall be used at all subsequent time points.

388

389 For both strategies, there are several common issues specific to the CT exam that may have an impact on
390 quantitative FDG-PET output, which need attention and protocol specification. These include (1) contrast
391 material administration, (2) respiratory motion compensation instructions and (3) CT scanning technique
392 (kVp, mAs and pitch). Below is a summary of the acceptable level of behavior/procedure for each of these
393 three issues.

394 At a minimum, all these issues should be addressed in the clinical trial protocol, ideally with consistency
395 across all sites and all subjects (both inter-subject, and intra- and inter-facility) with the target of
396 consistency across all time points for each given subject. The actual details of imaging for each subject at
397 each time point should always be recorded. Any particular clinical trial should NOT allow some sites to
398 implement one strategy and other sites to implement the alternative.

399 *CT Exam Variables and Specifications:*

400 Contrast Agents - The presence of a positive contrast agent (IV or oral), by affecting the CT attenuation
401 map, may affect SUV quantitation [Mawlawi 2006]. If this were the only consideration, then ideal would be
402 to prohibit CT contrast administration. However, in some clinical situations (dependent upon tumor type,
403 tumor behavior or level of anatomic interest), the benefit of CT contrast agents may outweigh the small
404 errors induced in SUV measurement that may include increased SUV variability. Each protocol should
405 specify the desired approach for the given study. Most importantly, for each subject, the same approach
406 should be followed for all imaging time points.

407 In cases where CT contrast agents are used, there are two main strategies:

408 Strategy 1: No IV; dilute positive oral contrast allowed

409 Strategy 2: Use negative or dilute positive oral contrast for the non-attenuation CT scan. Ensure that
 410 the diagnostic CT acquisition (which may be performed with IV contrast) is performed consistently
 411 for a given subject across all time points.

Parameter	Entity/Actor	Specification
CT Contrast agent	Technologist	CT contrast agents shall be given commensurate with the workflow strategy as selected from above.

412 **3.2.1 Imaging Procedure**

413 The PET/CT exam consists of two components, the PET emission scan and the CT transmission scan (which
 414 may have multiple components). From these data sets, the non-attenuation-corrected PET images may be
 415 reconstructed for quality control purposes and attenuation-corrected PET images are reconstructed for
 416 qualitative interpretation and quantitative analysis. Instrument specifications relevant to the Acquisition
 417 Device are included in Section 4 Compliance – Acquisition Device.

418 **3.2.1.1 Timing of Image Data Acquisition**

419 FDG uptake into both tumors and other body tissues is a dynamic process that may increase at different
 420 rates and peak at various time points dependent upon multiple variables. Therefore, it is extremely
 421 important that (1) in general, the time interval between FDG administration and the start of emission scan
 422 acquisition is consistent and (2) when repeating a scan on the same subject, it is essential to use the same
 423 interval between injection and acquisition in scans performed across different time points.

424 While the “target” tracer uptake time is 60 minutes, the “acceptable” window is from 55 to 75 minutes to
 425 ensure that imaging does not begin prematurely so as to allow adequate tumor uptake of FDG and to
 426 account for the practicality of work flow that can result in delays in imaging later than 60 minutes after FDG
 427 injection. The exact time of injection must be recorded; the time of injection initiation should be used as
 428 the time to be recorded as the radiotracer injection time. The injection and flush should be completed
 429 within one minute with the rate of injection appropriate to the quality of the vein accessed for FDG
 430 administration so as to avoid compromising the integrity of the injection vein.

431 When performing a follow-up scan on the same subject, especially in the context of therapy response
 432 assessment, it is essential to apply the same time interval with target window of ± 10 minutes (with an
 433 acceptable window of ± 15 minutes) provided that the scan must not begin prior to 55 minutes after the
 434 injection of FDG. If a limited anatomy scan is obtained at follow-up after a whole body scan was performed
 435 at baseline, one should consider adjusting the timing of the follow up scan to be congruent with the timing
 436 for the same anatomic region as achieved during the baseline study.

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

Parameter	Entity/Actor	Specification
Tracer Injection Time	Technologist	The time of FDG injection shall be entered into PET/CT scanner console during the acquisition.
Tracer Uptake Time:	Technologist	The Technologist shall ensure that the tracer uptake time for the baseline scan is 60 minutes, with an acceptable range of 55 to 75

Parameter	Entity/Actor	Specification
		minutes. When repeating a scan on the same subject, especially in the context of therapy response assessment, the Technologist shall apply the same time interval ± 10 minutes provided that the scan must not begin prior to 55 minutes after the injection of FDG.

The following sections describe the imaging procedure.

3.2.1.2 Subject Positioning (UPICT Section 7.2.1)

Consistent positioning avoids unnecessary variance in attenuation, changes in gravity-induced shape and fluid distribution, or changes in anatomical shape due to posture, contortion, etc. During PET-CT, subjects should be positioned in the center of the field of view (FOV), preferably with the subjects' arms positioned over head for whole-body imaging (to minimize beam hardening and FOV truncation artifacts). In the case of dedicated brain or head/neck scans, the arms should be positioned down along the body. If the subject is physically unable to maintain arms above head for the entire whole-body examination then the arms can be positioned along the side before the start of the scan, unless the protocol specifically excludes such subjects. Arm positioning in a particular subject should be consistent between the PET emission and CT transmission scans at each time point and should be as consistent as possible across all time points.

Respiratory motion causes SUV errors by two mechanisms: motion blurring and errors in attenuation correction due to mismatches between CT-based attenuation map and emission data [Liu 2009]. Various strategies could be used to minimize, document and compensate for respiratory motion. Shallow breathing shall be performed during CT AC acquisition (see UPICT Protocol section 7.1.1). The subject should (a) be monitored and if breathing pattern is not consistent with shallow breathing expectation, coached in the breathing protocol and (b) should remain motionless throughout the scan.

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

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

Positioning Non-compliance	Technologist	The Technologist shall document issues regarding subject non-compliance with positioning.
		The Technologist shall document issues regarding subject non-compliance with breathing and positioning using the common data format mechanism (Appendix E).

Parameter	Entity/Actor	Specification
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Parameter	Entity/Actor	Specification
Respiratory motion minimization	Technologist	The Technologist shall observe subject breathing. If the subject is not breathing commensurate with shallow breathing expectation, the Technologist shall provide verbal instruction to the subject to perform shallow breathing prior to and during CT and PET scans.
Respiratory motion minimization	PET/CT Scanner	The PET/CT scanner shall provide methods to minimize the PET image errors introduced by respiratory motion.

462

Parameter	Entity/Actor	Specification
Breathing and motion non-compliance	Technologist	The Technologist shall document issues regarding subject non-compliance with breathing and motion.
		The Technologist shall document issues regarding subject non-compliance with breathing and motion using the common data format mechanism (Appendix E).

463

464 3.2.1.3 Scanning Coverage and Direction (UPICT Section 7.1.1)

465 For most Oncology indications, anatomic coverage should include from the skull base (external auditory
466 meatus) to the mid-thigh. If other ranges are used, which may be appropriate for specific clinical trials, then
467 the clinical trial protocol should provide specific instructions with justification. Scanning direction should be
468 caudocranial to minimize effects from increasing bladder activity during the scan. Scanning direction
469 should be specified in the clinical trial protocol. It is critical that for a given subject, scanning direction on
470 baseline scans be duplicated at follow-up time points.

Parameter	Entity/Actor	Specification
Scanning Direction	Technologist	The Technologist shall scan the subject caudocranial for whole body examination unless otherwise specified by the protocol. Scanning direction shall be the same for each subject at all time points. The scanning direction shall be entered into the PET/CT console during the acquisition and will be recorded by the scanner into the appropriate DICOM field.
Anatomic Coverage	Technologist	The Technologist shall perform the scan such that the anatomic coverage is acquired according to the protocol specifications and the same for all time points.

471

472 3.2.1.4 Scanner Acquisition Mode Parameters

473 We define acquisition mode parameters as those that are specified by the Technologist at the start of the
474 actual PET/CT scan. These include the acquisition time per bed position, the bed overlap, the acquisition

mode (2D or 3D), with or without cardiac and/or respiratory gating and CT technique. These parameters do not include aspects of the acquisition that occur earlier (e.g. injected amount of 18F-FDG or uptake duration, CT contrast agent injection) or later (e.g. reconstruction parameters) in the overall scan process.

PET Acquisition

There are no data that support a rationale for variable PET acquisition mode parameters, specifically the acquisition time per bed position depending on subject weight and or injected amount of 18F-FDG.

Parameter	Entity/Actor	Specification
PET acquisition mode	Study Sponsor	The key PET acquisition mode parameters (time per bed position, bed overlap, acquisition mode, with or without gating) <u>shall be specified</u> in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key acquisition mode parameters shall be specified according to pre-determined harmonization parameters.
PET acquisition mode	Technologist	The key PET acquisition mode parameters (time per bed position, bed overlap, acquisition mode, with or without gating) <u>shall be set as specified</u> by study protocol and used consistently for all patient scans.

CT Acquisition

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

The actual kVp and exposure (CTDI, DLP) for each subject at each time point should be recorded. CT dose exposure should be appropriately chosen wherever possible and particularly in smaller patients and children. Note that this does not address radiation exposure considerations for staff, which should follow the principles of ALARA. Note also that ALARA principle is for radiation mitigation and does not address the diagnostic utility of an imaging test.

Parameter	Entity/Actor	Specification
CT acquisition mode	Study Sponsor	The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model and with the lowest radiation doses consistent for the

Parameter	Entity/Actor	Specification
		role of the CT scan: diagnostic CT scan, anatomical localization, or corrections for attenuation and scatter.
		If diagnostic or anatomical localization CT images are not needed, then the CT acquisition mode shall utilize the protocol that delivers the lowest possible amount of radiation dose to the subject (e.g. an ultra-low low dose protocol) that retains the quantitative accuracy of corrections for attenuation and scatter.
CT acquisition mode	Technologist	The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be set as specified by study protocol and used consistently for all subject scans.

499

500

Parameter	Entity/Actor	Specification
CT Technique: Protocol Design	Technologist / Physician / Medical Physicist	A team comprising a Technologist / Physician / Medical Physicist shall ensure that CT techniques protocols are designed such that dose exposure is the lowest radiation dose necessary to achieve the diagnostic objective in children and adults. Protocols defined by Image Gently and Image Wisely should be used where feasible. The protocol shall be recorded and documented.
CT Technique: Dose Exposure	Technologist	The Technologist shall ensure that CT dose exposure is the lowest radiation dose necessary to achieve the diagnostic objective in children and adults.

501

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

510 3.3. Imaging Data Reconstruction and Post-Processing

511 3.3.1 Imaging Data Reconstruction (UPICT Section 7.3)

512 Reconstructed image data is the PET image exactly as produced by the reconstruction process on the
513 PET/CT scanner, i.e. a PET image volume with no processing other than that occurring during image

514 reconstruction. This is always a stack of DICOM slices/files constituting a PET image volume that can be
 515 analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS
 516 system, etc. See Section 4 Compliance – Image Reconstruction Software for specifications.

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

524

Parameter	Entity/Actor	Specification
PET image reconstruction	Study Sponsor	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model.
		The key PET image reconstruction parameters shall be specified according to pre-determined harmonization parameters.
PET image reconstruction	Technologist	The key PET reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be followed and set as specified in order to produce comparable results regardless of the scanner make and model.
PET Matrix/Voxel size	Technologist	The Technologist shall perform the image reconstruction such that the matrix, slice thickness, and reconstruction zoom shall yield a target voxel size of 3 – 4 mm in all three dimensions, although not necessarily isotropic. The final size shall not achieved by re-binning, etc., of the reconstructed images.
Correction factors	Technologist	All quantitative corrections shall be applied during the image reconstruction process. These include attenuation, scatter, randoms, dead-time, and efficiency normalizations.
Calibration factors	Scanner	All necessary calibration factors needed to output PET images in units of Bq/ml shall be automatically applied during the image reconstruction process.

525

526 As part of the image reconstruction and analysis, correction factors for known deviations from the
 527 acquisition protocol can potentially be applied. These corrections can include, for example, compensation
 528 for mistakes in data entry [Kinahan 2010], variations in FDG uptake period [Beaulieu 2003], and errors in
 529 scanner calibration factors [Lockhart 2011]. Corrections for known data entry errors and errors in scanner
 530 calibration factors should be corrected prior to the generation of the reconstructed images, or immediately
 531 afterwards. Corrections that are more ad-hoc in nature, e.g. corrections for variations in FDG uptake period

532 or plasma glucose levels or partial volume correction, should only be applied as part of the image analysis
 533 step. That is, not used to modify the reconstructed PET image.

534 **3.3.2 Image Data Post-processing (UPICT Section 8)**

535 Processed image data are images that have been transformed in some manner, including but not limited to:
 536 smoothing, sharpening, image zoom, rotation/translation, resampling, interpolation, slice averaging, MIP,
 537 etc. This is typically a stack of DICOM slices/files constituting a PET image volume.

538 Standard whole-body FDG-PET oncology studies typically include all necessary data corrections and
 539 processing within the reconstruction process and do not require additional processing other than (e.g.) data
 540 de-identification. More advanced studies such as those including dynamic imaging may require additional
 541 processing as specified in the individual protocol.

Parameter	Entity/Actor	Specification
Post-Processing	PET/CT Scanner and Display Workstation	All processing parameters in a protocol shall be used consistently for all subjects and studies in the trial. The parameters shall be recorded in the appropriate DICOM fields according to the DICOM conformance statement for the PET/CT scanner. This information shall also be recorded into relevant case report forms (CRFs) as stipulated by individual trials. Quantitative analysis (e.g. calculating SUVmean or SUVmax within ROIs) shall only be performed on unprocessed images, i.e. not images that have been interpolated, scaled, rotated or otherwise transformed.
Data Archiving	Technologist	The originally reconstructed PET images set shall always be archived at the local site. If processed PET images are required, they should be archived as separate secondary datasets.

542 Briefly described here are concepts presented in UPICT Section 8.2.3 regarding difference between
 543 ‘visualized data’ and ‘data used for quantification’. At the acceptable level, for visual
 544 inspection/interpretation of PET/CT data using the display workstation, bi-linear or tri-linear interpolation
 545 and zooming may be used to display the images in a different matrix size than the original data. In addition,
 546 so-called maximum intensity projections (MIP) may be generated as they may facilitate localization and
 547 detection of lesions. Additional processing, such as zooming, re-binning, reorientation and filtering may be
 548 applied upon user request only. User should be able to manipulate color scale settings (window/level and
 549 color table). It should always be possible to revert to the default orientation, zoom and bin size (preferably
 550 a ‘revert to default’ button is available).

551 **3.3.3 Imaging Data Storage and Transfer**

552

Parameter	Entity/Actor	Specification
Data archiving	Technologist	The originally reconstructed PET images, with and without

Parameter	Entity/Actor	Specification
		<p>attenuation correction, and CT images shall always be archived at the local site.</p> <p>If processed PET images are required, they shall be archived as separate secondary datasets.</p>

553

554 **3.4. Image Analysis (UPICT Section 9)**

555 The Image Analyst, through interaction with the Workstation Analysis tools, shall be able to perform
556 specified measurements. Image Analysis has qualitative and quantitative tasks. Both require consistency
557 and images of sufficient quality. Quantitative imaging requires additional system characteristics described
558 further in this Profile.

559 ***3.4.1 Input Data***

560 The output images of Reconstruction, but not Post processing, are considered the input for Image Analysis.
561 If the Image Analyst alters input data (e.g. zoom), the original input data will be maintained as a separate
562 file, both to be stored. (See Section 3.2)

563 ***3.4.2 Methods to Be Used***

564 Each tissue/organ to be investigated quantitatively (either tumor lesion or normal tissue) is characterized
565 by defining a region-of-interest (ROI) and calculating a parameter such as the maximum SUV within the ROI.
566 The image analyst will use tools (as defined in Section 4.4 Compliance – Image Analysis Workstation) to
567 define ROIs and measure SUVs.

568 ***3.4.3 Required Characteristics of Resulting Data (UPICT Section 9.3)***

569 The specific trial protocol shall prospectively define the SUV parameter that is required for each lesion, or
570 normal tissue, which will be used for the imaging endpoint. Some studies may also compare different
571 metrics and will require recording multiple parameters. SUV measures (and the analysis tools used to
572 obtain them, including software version) shall be specified for each protocol and shall be used consistently
573 across all subjects and across all sequential lesion measurements.

574 It should be clear which values belong to which lesion. This can be done by capturing DICOM coordinates
575 along with the SUV or secondary screen captures of the ROI for identification. It should be reported which
576 SUV measure is used, i.e. statistic and type of normalization.

577 If a reference tissue (e.g. liver) SUV is measured, then, that SUV should be reported along with lesion SUV
578 data.

579 The analysis software should generate a report.

580 **3.5. Image Interpretation and Reporting (UPICT Section 10)**

581 No QIBA Profile specification can be provided for image interpretation at this time. Image Interpretation is
582 considered to be beyond the scope of this document. Refer to FDG-PET/CT UPICT Protocol (Section 10). In
583 addition, further interpretation of the quantitative results (e.g. PERCIST [Wahl 2009]) and/or normalizing
584 SUV to reference tissue values (e.g. liver or blood pool) can also be specified as part of a specific trial

585 protocol.

586 Typically the trial protocol will state how quantitative response is measured. For example, response can be
587 based on the hottest lesion, but sometimes the change of the sum of SUVs is used. In other words, how
588 quantitative response is measure should be specified *a priori* by the trial itself. This also applies to target
589 lesion selection.

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

592 3.6. Quality Control

593 The following section deals with multiple aspects of quality control in FDG-PET/CT studies. (See FDG-PET/CT
594 UPICT Protocol Section 12 for additional information). This includes selecting and qualifying a PET/CT
595 imaging facility, imaging personnel and PET/CT scanners and ancillary equipment. In addition, the use of
596 phantom imaging (prior to study initiation and ongoing) is discussed as well as identifying subjects whose
597 data may need to be censored due to lack of data integrity. Finally, post-image-acquisition quality
598 assessment is detailed.

599 3.6.1 Imaging Facility

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

- 605 • Identification of appropriate imaging equipment intended for use in the trial
- 606 • Documented performance of required quality control procedures of the scanner and ancillary
607 equipment (e.g. radionuclide calibrator, glucose meter, etc.)
- 608 • Radiotracer quality control procedures
- 609 • Experience of key personnel (technologists, radiologists, physicists and/or other imaging experts)
- 610 • Procedures to ensure imaging protocol compliance during the trial

611 3.6.1.1 Site Accreditation/Qualification Maintenance

612 Whilst imaging facility accreditation is generally considered to be adequate for routine clinical practice
613 purposes (e.g., ACR, IAC, and TJC), facility qualification (e.g., SNM-CTN, ACRIN, and imaging core labs) is
614 required for clinical research/clinical trial participation. In order to be considered to be compliant with this
615 Profile, an imaging facility must provide documentation of current qualified status. Appropriate forms,
616 checklists or other process documents should be maintained and presented upon request to verify that
617 ongoing quality control procedures are being performed in a timely manner as dictated by specific clinical

618 study requirements. If exceptions to any of the performance standards stated below occur and cannot be
 619 remediated on site, the site should promptly communicate the issue to the appropriate internal overseer
 620 for advice as to how the irregularity should be managed. In addition to documenting the level of
 621 performance required for this Profile (and the level of performance achieved), the frequency of facility
 622 accreditation/qualification also needs to be described.

623 It is important to note that that imaging facility Accreditation and/or Qualification, as defined in this Profile,
 624 are considered necessary, but are not sufficient for compliance with this Profile. For compliance with the
 625 Profile, and thus to support the claims of the Profile, all normative requirements must be met.

Parameter	Entity/Actor	Specification
Accreditation / Qualification	Imaging Site	Shall maintain and document Accredited status for clinical practice (ACR, IAC, TJC, etc.) or Qualified status for clinical trials (e.g. ACRIN, SNM-CTN, CALGB, CROs, etc.).

626 **3.6.2 Imaging Facility Personnel**

627 For each of the personnel categories described below, there should be training, credentialing, continuing
 628 education and peer review standards defined. Guidelines for training/credentialing for each resource
 629 category are summarized below (UPICT Protocol Section 2.1).

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

Parameter	Entity/Actor	Specification
		performed and/or interpreted.

630

631 **3.6.3 FDG-PET/CT Acquisition Scanner**

632 FDG-PET/CT studies as described in this Profile require a dedicated PET/CT scanner. PET/CT scanners should
 633 be identified based on manufacturer, name and model. Hardware specifications should be documented.
 634 Scanner software name and version should be documented at the time of trial initiation and at the time of
 635 any and all updates or upgrades.

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

640 If there is more than one PET/CT scanner at a facility which will be used for clinical trial purposes, including
 641 potential use as a replacement in case of primary scanner failure, then all such scanners should be
 642 qualified. For consistency, however, clinical trial subjects should be imaged on the same device over the
 643 entire course of a study. It is imperative, therefore, that the trial sponsor be notified of scanner substitution
 644 if it occurs. In addition, as noted elsewhere, a subject should have all scans performed on only one scanner
 645 unless quantitative equivalence can be clearly demonstrated. However, it should be noted that there are no
 646 accepted criteria for demonstrating quantitative equivalence between scanners.

Parameter	Entity/Actor	Specification
Physical Inspection	Technologist	Shall, on a daily basis, check gantry covers in tunnel and subject handling system.
QA/QC Checks	Technologist	At a minimum, QA/QC procedures shall be performed each day according to vendor recommendations. A table of QA/QC procedures for a subset of specific PET/CT scanners from each vendor is included in Appendix G.2. Daily QC procedures shall be performed prior to any subject scan.

647 **3.6.3.1 Ancillary Equipment**

648 **3.6.3.1.1 Radionuclide Calibrator**

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

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

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

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

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

658

659 3.6.3.1.2 Scales and stadiometers

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

661

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

662 3.6.3.1.3 Blood glucose level measurement device

663 Glucose measurements should be made using a CLIA-approved, CLIA-cleared, or equivalent (outside the US)
664 glucose measurement technique.

Parameter	Entity/Actor	Specification
Blood glucose level measurement	Approved personnel	Shall have QA/QC testing and calibration performed using a CLIA-approved, CLIA-cleared, or equivalent (outside US) procedure.

Parameter	Entity/Actor	Specification
device		

665

666 3.6.3.1.4 Clocks and timing devices

667 PET/CT scanner computer and all clocks in an imaging facility used to record activity/injection
668 measurements should be synchronized to standard time reference within +/-1 minute. These include any
669 clocks or timekeeping systems that are connected with a subject's FDG-PET/CT study, in particular those
670 associated with the radionuclide calibrator, the injection room, the scanner, and the acquisition
671 computer(s). The synchronization of all clocks should be monitored periodically as part of ongoing QA
672 program. In particular, clocks should be inspected immediately after power outages or civil changes for
673 Daylight Savings (NA) or Summer Time (Eur).

Parameter	Entity/Actor	Specification
Scanner and site clocks	Approved personnel	Synchronization of all clocks used in the conduct of the FDG-PET/CT study shall be checked weekly and after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur) PET/CT scanner computer and all clocks in an Imaging facility used to record activity/injection measurements shall be synchronized to standard time reference within +/-1 minute.

674

675 **3.6.4 Phantom Imaging**

676 To qualify the PET/CT scanner for clinical practice or for a clinical trial, a phantom imaging procedure is
677 required. In addition to certain generally available, commonly used phantoms, purpose-specific phantoms
678 may be provided to simulate certain types of cancers or anatomic locations and therefore might vary from
679 trial to trial based on the need to evaluate particular diagnostic, staging and/or treatment response
680 performance and/or anatomic location. Options that might be considered on a per-protocol basis include,
681 but are not limited to:

- 682 1. each site uses a single phantom for the duration of the trial but not necessarily the same model of
683 phantom used at other sites
- 684 2. all sites use phantoms of the same model for the duration of the trial
- 685 3. all sites use phantoms built to precise specifications for the duration of the trial
- 686 4. all sites share a single phantom for the duration of the trial.

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

693 Image noise levels are measured using an anthropomorphic phantom (e.g. NEMA, ACR, SNM, EANM) with a
694 uniform area to assess image 'noise' by means of the coefficient of variation (COV), also known as the

relative standard deviation (%RSD), which is expressed as a percentage and is defined as $COV = (SD / Mean) \times 100$, for the voxel values within a specified volume of interest (VOI). The phantom should be filled such that the activity concentration in the uniform area is approximately 3.7 – 7.4 kBq/ml (0.1 to 0.2 uCi/ml), similar to the expected average normal tissue concentration at the time of imaging in an average weight (70-80 kg) subject in combination with the intended FDG dosage. The phantom should be scanned using the minimal time per bed specified in the trial protocol or using the routinely applied time per bed in the local clinical setting. Moreover, image reconstruction methods and settings should equal those specified in the trial protocol or equal those routinely applied in the local clinical setting. A region of interest (ROI) should be positioned entirely within the phantom's uniform area and as much as possible centrally located within the phantom. The ROI should be a cubical or rectangular volume, with the length of each side as close as possible to, but no less than, 3 cm. A sphere measuring no less than 3 cm. in diameter may also be used as the ROI on systems that have the capability to accommodate this strategy. The COV of the voxel values thus determined should be recorded and should be below 15%. If the COV of the voxel values thus determined is above 15%, the acquisition time should be increased accordingly.

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

Parameter	Entity/Actor	Specification
Phantom tests: Frequency	Imaging Site	Shall perform and document results of all tests no less than quarterly.
Phantom tests: cross calibration with radionuclide calibrator	Imaging Site	Shall perform quarterly and after scanner upgrades, maintenance or repairs, new setups and modifications to the radionuclide calibrator.
Phantom tests: SUV measurements	Imaging Site	Using ACR or uniform cylinder phantom or equivalent shall obtain an SUV for a large central ROI of 1.0 with an acceptable range of 0.9 to 1.1.
		Using ACR or uniform cylinder phantom or equivalent shall obtain an SUV for a large central ROI of 1.0 with an acceptable range of 0.95 to 1.05.
Phantom tests: axial uniformity measurements	Imaging Site	Using uniform cylinder phantom or equivalent shall obtain a slice-to-slice variability of less than 10%.
		Using uniform cylinder phantom or equivalent shall obtain a slice-to-slice variability of less than 5%.
Phantom tests: resolution measurements	Imaging Site	The lower portion of the ACR phantom contains six sets of acrylic rods arranged in a pie-shaped pattern with the following diameters: 4.8, 6.4, 7.9, 9.5, 11.1, and 12.7 mm. The 9.5, 11.1, and 12.7 mm diameter rods must be visible. In addition the 12 mm diameter cylinder must be visible. Also see Section 3.6.4.2.
		Harmonized image reconstruction protocols are available. (i.e.,

Parameter	Entity/Actor	Specification
		known recovery coefficients versus size for a given test object such as the modified NEMA NU-2 Image Quality phantom.
Phantom tests: noise measurements	Imaging Site	The phantom shall be filled with an FDG concentration of activity concentration in the uniform area is (approximately 0.1 to 0.2 $\mu\text{C}/\text{ml}$) and scanned using the intended acquisition protocol. Using a rectangular or spherical region as close as possible to, but no smaller than, 3cm to a side, the COV of the voxel values within the region should be below 15%.

711

712 3.6.4.1 Uniformity and Calibration

713 Verification of scanner normalization with a uniform phantom is a minimum requirement for all scanners
714 used in clinical trials including those that only have qualitative endpoints. For trials with quantitative PET
715 measurements, this assessment should also include a comparison against a radionuclide calibrator to
716 ensure quantitative accuracy; that is, a comparison of the absolute activity measured versus the measured
717 amount injected should be performed. This comparison is particularly important after software or
718 hardware upgrades. If the trial requires absolute quantification in baseline images or absolute changes in
719 longitudinal studies, it should be considered to include an image quality and/or contrast recovery QC
720 assessment as part of the routine QC procedures and/or scanner validation process, see Appendix E of the
721 UPICT Protocol. Clinical trials using only relative changes in longitudinal studies may not require contrast
722 recovery assessments provided there is appropriate consideration for the minimum size of target lesions
723 based on the partial volume effect.

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

Parameter	Entity/Actor	Specification
Uniformity QC	Technologist	At least quarterly and following software upgrades, shall assess transverse and axial uniformity across image planes by imaging a uniform cylinder phantom. <ol style="list-style-type: none"> 1. The standard deviation of a large central 2D ROI shall be compared with similar previous scans to check for measurable differences. 2. The mean values of a large central 2D ROI for all image slices shall be compared with similar previous scans to check for measurable differences.
Cross Calibration	Technologist	At least quarterly and following software upgrades or changes to the radionuclide calibrator, shall perform checks to monitor and identify discrepancies between the PET scanner and radionuclide calibrator.

728

729 **3.6.4.2 Resolution (UPICT Section 12.1.1.11)**

730 The assessment of adequate resolution should include both a qualitative evaluation (using clinical images)
 731 and quantitative assessment (using phantom-defined criteria). The phantom-defined requirements are
 732 more completely described in UPICT protocol Section 12.1.1.11.

Parameter	Entity/Actor	Specification
Resolution	Nuclear Medicine Physician	Shall perform, on at least an annual basis, and document a qualitative resolution QC test by using the manufacturer's settings and demonstrating resolution of normal gross anatomic features within clinical images of the brain, heart and abdomen.
Resolution	Medical Physicist	Shall perform (on at least an annual basis) and document performance of a quantitative assessment (using a phantom with differing size defined targets such as the ACR or NEMA IQ phantoms) for lesion resolution.

733 **3.6.4.3 Noise (UPICT Section 12.1.1.12)**

Parameter	Entity/Actor	Specification
Noise	Medical Physicist	Shall perform qualitative assessment of image noise in phantom images to be of consistent and acceptable quality.

734

735 **3.6.4.4 Phantom imaging data analysis**

736 For PET image analysis, there are many combinations of hardware and software that are used. The software
 737 alone comprises multiple layers including the operating system, several base modules for input and display,
 738 and the components that draw/calculate ROIs and calculate SUVs. It has been demonstrated that even
 739 changes in the underlying operating system can produce changes in the quantitative output produced by
 740 the display and analysis system [Gronenschild 2012]. Surprisingly little effort (outside manufacturer's
 741 internal processes) has been applied to testing or validating the quantitative accuracy of SUV
 742 measurements produced by display and analysis methods.

743 To provide a method for testing and validating quantitative accuracy of SUV measurements produced by
 744 display and analysis methods, the QIBA FDG-PET/CT Technical Committee has developed an FDG-PET/CT
 745 digital reference object (DRO), which is a synthetic test object comprised of stacked DICOM images
 746 representing an FDG-PET image volume and an aligned CT image volume. The PET and CT images are based
 747 on the NEMA/MITA NU-2 Image Quality phantom. The DRO has pre-determined test objects to evaluate
 748 ROI functionality and pre-determined DICOM header information to test SUV calculations. Since the DRO is
 749 created synthetically, any image display software is expected to reproduce the known values exactly,
 750 except for the insignificant machine precision errors. Further details are given in Appendix F.
 751 Recommended versions of vendor-neutral pseudo-codes for SUV calculation are given in Appendix G.

Parameter	Entity/Actor	Specification
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Parameter	Entity/Actor	Specification
Frequency of testing	Imaging site	Shall perform testing, using the FDG-PET/CT DRO (Appendix F), of image analysis software when installed and after hardware or software updates.
Accuracy of SUV estimates	Imaging site analysis software	Shall reproduce exact known values for the FDG-PET/CT DRO (Appendix F). There are six test objects. The reported values include SUVmax, SUVmean, SUVmin, StdDev, and diameter/area. The normalizations include body weight and lean body mass. The results of the DRO testing shall be recorded in accordance with directions as included in Appendix F and stored on site.
		SUVpeak shall also be included as a reported value for the FDG-PET/CT DRO.

3.6.5 Quality Control of FDG-PET/CT studies

3.6.5.1 Data Integrity

The integrity of DICOM image headers should be reviewed and confirmed for DICOM standard compliance, regulatory compliance (including privacy protection, such as may be required by such rules as the HIPAA Privacy Rule if applicable), protocol compliance, sufficiency for the intended analysis (e.g., to compute SUV) and consistency with source data such as CRFs. In some cases, internal references such as the liver can be used for quality control to confirm acceptable ranges of SUVs.

3.6.5.2 Determination of Image Quality

CT images should be reviewed by the Image Analyst for assessment of image quality and for potential artifacts such as beam hardening, metal objects, and motion. PET images should be compared to the CT images for proper image registration and potential attenuation correction artifacts. Both uncorrected and attenuation corrected images may need to be assessed to identify any artifacts caused by contrast agents, metal implants and/or subject motion. For example, movement or mis-registration can lead to poor quality quantitative data and invalid numbers. Some images may be too poor in quality to quantify. Statistical quality of images is important to report, but not a full substitute for quality. Liver noise assessment as defined per PERCIST [Wahl 2009] is considered a reasonable start.

3.6.5.3 Determination of Evaluable Tumor Lesions

The definition of specific tumors that are evaluable should be addressed prospectively in the clinical trial protocol. Protocol-specific guidelines should document whether or not minimum size criteria and/or minimum baseline SUV criteria for target lesion qualifications are used, and if so, how such criteria will be used.

The criteria below represent the best known practices based on published data, and can provide a guideline for determining evaluability.

Selection of Target Lesions (UPICT Section 10.2.1.1)

The lesion to be measured should be free of artifacts, for example, from nearby intense FDG containing structures (like the bladder) or due to motion or attenuation correction artifacts.

778 Minimum Baseline SUV (UPICT Section 10.2.1.1.1)

779 From the SNM Global Harmonization Summit (2010) and in the meta-analysis by de Langen et al (2012),
780 there was consensus that to reliably measure a change in the FDG uptake of a lesion, a high baseline FDG
781 uptake is necessary. For illustration, a 30% decrease in lesion uptake may be more reliably measured, and
782 potentially more meaningful, if the initial lesion uptake had an SUV of 5 g/ml as opposed to an SUV of 2
783 g/ml.

784 UPICT Acceptable level: Baseline lesion SUV of 1.7 x mean SUV of liver, which is based on the PERCIST
785 criteria [Wahl 2009]. The measurement for mean liver SUV is made using a 3-cm diameter spherical ROI
786 placed in the right lobe of the liver at the level of main portal vein and equidistant between the porta
787 hepatis and lateral liver margin. Care should be taken to avoid placing the ROI close to the edge of the liver
788 [Subramaniam 2012]. Further details are given in UPICT Section 10.2.1.1.1. If the liver is not in the field of
789 view or is abnormal to a degree that normal liver cannot be assessed, then the alternate comparator is to
790 use a minimum threshold level of 2.0 x mean SUV of blood pool in a 3D ROI defined as a 1 cm diameter
791 cylinder in the descending thoracic aorta extending over 2 cm, tracking the long axis of the aortic lumen,
792 avoiding the wall of the aorta or areas of plaque or calcification. If the descending aorta is not evaluable a
793 VOI of the same volume should be measured from elsewhere in the thoracic aorta.

794 Minimum Lesion Size

795 The SNM Global Harmonization Summit suggests that tumors should typically be over 2 cm in diameter for
796 target lesion inclusion at baseline. Lesions smaller than 2 cm (or otherwise not easily measurable) with a
797 high enough FDG uptake, may still be evaluable.

798 Evaluation of lesion size (e.g., longest diameter) may be difficult. This may be due to intrinsic lesion
799 characteristics (e.g., infiltrative or CT lesion isodensity to surrounding tissue) or due to the anatomic
800 location of tumor (e.g., bone marrow site). Lesions subject to partial volume effect of SUV measurement,
801 notably due to anatomic location and attenuation correction errors (e.g., peri-diaphragmatic lesions at
802 either lung base or hepatic dome) potentially should be excluded.

803 **3.6.5.4 Determination of subjects unsuitable for FDG-PET/CT analysis**

804 Reference Section 3.1.1 "Subject Selection, Timing, and Blood Glucose Levels"

805 ***3.6.6 Quality Control of Interpretation***

806 To promote quantifiable performance standards for the quality control of interpretation there is a need for
807 intra-reader variability studies. In a 2-Reader paradigm, then inter-reader variability is needed as well. It is
808 currently unclear what statistics to evaluate and how these performance metrics should be used in the
809 analysis.

810 **4. Compliance**

811 **Relation of this Profile to Expectations for QIBA Profile Compliance**

812 Definitions (from Appendix C):

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

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

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

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

823 4.1. Image Acquisition Site

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

- 826 • Appropriate imaging equipment and quality control processes,
- 827 • Appropriate ancillary equipment and access to radiotracer and contrast material,
- 828 • Experienced Technologists (CT and PET trained) for the subject handling and imaging procedure,
- 829 • Appropriately trained Radiologists/Nuclear Medicine Physicians for image analysis and diagnostic
830 interpretation,
- 831 • Appropriately trained image analysts, with oversight by a Radiologist or Nuclear Medicine Physician,
- 832 • Medical Physics support to ensure appropriate scanner and equipment calibration,
- 833 • Processes that assure imaging QIBA Profile-compliant image generation in appropriate time window

834 A QA/QC program for PET/CT scanners and ancillary devices must be in place to achieve the goals of the
835 clinical trial. The minimum requirements are specified above. This program shall include (a) elements to
836 verify that imaging facilities are performing imaging studies correctly and (b) elements to verify that
837 facility's PET/CT scanners are performing within specified calibration values. These may involve
838 additional PET and CT phantom testing that address issues relating to both radiation dose and image
839 quality (which may include issues relating to water calibration, uniformity, noise, spatial resolution – in
840 the axial plane-, reconstructed slice thickness z-axis resolution, contrast scale, and others. This phantom
841 testing may be done in addition to the QA program defined by the device manufacturer as it evaluates
842 performance that is specific to the goals of the clinical trial.

843

Parameter	Entity/Actor	Specification
PET/CT Scanner	Acquisition Facility	This Profile shall only address full ring PET/CT scanners.
CT Scanner Calibration	Technologist	Shall perform daily water equivalent phantom analysis; ensure that output is acceptable and manually enter on form /electronic database.
PET Scanner Calibration	Technologist	Shall perform daily/weekly/monthly scanner QA; ensure that output values are acceptable and manually enter on form/electronic database
Radionuclide		Calibrated to F-18 using NIST traceable source or equivalent.

Parameter	Entity/Actor	Specification
calibrator		

844

845 4.2. PET/CT Acquisition Device

846 The PET/CT scanner should use DICOM attributes to follow version numbers of software for: 1 Acquisition,
847 2 Reconstruction, 3 Post-processing, 4 Display/ROI analysis, 5 Dynamic Analysis. The PET/CT scanner should
848 be able to build a list on the console of the dates of all software versions. The scanner software version
849 should be identified and tracked across time, with updates and changes in scanner software noted during
850 the course of the trial.

851 The PET scan acquisition start time should be used for the decay reference time and the integral model
852 should be used for decay correction. The scanner should perform all decay corrections (i.e. not the
853 operator). Image data are to be given in units Bq/ml.

854 The Decay Correction (0054,1102) field is the real-world event to which images in this Series were decay
855 corrected. If decay correction is applied, all images in the Series shall be decay corrected to the same time.

856 The Defined Terms and definitions are:

857 NONE = no decay correction

858 START= acquisition start time, Acquisition Time (0008,0032)

859 ADMIN = radiopharmaceutical administration time, Radiopharmaceutical Start Time (0018,1072).

860 The time to which images have been decay corrected can be derived from Decay Factor (0054,1321), Frame
861 Reference Time (0054,1300), Radionuclide Half Life (0018,1075), Series Date (0008,0021), and Series Time
862 (0008,0031).

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

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

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

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

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

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

892

Parameter	Entity/Actor	Specification
CT calibration tracking	Acquisition Device	Daily water equivalent phantom values shall be tracked in the DICOM header.
PET calibration tracking	Acquisition Device	Daily/weekly/monthly scanner QA values shall be included in the DICOM header.
Radionuclide calibrator calibration tracking	Acquisition Device	Calibration factor for an F-18 NIST -traceable (or equivalent) source with identifying information shall be tracked in the DICOM header.
PET Scanner calibration	Acquisition Device	<p>Shall be able to be calibrated according to the following specifications:</p> <ul style="list-style-type: none"> Using an ACRIN type uniform cylinder containing FDG in water (ideally the same used for radionuclide calibrator cross-calibration) Using a long scan time of 60 min or more, and an ACRIN-type ROI analysis <p>The average measured SUV shall be in the range of 0.98 to 1.02.</p> <p>Slice-to-slice variability shall be no more than $\pm 5\%$. (not including end slices, as per ACRIN).</p>
		In-plane uniformity for above phantom shall be less than 5 %.
Weight	Acquisition Device	<p>Shall be able to record patient weight in lbs or kg as supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Weight field (0010,1030) in the DICOM image header, as per DICOM standard.</p>
		<p>Patient weight shall be specifiable with 4 significant digits.</p> <p>Patient weight is transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still requiring operator verification.</p>
Height	Acquisition	Shall be able to record patient height in feet/inches or cm/m as

Parameter	Entity/Actor	Specification
	Device	<p>supplied from the modality worklist and/or operator entry into scanner interface. Shall be stored in Patient Size field (0010,1020) in the DICOM image header, as per DICOM standard.</p> <p>Patient height shall be specifiable with 3 significant digits.</p> <p>Patient height is transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still requiring operator verification.</p>
Blood glucose level	Acquisition Device	<p>Shall be able to Record patient blood glucose level, in units of mg/dl, or mMol/l, time of measurement, as supplied by operator entry into the scanner interface. Shall be recorded in a dedicated field in the DICOM image header.</p> <p>Patient blood glucose level is transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still requiring operator verification.</p>
Administered Radionuclide	Acquisition Device	<p>Shall be able to accept the radionuclide type (i.e. F-18) from the DICOM Modality Worklist.</p> <p>Shall be able to enter the radionuclide type (i.e. F-18) by operator entry into the scanner interface.</p> <p>Shall be recorded in Radionuclide Code Sequence (0054,0300) in the DICOM image header (e.g., (C-111A1, SRT, “¹⁸Fluorine”)).</p> <p>Shall be able to accept the radionuclide type (i.e. F-18) directly from the measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still requiring operator verification.</p>
Administered Radiotracer	Acquisition Device	<p>Shall be able to record the radiotracer (i.e. FDG), as supplied by operator entry into the scanner interface. Shall be recorded in Radiotracer Code Sequence field (0054,0300) in the DICOM image header, e.g., (C-B1031, SRT, “Fluorodeoxyglucose F¹⁸”).</p>
Administered Radiotracer radioactivity	Acquisition Device	<p>Shall be able to record the administered radioactivity , in both MBq and mCi , as supplied by operator entry into the scanner interface. Shall be recorded in Radionuclide Total Dose field (0018,1074) in the DICOM image header.</p> <p>Shall be able to record with separate entry fields on scanner interface:</p> <ol style="list-style-type: none"> (1) the pre-injection FDG radioactivity (2) time of measurement of pre-injection FDG radioactivity (3) the residual activity after injection (4) time of measurement the residual radioactivity after injection

Parameter	Entity/Actor	Specification
		<p>Shall automatically calculate the administered radioactivity and store in the Radionuclide Total Dose field (0018,1074) in the DICOM image header.</p> <p>Patient Administered Radiotracer radioactivity information shall be transferred directly from measurement device into scanner by electronic, HIS/RIS, or other means, bypassing all operator entry, but still requiring operator verification.</p>
Administered Radiotracer Time	Acquisition Device	Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072).
		Shall be able to record the time of the start of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Start Date Time field (0018,1078). I.e. not Radiopharmaceutical Start Time field (0018,1072).
		Shall be able to record the time of the stop of activity injection as supplied by operator entry into the scanner interface. Shall be recorded in Radiopharmaceutical Stop Date Time field (0018,1079).
Decay Correction Methodology	Acquisition Device	<p>Encoded voxel values with Rescale Slope field (0028,1053) applied shall be decay corrected by the scanner software (not the operator) to a single reference time (regardless of bed position), which is the start time of the first acquisition, which shall be encoded in the Series Time field (0008,0031) for original images.</p> <p>Corrected Image field (0028,0051) shall include the value "DECY" and Decay Correction field (0054,1102) shall be "START".</p>
Scanning Workflow	Acquisition Device	Shall be able to support Profile Protocol (Section 3) PET and CT order(s) of acquisition.
		Shall be able to pre-define and save (by imaging site) a Profile acquisition Protocol for patient acquisition.
		<p>Shall be able to interpret previously-reconstructed patient images to regenerate acquisition protocol.</p> <p>Shall be configurable to store (or receive) acquisition parameters as pre-defined protocols (in a proprietary or standard format), to allow re-use of such stored protocols to meet multi-center specifications and to achieve repeatable performance across time points for the same subject.</p>
CT Acquisition Parameters	Acquisition Device	Shall record all key acquisition parameters in the CT image header, using standard DICOM fields. Includes but not limited to: Actual Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, Tube Current, Rotation

Parameter	Entity/Actor	Specification
		Time, Exposure and Slice Width in the DICOM image header.
CT based attenuation correction	Acquisition Device	Shall record information in PET DICOM image header which CT images were used for corrections (attenuation, scatter, etc.).
PET-CT Alignment	Acquisition Device	Shall be able to align PET and CT images within ± 2 mm in any direction.
		Shall be able to align PET and CT images within ± 2 mm in any direction under maximum load over the co-scan length.
CT Absorbed Radiation Dose	Acquisition Device	Shall record the absorbed dose (CTDI, DLP) in a DICOM Radiation Dose Structured Report.
PET Radiation Dose	Acquisition Device	Shall record the radiation dose from the administered activity and accompanying information in a DICOM Radiopharmaceutical Administration Radiation Dose Structured Report.
Activity Concentration in the Reconstructed Images	Acquisition Device	Shall be able to store and record (rescaled) image data in units of Bq/ml and use a value of BQML for Units field (0054,1001).
Tracer Uptake Time	Acquisition Device	Shall be derivable from the difference between the Radiopharmaceutical Date Time field (0018,1078) (preferred) or Radiopharmaceutical Start Time field (0018,1072) and the Series Time field (0008,0031) or earliest Acquisition Time field (0008,0032) in the series (i.e., the start of acquisition at the first bed position), which should be reported as series time field (0008,0031).
PET Voxel size	Acquisition Device	Shall be able to reconstruct PET voxels with a size of 3 to 4 mm in all three dimensions (as recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices). Pixels shall be square, although voxels are not required to be isotropic in the z (head-foot) axis.
		Shall be able to reconstruct PET voxels with a size of 1-3 mm in all three dimensions (as recorded in Voxel Spacing field (0028,0030) and computed from the reconstruction interval between Image Position (Patient) (0020,0032) values of successive slices). Voxels shall be isotropic.
CT Voxel size	Acquisition Device	Shall be no greater than the reconstructed PET voxel size. Voxels shall be square, although are not required to be isotropic in the Z (head-foot) axis.

Parameter	Entity/Actor	Specification
		Not required to be the same as the reconstructed PET voxel size.
Subject Positioning	Acquisition Device	Shall be able to record the subject position in the Patient Orientation Code Sequence field (0054,0410) (whether prone or supine) and Patient Gantry Relationship Code field Sequence (0054,0414) (whether head or feet first).
Scanning Direction	Acquisition Device	Shall be able to record the scanning direction (craniocaudal v. caudocranial) into an appropriate DICOM field.
Documentation of Exam Specification	Acquisition Device	Shall be able to record and define the x-y axis FOV acquired in Field of View Dimensions (0018,1149) and reconstructed in Reconstruction Diameter (0018,1100).
		Shall be able to define the extent of anatomic coverage based on distance from defined landmark site (e.g. vertex, EAM). (both the landmark location (anatomically) and the distance scanned from landmark) would require DICOM tags). Shall be able to be reportable for future scanning sessions. The Acquisition Device shall record the z-axis FOV which represents the actual distance of scan anatomic coverage (cms) as well as the number of bed positions.
Bed Position Temporal Differences	Acquisition Device	Shall be able to provide and document non uniform scan times for different bed positions dependent upon areas of clinical concern.
DICOM Compliance	Acquisition Device	All image data and scan parameters shall be transferable using appropriate DICOM fields according to the DICOM conformance statement for the PET/CT scanner.
DICOM Data transfer and storage format	PET/CT Scanner or Display Workstation	PET images shall be encoded in the DICOM PET or Enhanced PET Image Storage SOP Class, using activity-concentration units (Bq/ml) with additional parameters stored in public DICOM fields to enable calculation of SUVs. PET images shall be transferred and stored without any form of lossy compression.

893

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

894

4.3. Reconstruction Software

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

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

Data can be reconstructed including all corrections needed for quantification as well as without scatter and attenuation correction. Analytical or iterative reconstruction methods should be applied.

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

Parameter	Entity/Actor	Specification
Data Corrections	Reconstruction Software	PET emission data must be able to be corrected for geometrical response and detector efficiency, system dead time, random coincidences, scatter and attenuation.
Reconstruction Methodology	Reconstruction Software	Shall be able to provide both iterative and analytical (e.g. filtered back projection) reconstruction algorithms. Shall be able to 'turn off' resolution recovery and/or time of flight (TOF) capabilities (if available) for purposes of reconstruction.
Reconstruction Methodology / Output	Reconstruction Software	Shall be able to perform reconstructions with and without scatter and attenuation correction.
Data Reconstruction 2D/3D Compatibility	Reconstruction Software	Shall be able to perform reconstruction of data acquired in 3D mode using 3D image reconstruction algorithms. If 3D mode data can be re-binned into 2D mode, shall be able to perform reconstruction of data acquired in 3D mode using 2D image reconstruction algorithms. Shall be able to perform reconstruction of data acquired in 2D mode using 2D image reconstruction algorithms.
Quantitative calibration	Reconstruction software	Shall apply appropriate quantitative calibration factors such that all images have units of activity concentration, e.g. kBq/mL.
Multi-bed data	Reconstruction software	Shall combine data from multiple over-lapping bed positions (including appropriate decay corrections) so as to produce a single three dimensional image volume.
Voxel size	Reconstruction software	Shall allow the user to define the image voxel size by adjusting the matrix dimensions and/or diameter of the reconstruction field-of-

Parameter	Entity/Actor	Specification
		view.
Reconstruction parameters	Reconstruction software	Shall allow the user to control image noise and spatial resolution by adjusting reconstruction parameters, e.g. number of iterations, post-reconstruction filters.
Reconstruction protocols	Reconstruction software	Shall allow a set of reconstruction parameters to be saved and automatically applied (without manual intervention) to future studies as needed.

902

903 4.4. Image Analysis Workstation

904 The image analysis workstation shall have the ability to receive and propagate the data output (imaging and
 905 metadata) collected from the prior activities (Subject Handling, Image Acquisition, Reconstruction and Post-
 906 Processing). With the input data, the analysis workstation (and software analysis tools) will be able to make
 907 use of certain attribute values to perform certain measurements and computational analysis. The analysis
 908 workstation and software may be coupled to the PET/CT scanner system or provided by a 3rd-party vendor.

Parameter	Entity/Actor	Specification
Metadata	Image Analysis Workstation	Shall be able to accurately propagate the information collected at the prior stages and extend it with those items noted in the Image Analysis Workstation section.
		Shall be able to display all information that affects SUVs either directly in calculation (e.g. patient weight, injected activity) or indirectly (uptake time, plasma glucose concentration).

909

910 Input for Image Analysis is considered output of Reconstruction and Post processing software activity. If the
 911 Image Analyst alters input data (e.g. zoom) this is considered part of Image Analysis activity. If this occurs,
 912 the original input data will be maintained as a separate file, both to be stored, including description of
 913 manipulation in an audit trail file or in a dedicated DICOM tag section (Section 3.2).

914 A check should be performed by receiving devices that the Series Time field (0008,0031) is not later than
 915 the earliest Acquisition Time field (0008,0032) of all images in the Series in case the images have been
 916 derived (i.e. changing the time to an inappropriate value for decay correction).

Parameter	Entity/Actor	Specification
Reference time for decay correction	Image Analysis Workstation	Shall check that the Series Time field (0008,0031) is not later than the earliest Acquisition Time field (0008,0032) for all images in the Series. If not, the earliest Acquisition Time (0008,0032) shall be used as the reference time for decay correction.

917

4.4.1 Region of Interest (ROI) definition

The scanner-display-analysis system shall provide a tool for the user to define both 2D and 3D regions of interest (ROIs). These ROIs will then be used calculate SUV values as described in the next section.

The specifications below are for defined regions for the calculation of (1) average value within an ROI (i.e. SUVmean) (2) maximum value within an ROI (i.e. SUVmax) (3) average value within a fixed-size ROI (i.e. SUVpeak) (4) average value within a fixed-size ROI (i.e. SUVpeak), but with the location automatically selected to maximize the mean value. For SUVpeak measures, the use of partial voxel values to secure a 1.2cm diameter sphere (or 1cc volume) ROI is appropriate and desirable.

Parameter	Entity/Actor	Specification
Voxel Inclusion Policy	Analysis Tool	Shall describe methodology describing voxel inclusion and weighting policy including placement criteria, total volume, and geometry of resulting ROI (e.g. rectangular volume or spherical).
		Use weighting for partial voxels; fully included voxels use weight of 1.0. Weighting should be proportionate to volumes of voxels that are partly included.
ROI Specifications	Analysis Tool	Shall describe capabilities and limits of ROI specification and placement.
		Dimensions and center location of ROI (box, ellipse, or ellipsoid) shall be specifiable to ± 1 mm. For SUVpeak measures, the location within a target search region that yields the highest mean value of a 1 cc region shall be found automatically and reproducibly.
ROI Definition Tools	Analysis Tool	Shall provide a tool and user strategy to allow the placement of an ROI to determine the <u>average</u> value within the ROI. Shall provide a tool and user strategy to allow the placement of an ROI to determine the value and location of the voxel with the <u>maximum</u> value within an ROI. Shall provide a tool and user strategy to allow the placement of a 1 cm diameter ROI (either 2D or 3D) to determine the average value within the ROI.
		Shall provide a tool and user strategy to allow automatic placement of a 1 cm diameter ROI (either 2D or 3D) such that the average value within the ROI is maximized.
Edge/Volume Detection	Analysis Tool	Shall provide threshold methods for defining an ROI based on image values. Shall clearly specify which threshold method is used and relevant parameters values.

Parameter	Entity/Actor	Specification
		Three ROI definition methods shall be provided: Fixed value, % of maximum voxel, or edge detection/segmentation methods.
ROI saving/retrieve	Analysis/Archival	Shall have the capability to label, save, recall ROIs using DICOM structured sets.
		Shall have the capability to track tumor information across longitudinal scans.
ROI Output Statistics	Analysis Tool	Shall have the capability to output to the screen display the selected statistics of the ROI. These include, but are not limited to: Area, volume, mean, maximum, minimum, standard deviation. Units can be selectable as activity concentration [Bq/ml] or SUV [g/ml].
		Shall output results with at least two decimal places.
		Shall output ROI Output Statistics to Structured Data Reporting DICOM files.
		Shall calculate results directly from the originally reconstructed voxels (not from interpolated and/or zoomed images).

926 The workstation and repository shall be able to create, store and retrieve markups (i.e. ROIs) used for SUV
927 measurements in accordance with a standard definition for ROIs that provides a known balance between
928 precision and accuracy.

929 **4.4.2 Calculation of Standardized Uptake Value (SUV)**

930 The ROI definition and analysis software is responsible for SUV calculation, e.g. with decay correction to the
931 appropriate reference time. Moreover, the manufacturer should implement both versions of SUV
932 normalizations (body weight or lean body mass). Recommended vendor-neutral pseudo-codes for SUV
933 calculation are given in Appendix G.

934

Parameter	Entity/Actor	Specification
SUV Calculation	Analysis Tool	Shall have the capability to correctly calculate SUVs according to the vendor-neutral pseudo-codes for SUV calculation given in Appendix G.
Volume of Distribution Surrogate	Analysis Tool	Shall have the capability to calculate SUVs using as a surrogate for the Volume of Distribution: body weight, lean body mass, and body surface area (BSA). Lean body mass shall be calculated according to the formula of James [James 1976, Hallynck 1981]: Males: $LBM = 1.10(w) - 128(w^2/h^2)$ Females: $LBM = 1.07(w) - 148(w^2/h^2)$

Parameter	Entity/Actor	Specification
		Body surface area shall be calculated according to the Du Bois formula: $BSA (m^2) = (0.007184)((w)^{(0.425)})(h)^{(0.725)}$ [Vu 2002] Where w = weight in kg and h = height in cm.

935

936 4.4.3 Image Analysis Workstation Performance Specifications

937 The digital reference object (DRO), which is a synthetic PET (and CT) image, shall be used in order to
 938 evaluate compliance to the level of performance of analysis station/display station. Users should use the
 939 DRO (as per the DRO user's guide in Appendix F) to verify correct implementation of ROI placement, SUV
 940 calculations, and PET and CT image alignment.

Parameter	Entity/Actor	Specification
Performance Evaluation	Analysis Workstation	Shall use the DRO to verify adequate performance as described in Appendix F.
Analysis Accuracy	Analysis Workstation	For each of the specified ROIs in the DRO (Appendix F) the correct SUV values shall be replicated by the Analysis Workstation.
Alignment Accuracy	Analysis Workstation	The PET and CT DRO object shall appear perfectly aligned in the transverse, coronal, and sagittal views.
DICOM Compliance	Analysis Workstation	All image data and scan parameters shall be readable and transferable using appropriate DICOM fields according to the DICOM conformance statement for the originating PET/CT scanner.

941

942 4.5. Software version tracking

943 At a minimum, Software Versions should be manually recorded during the qualification along with the
 944 phantom imaging performance data and the record should be updated for every software-upgrade over the
 945 duration of the trial. This includes the flagging of the impact on quantification for now; in the future, record
 946 all software version numbers in DICOM header.

Parameter	Entity/Actor	Specification
Hardware Version tracking	Service Engineers	Shall update Hardware Version in scanner after any major equipment upgrade.
Hardware Version tracking	Scanner	Shall enter Hardware Version in appropriate DICOM field.

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

947

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1061

1062 Appendices

1063 Appendix A: Acknowledgements and Attributions

1064 This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging
 1065 Biomarker Alliance (QIBA) FDG-PET/CT Technical Committee. The FDG-PET/CT Technical Committee is
 1066 composed of physicians, scientists, engineers and statisticians representing the imaging device
 1067 manufacturers, image analysis software developers, image analysis facilities and laboratories,
 1068 biopharmaceutical companies, academic institutions, government research organizations, professional
 1069 societies, and regulatory agencies, among others. A more detailed description of the QIBA FDG-PET/CT
 1070 group and its work can be found at the following web link: [http://qibawiki.rsna.org/index.php?title=FDG-](http://qibawiki.rsna.org/index.php?title=FDG-PET_tech_ctte)
 1071 [PET_tech_ctte](http://qibawiki.rsna.org/index.php?title=FDG-PET_tech_ctte)

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1076

1077 Appendix B: Background Information for Claim

1078 A number of publications report test-retest repeatability for tumor SUV measurements with FDG PET
1079 [1,2,3,4,5,6,7,8]. Table 1 lists these publications and summarizes some of their results. Comparing
1080 repeatability measurements from the various reports is complicated by the different methodologies
1081 employed in each study and also the different metrics used to characterize repeatability.

1082 As expected, the region-of-interest (ROI) or volume-of-interest (VOI) methodology varied between
1083 publications. Minn et al [1] report SUV_{mean} derived from a fixed size 1.2 × 1.2 cm region-of-interest.
1084 Weber et al [2] report SUV_{mean} derived from a volume-of-interest defined by a 50% isocontour. The
1085 remaining papers report SUV_{max}, although data for multiple ROI definitions were sometimes reported.
1086 Because SUV_{max} was more commonly reported amongst these repeatability papers and was more
1087 comparable between studies, table 1 focused primarily on SUV_{max}.

1088 Nahmias and Wahl [5] report SUV_{max} but, unlike the other publications, they present their results in
1089 absolute SUV units, as opposed to relative units. Direct comparison with the other reports was therefore
1090 not possible. Kamibayashi et al [6] compared the repeatability of SUVs measured on different scanner
1091 systems, whereas the other reports involve test-retest studies on the same scanner. For this reason the
1092 Kamibayashi data were also not directly comparable with the other papers. The remaining publications
1093 [3,4,7,8] are amenable to more direct comparison as they all report the repeatability of SUV_{max}, with test
1094 and retest studies both performed on the same scanner system.

1095 A further complication when comparing reports is the different metrics used to characterize repeatability.
1096 In table 1 we translate the reported repeatability measurements to a within-subject coefficient of variation
1097 (wCOV) to allow a more direct comparison. Based on the data in the last 4 rows of table 1 [3,4,7,8], it can
1098 be seen that the within subject coefficient of variation for SUV_{max} was in the range 10.01 – 11.9 %.

1099 Table 2 summarizes the relationships that were involved in converting the published repeatability
1100 parameters to within-subject coefficient of variation.

Table 1. Selected repeatability parameters extracted from literature publications. Where multiple SUV types were reported, preference was given to SUVmax as this SUV definition was more comparable between studies. The column marked "Inferred wCV" is an estimate of the within-subject coefficient of variation based upon the reported parameters and may not appear in the original manuscripts. Details of how these "Inferred wCV" values were derived are described in the text and table 2.

Publication	SUV Type	Repeatability Parameter	Parameter Value	Where in Manuscript	Inferred wCV	Comment
Minn 1995 [1]	SUVmean	Mean absolute percentage difference	10 %	Table 4	8.86 %	n=10; 1.2 x 1.2 cm ROI
Weber 1999 [2]	SUVmean	SD of the percentage difference	9.1 %	Table 2	6.43 %	n=16; 50 % isocontour VOI
Nahmias 2008 [5]	SUVmax	SD of the difference	1.14 SUV	Page 1806	Not available	n=26; Results reported in absolute SUV units
Kamibayashi 2008 [6]	SUVmax	Mean absolute percentage difference	16.1 %	Table 4	14.27 %	n=45; Two different PET scanners
Nakamoto 2002 [3]	SUVmax	Mean absolute percentage difference	11.3 %	Table 4	10.01 %	n=10
Krak 2005 [4]	SUVmax	Mean absolute percentage difference	13 %	Table 2	11.52 %	n=29
Velasquez 2009 [7]	SUVmax	Within subject coefficient of variation	11.9 %	Table 5	11.9 %	n=45; Multi-center study after centralized quality assurance and analysis
Hatt 2010 [8]	SUVmax	SD of the percentage difference	16.7 %	Table 2	11.81 %	n=17

Table 2. Relationships used to compare repeatability metrics found in the literature.

Parameter	Symbol	Relationship	Comment
Percentage difference	D	$100 \times (SUV_2 - SUV_1) / 0.5 \times (SUV_1 + SUV_2)$	Test-retest difference expressed as a percentage of the mean
Mean absolute percentage difference of D	D_MAD	Mean of D over all subjects	D is the absolute value of D
Standard deviation of D	D_SD	Standard deviation of D over all subjects	$D_SD = D_MAD / \sqrt{2/\pi}$ for normally distributed data
Within subject coefficient of variation	wCV	$D_SD / \sqrt{2}$	Reflects repeatability of a single measurement
Repeatability		$1.96 \times \sqrt{2} \times wCV$	Reflects 95 % limits of repeatability for the difference between two measurements

One assumption that was made during these conversions was that the percentage difference (D) between test-retest SUV measurements was normally distributed with zero mean. While this assumption may not be strictly applicable over a wide range of SUVs, it is an assumption that is implicitly being made whenever 95% limits of repeatability are employed [7,8]. Applying this same assumption to the studies that report the mean absolute percentage difference (D_MAD) allows their results to be simply related to the other publications that report the standard deviation by $D_MAD = (\sqrt{2/\pi})\sigma$; 0.80σ , as shown below.

$$D_MAD = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\infty} |x - \mu| e^{-\frac{(x-\mu)^2}{2\sigma^2}} dx$$

$$= \frac{2}{\sigma\sqrt{2\pi}} \int_0^{\infty} (x - \mu) e^{-\frac{(x-\mu)^2}{2\sigma^2}} dx$$

$$\text{let } r = \frac{(x - \mu)^2}{2\sigma^2}, \text{ and } dr = \frac{(x - \mu)}{\sigma^2} dx, \text{ and limits are unchanged } \int_{x=0}^{x=\infty} \rightarrow \int_{r=0}^{r=\infty}$$

then,

$$D_MAD = \sqrt{\frac{2}{\pi}} \sigma \int_0^{\infty} e^{-r} dr = \sqrt{\frac{2}{\pi}} \sigma e^{-r} \Big|_0^{\infty} = \sqrt{\frac{2}{\pi}} \sigma [1 - 0] = \sqrt{\frac{2}{\pi}} \sigma ; 0.80\sigma$$

References

- 1 Minn H, Zasadny KR, Quint LE, Wahl RL. Lung cancer: reproducibility of quantitative measurements for evaluating 2-[F-18]-fluoro-2-deoxy-D-glucose uptake at PET. *Radiology*, 196, 1 (1995), 167-173.
- 2 Weber WA, Ziegler SI, Thodtmann R, Hanauske A-R, Schwaiger M. Reproducibility of metabolic measurements in malignant tumors using FDG PET. *J Nucl Med*, 40, 11 (1999), 1771-1777.
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- 4 Krak NC, Boellaard R, Hoekstra OS, Twisk JWR, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. *Eur J Nucl Med Mol Imaging*, 32, 3 (2005), 294-301.
- 5 Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by 18F-FDG PET in malignant tumors. *J Nucl Med*, 49, 11 (2008), 1804-1808.
- 6 Kamibayashi T, Tsuchida T, Demura Y, et al. Reproducibility of semi-quantitative parameters in FDG-PET using two different PET scanners: influence of attenuation correction method and examination interval. *Mol Imaging Biol*, 10 (2008), 162-166.
- 7 Velasquez LM, Boellaard R, Kollia G, et al. Repeatability of 18F-FDG PET in a multicenter phase 1 study of patients with advanced gastrointestinal malignancies. *J Nucl Med*, 50, 10 (2009), 1646-1654.
- 8 Hatt M, Cheze-Le Rest C, Aboagye EO, Kenny LM, Rosso L, Turkheimer FE, Albarghach NM, Metges JP, Pradier O, Visvikis D. Reproducibility of 18F-FDG and 3'-deoxy-3'-18F-fluorothymidine PET tumor volume measurements. *J Nucl Med.*, 51 (2010), 1368-1376.

Appendix C: Conventions and Definitions

Convention Used to Represent Profile requirements

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

1139 Profile.

1140 Illustrative example:

1141 Parameter Entity/Actor Normative text: Clear boxes are current requirements
 1142 Shaded boxes are intended for future requirements

Lesion Analysis: Multiple Voxels	Analysis Tool	Shall provide tools to measure and report SUVmean and SUVmax normalized to body weight.
		Shall provide tools to measure and report SUVmean SUVmax and SUVpeak, normalized to body weight or lean body mass.

1143 Items within tables are normative (i.e. required in order to be compliant with the QIBA protocol). The intent
 1144 of the normative text is to be prescriptive and detailed to facilitate implementation. In general the intent is
 1145 to specify the final state or output, and not how that is to be achieved.

1146 All other text outside of these tables is considered informative only.

1147 **Definitions**

1148 ROI: Region of interest. A region in an image that is specified in some manner, typically with user-controlled
 1149 graphical elements that can be either 2D areas or 3D volumes. These elements include, but not limited
 1150 to, ellipses, ellipsoids, rectangles, rectangular volumes, circles, cylinders, polygons, and free-form
 1151 shapes. An ROI can also defined by a segmentation algorithm that operates on the image. Segmentation
 1152 algorithms include, but are not limited to, fixed-value thresholding, fixed-percentage thresholding,
 1153 gradient edge detection, and Bayesian methods. With the definition of an ROI, metrics are then
 1154 calculated for the portion of the image within the ROI. These metrics can include, but are not limited to,
 1155 mean, maximum, standard deviation, and volume or area. Note that the term ROI can refer to a 2D area
 1156 on a single image slice or a 3D volume. In some cases the term ROI is used to refer to 2D area and the
 1157 term volume of interest (VOI) is used to refer to a 3D volume. In this Profile the term ROI is used to
 1158 refer to both 2D areas and 3D volumes as needed.

1159 VOI: Volume of interest. See definition for ROI.

1160 Dose: Can refer to either radiation dose or as a jargon term for 'total radioactivity'. For example, 10 mCi of
 1161 18F-FDG is often referred to as a 10 mCi dose.

1162 SUV: Standardized uptake value. A measure of relative radiotracer uptake within the body. Typically
 1163 defined for a time point t as $SUV(t) = \frac{r(t)}{d' / \tilde{V}}$ where $r(t)$ is the measured radioactivity concentration
 1164 within the ROI, d' is the decay-corrected injected radioactivity (or 'dose'), and \tilde{V} is a surrogate for the
 1165 distribution volume. Typically patient weight or lean body mass are used for \tilde{V} .

1166 Notes:

- 1167 1. The SUV can change over time, so measuring $r(t)$ at a consistent time point is recommended.
- 1168 2. Either body weight or lean body mass are used for a surrogate for the distribution volume, so the
 1169 SUV units are g/ml.
- 1170 3. For a uniform distribution of radiotracer, the SUV everywhere would be exactly 1 g/ml.
- 1171 4. The measured SUV statistic is typically one of the following:

- 1172 i. SUVmean: The average SUV within the ROI.
1173 ii. SUVmax: The maximum SUV within the ROI.
1174 iii. SUVpeak: The average SUV within a fixed-sized ROI, typically a 1 cm diameter sphere. The
1175 spheres location is adjusted such that the average SUV is maximized.
1176 iv. TLG: Total lesion glycolysis. The summed SUV within the ROI.

1177 Profile:

1178 18F-FDG or FDG: 2-deoxy-2-(18F)fluoro-D-glucose, a glucose analog, with the positron-emitting radioactive
1179 isotope fluorine-18 substituted for the normal hydroxyl group at the 2' position in the glucose molecule.
1180 FDG is the most commonly used (>90%) radiotracer in PET imaging.

1181 PET: Positron emission tomography (PET) is a tomographic imaging technique that produces an image of
1182 the in vivo distribution of a radiotracer, typically FDG.

1183 PET/CT: Positron emission tomography / computed tomography (PET/CT) is a medical imaging system that
1184 combines in a single gantry system both Positron Emission Tomography (PET) and an x-ray Computed
1185 Tomography (CT) scanners, so that images acquired from both devices can be taken nearly-
1186 simultaneously.

1187 CT: X-ray computed tomography (CT) is a medical imaging technique that utilizes X-rays to produce
1188 tomographic images of the relative x-ray absorption, which is closely linked to tissue density.

1189 TOF: Time of Flight (TOF) is a PET imaging technique utilizing differential annihilation photon travel times
1190 to more accurately localize the in vivo distribution of a radiotracer.

1191 UPICT: Uniform Protocols For Imaging in Clinical Trials (UPICT). A RSNA-QIBA initiative that seeks to provide
1192 a library of annotated protocols that support clinical trials within institutions, cooperative groups, and
1193 trials consortia. The UPICT protocols are based on consensus standards that meet a minimum set of
1194 criteria to ensure imaging data quality.

1195 DICOM: Digital Imaging and Communications in Medicine (DICOM) is a set of standards for medical images
1196 and related information. It defines formats for medical images that can be exchanged in a manner that
1197 preserves the data and quality necessary for clinical use.

1198 CRF: Case Report Form (CRF) is a paper or electronic questionnaire specifically used in clinical trial research.
1199 The CRF is used by the sponsor of the clinical trial (or designated CRO etc.) to collect data from each
1200 participating site. All data on each patient participating in a clinical trial are held and/or documented in
1201 the CRF, including adverse events.

1202 mCi: millicuries. A non-SI unit of radioactivity, defined as $1 \text{ mCi} = 3.7 \times 10^7$ decays per second. Clinical
1203 FDG-PET studies inject (typically) 5 to 15 mCi of 18F-FDG.

1204 MBq: megabecquerel. An SI-derived unit of radioactivity defined as 1.0×10^6 decays per second.

1205 PMD: Progressive Metabolic Disease: Any of the following:

- 1206 • An increase in the SUVmean of $\geq 25\%$ within the tumor region defined on the baseline scan
- 1207 • Visible increase in the extent of FDG tumor uptake 20% in the longest diameter
- 1208 • An unequivocal new PET-avid lesion

1209 SMD: Stable Metabolic Disease. Either of the following:

- 1210 • An increase in tumor SUVmean <25% and no visible increase in the extent of the tumor uptake (< 20%
1211 in the longest diameter)
- 1212 • A decrease of <25% in tumor SUVmean
- 1213 PMR: Partial Metabolic Response. A reduction of $\geq 25\%$ in tumor SUVmean
- 1214 CMR: Complete Metabolic Response. A complete resolution of FDG-PET uptake within the all tumor volume
1215 so that it is indistinguishable from the surrounding normal tissue
- 1216 QA: Quality Assurance. Proactive definition of the process or procedures for task performance. The
1217 maintenance of a desired level of quality in a service or product, esp. by means of attention to every
1218 stage of the process of delivery or production.
- 1219 QC: Quality Control. Specific tests performed to ensure target requirements of QA program are met.
1220 Typically by testing a sample of the output against the specification.
- 1221 Accreditation: Approval by an independent body or group for broad clinical usage (requires ongoing
1222 QA/QC) e.g. ACR, IAC, TJC.
- 1223 Qualification: Approved by an independent body or group for either general participation in clinical
1224 research (ACRIN-CQIE , SNM-CTN others) or for a specific clinical trial (requires ongoing QA/QC). This
1225 includes CROs, ACRIN, SNM-CTN, CALGB and other core laboratories.
- 1226 Compliance: Meeting the list of requirements described in this document, which are necessary to meet the
1227 measurement claims for this QIBA Profile.
- 1228 RECIST: Response Evaluation Criteria in Solid Tumors (RECIST). A set of published rules that define when
1229 cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during
1230 treatments. Based on anatomical size changes of solid tumors. Commonly used but also controversial.
- 1231 PERCIST: PET Response Criteria for Solid Tumors. A framework proposed for using FDG-PET imaging as a
1232 cancer therapy response criteria for solid tumors. Proposed as a more accurate alternative to RECIST for
1233 several types of solid tumors.
- 1234 LBM: Lean Body Mass is calculated by subtracting body fat weight from total body weight. The Lean body
1235 mass (LBM) has been described as an index superior to total body weight for prescribing proper levels
1236 of medications and for assessing metabolic disorders.
- 1237 AC: Attenuation Correction. Attenuation is a an effect that occurs when photons emitted by the radiotracer
1238 inside the body are absorbed by intervening tissue. The result is that structures deep in the body are
1239 reconstructed as having falsely low (or even negative) tracer uptake. Contemporary PET/CT scanners
1240 estimate attenuation using integrated x-ray CT equipment. While attenuation-corrected images are
1241 generally faithful representations of radiotracer distribution, the correction process is itself susceptible
1242 to significant artifacts.
- 1243
- 1244 *Organizations*
- 1245 QIBA: Quantitative Imaging Biomarkers Alliance. The Quantitative Imaging Biomarkers Alliance (QIBA) was
1246 organized by RSNA in 2007 to unite researchers, healthcare professionals and industry stakeholders in the
1247 advancement of quantitative imaging and the use of biomarkers in clinical trials and practice.
- 1248 RSNA: Radiological Society of North America (RSNA). A professional medical imaging society with more than

1249 47,000 members, including radiologists, radiation oncologists, medical physicists and allied scientists. The
1250 RSNA hosts the world's largest annual medical meeting.

1251 SNMMI: Society of Nuclear Medicine and Molecular Imaging (formerly called the Society of Nuclear
1252 Medicine (SNM)). A nonprofit scientific and professional organization that promotes the science,
1253 technology and practical application of nuclear medicine and molecular imaging. SNMMI represents 18,000
1254 nuclear and molecular imaging professionals worldwide. Members include physicians, technologists,
1255 physicists, pharmacists, scientists, laboratory professionals and more

1256 CTN: The Clinical Trials Network (CTN) was formed by SNMMI in 2008 to facilitate the effective use of
1257 molecular imaging biomarkers in clinical trials.

1258 AAPM: The American Association of Physicists in Medicine is a member society concerned with the topics
1259 of medical physics, radiation oncology, imaging physics. The AAPM is a scientific, educational, and
1260 professional organization of 8156 medical physicists.

1261 EANM: The European Association of Nuclear Medicine (EANM) constitutes the European umbrella
1262 organization of nuclear medicine in Europe

1263 EORTC: The European Organization for Research and Treatment of Cancer or EORTC is an international non-
1264 profit organization that develops, coordinates, and stimulates cancer laboratory and clinical research in
1265 Europe.

1266 EARL: EANM Research Ltd (EARL) was formed by EANM in 2006 to promote multicentre nuclear medicine
1267 and research.

1268 ACR: The 36,000 members of |include radiologists, radiation oncologists, medical physicists, interventional
1269 radiologists, nuclear medicine physicians and allied health professionals.

1270 ACRIN: The American College of Radiology Imaging Network (ACRIN) is a program of the American College
1271 of Radiology and a National Cancer Institute cooperative group. Focused on cancer-related research in
1272 clinical trials.

1273 ECOG-ACRIN: A National Cancer Institute cooperative group formed from the 2012 merger of the Eastern
1274 Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN).

1275 IAC: The Intersocietal Accreditation Commission (IAC) provides accreditation programs for Vascular Testing,
1276 Echocardiography, Nuclear/PET, MRI, CT/Dental, Carotid Stenting and Vein Center.

1277 TJC: The Joint Commission (TJC) accredits and certifies health care organizations and programs in the
1278 United States.

1279 CRO: Contract Research Organization A commercial or not-for-profit organization designated to perform a
1280 centralized and standardized collection, analysis, and/or review of the data generated during a clinical trial.
1281 Additional activities which may be performed by an imaging core lab include training and qualification of
1282 imaging centers for the specific imaging required in a clinical trial, development of imaging acquisition
1283 manuals, development of independent imaging review charters, centralized collection and archiving of
1284 images received from study sites, performing pre-specified quality control checks/tests on incoming images
1285 and development and implementation of quality assurance processes and procedures to ensure that
1286 images submitted are in accord with imaging time points specified in the study protocol and consistent with
1287 the quality required to allow the protocol-specified analysis /assessments

1288 CQIE: The Centers of Quantitative Imaging Excellence (CQIE) program was developed by ACRIN in response
1289 to a solicitation for proposals issued in December 2009 by SAIC-Frederick on behalf of the National Cancer

1290 Institute (NCI). The primary objective of the CQIE Program is to establish a resource of 'trial ready' sites
1291 within the NCI Cancer Centers Program that are capable of conducting clinical trials in which there is an
1292 integral molecular and/or functional advanced imaging endpoint.

1293 CLIA: Clinical Laboratory Improvement Amendments: Accreditation system for establishing quality
1294 standards for laboratory testing.

1295 USP: United States Pharmacopeial Convention establishes written and physical (reference) standards for
1296 medicines, food ingredients, dietary supplement products and ingredients in the U.S.

1297 EMA: European Medicines Agency is a European Union agency for the evaluation of medicinal products.
1298 Roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization.

1299 FDA: Food and Drug Administration is responsible for protecting and promoting public health in the U.S.
1300 through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription
1301 and over-the-counter pharmaceutical medications, vaccines, biopharmaceuticals, blood transfusions,
1302 medical devices, electromagnetic radiation emitting devices, and veterinary products.

1303 NIST: National Institute of Standards and Technology is a measurement standards laboratory which is a
1304 non-regulatory agency of the United States Department of Commerce.

1305 NEMA: National Electrical Manufacturers Association is a forum for the development of technical standards
1306 by electrical equipment manufacturers.

1307 MITA: The Medical Imaging & Technology Alliance is a division NEMA that develops and promotes
1308 standards for medical imaging and radiation therapy equipment. These standards are voluntary guidelines
1309 that establish commonly accepted methods of design, production, testing and communication for imaging
1310 and cancer treatment products.

1311 NCRI: National Cancer Research Institute. The National Cancer Research Institute (NCRI) is a UK-wide
1312 partnership between the government, charity and industry which promotes co-operation in cancer
1313 research among the 22 member organisations for the benefit of patients, the public and the scientific
1314 community.

1315

1316 **Appendix D: Model-specific Instructions and Parameters**

1317 The presence of specific product models/versions in the following tables should not be taken to imply that
1318 those products are fully compliant with the QIBA Profile. Compliance with a Profile involves meeting a
1319 variety of requirements of which operating by these parameters is just one. To determine if a product (and
1320 a specific model/version of that product) is compliant, please refer to the QIBA Conformance Document for
1321 that product.

1322 ***D.1. Image Acquisition Parameters***

1323 The following technique tables list acquisition parameter values for specific models/versions that can be
1324 expected to produce data meeting the requirements of Section 3.6.4 ('Phantom Imaging').

1325 These technique tables may have been prepared by the submitter of this imaging protocol document, the
1326 clinical trial organizer, the vendor of the equipment, and/or some other source. (Consequently, a given
1327 model/version may appear in more than one table.) The source is listed at the top of each table.

1328 Sites using models listed here are encouraged to consider using these parameters for both simplicity and

1329 consistency. Sites using models not listed here may be able to devise their own acquisition parameters that
 1330 result in data meeting the requirements of Section 3.6.4 and conform to the considerations in Section 4. In
 1331 some cases, parameter sets may be available as an electronic file for direct implementation on the imaging
 1332 platform.

1333 **D.2. Quality Assurance Procedures**

1334 Examples of recommend quality assurance procedures are shown for specific GE, Philips, and Siemens
 1335 PET/CT scanners in the tables below.

1336

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

1337

1338

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

QA procedures and schedules for Siemens Biograph 6/16 Hi-Rez, Biograph 16 Truepoint, Biograph 16 Truepoint with TrueV, PET Syngo 2010A, Biograph mCT			
Device	QA Procedure	Frequency	
Computers	Restart computers	Daily at Startup	
	Clear scheduler	Daily	
	Clear network, local, and film queues	Four times daily	
	Archive patient data	Daily	
	System cleanup/defragmentation	Weekly	
CT	CT Checkup/Calibration	Daily, after 60 minutes of full load, within 1 hour of patient scan	
	CT Quality	Water HU	Daily
		Pixel noise	Daily
Tube voltages		Daily	
PET	PET Daily QC	Daily normalization	Daily
		Computation/ verification of the PET calibration factor (ECF)	Daily
		Normalization results display and sinogram inspection	Daily
		System quality report	Daily
		Partial detector setup: generate crystal region maps/energy profiles	Weekly
Full detector setup and time alignment	Quarterly		

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

The list below comprises meta-information (i.e. in addition to image values of kBq/ml) that is necessary for quantitatively accurate (i.e. known and minimal uncertainties) of PET SUVs. The actual format is not specified. The format can range from paper notes to electronic databases. The intent here is to list what information should be captured rather than the mechanism itself. The mechanism is currently unspecified,

1347 but ranges from paper notes, to scanned forms or electronic data records, to direct entry from the
1348 measurement equipment (i.e. the PET/CT scanner or auxiliary measurement devices such as the
1349 radionuclide calibrator) into pre-specified DICOM fields. Ideally all of the specified meta data will be
1350 captured by direct electronic entry to DICOM fields, after suitable modification of the DICOM format for
1351 PET imaging.

1352 The concept endorsed here is that the needed meta-data is identified. Through revisions of this Profile, the
1353 DICOM standard, and technology the meta-data is inserted into the analysis stream (Figure 3) in a more
1354 direct manner and technology and accepted standards evolve.

- 1355 • The needed information, where feasible, is listed in order from least frequently changing to most
1356 frequently changing.
- 1357 • In all cases note whether measurements are made directly or estimated. If the latter case, note the
1358 source of information and the date and time (e.g. if subject cannot be moved from bed to measure
1359 weight or height).

1360 Data fields to be recorded:

- 1361 1. Site specific
 - 1362 a. Site information (include name and/or other identifiers)
 - 1363 b. Scanner make and model
 - 1364 c. Hardware Version numbers
 - 1365 d. Software Version numbers
 - 1366 e. Confirmation that scanner used was previously qualified (or not)
- 1367 2. Protocol specific
 - 1368 a. PET
 - 1369 i. Duration per bed
 - 1370 ii. Bed overlap
 - 1371 iii. Acquisition mode (2D or 3D)
 - 1372 iv. Reconstruction method
 - 1373 b. CT technique
- 1374 3. Scanner specific QA/QC
 - 1375 a. Most recent calibration factors (scanner)
 - 1376 b. Scanner daily check values
 - 1377 c. most recent clock check
 - 1378 d. most recent scanner QA/QC
- 1379 4. Subject exam specific
 - 1380 a. Height
 - 1381 b. Weight
 - 1382 c. Fasting time assessment
 - 1383 d. Blood glucose concentration and time of sampling
 - 1384 e. Pre- and post-injection assayed activities and times of assay
 - 1385 f. Injection time
 - 1386 g. Site of injection (and assessment of infiltration)
 - 1387 h. Net injected activity (calculated including decay correction)
 - 1388 i. Uptake time

1389

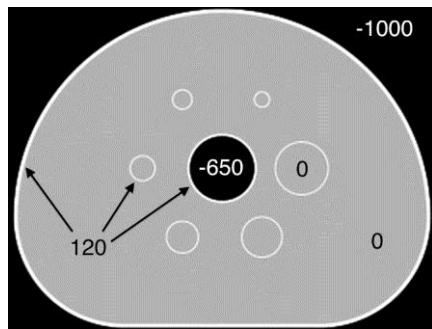
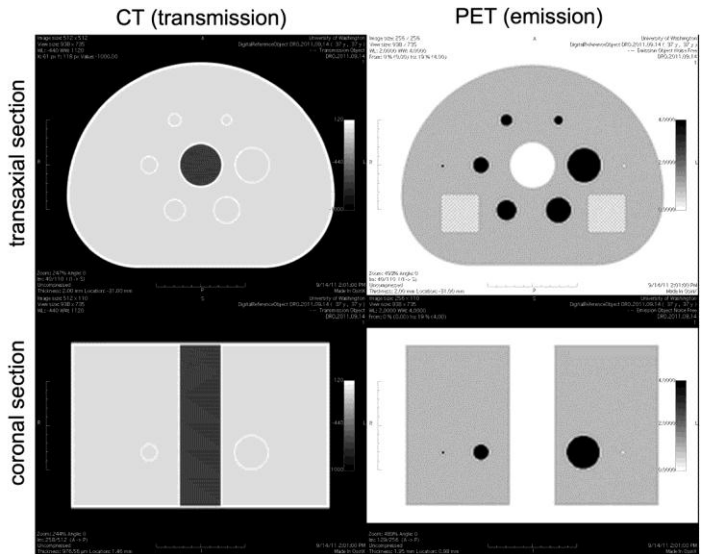
Appendix F: Testing PET/CT Display and Analysis Systems with the FDG-PET/CT Digital Reference Object

The PET/CT Digital Reference Object (DRO) is a synthetically generated set of DICOM image files of known voxel values for positron emission tomography (PET) and x-ray computed tomography (CT). The PET/CT DRO is intended to test the computation of standardized uptake values (SUVs) by PET/CT display stations. It is also intended to test region of interest (ROI) calculations and alignment between the PET and CT images. This is motivated by vendor-specific variations in PET DICOM formats used for SUVs. The development of the PET/CT DRO is supported by the Quantitative Imaging Biomarker Alliance (QIBA).

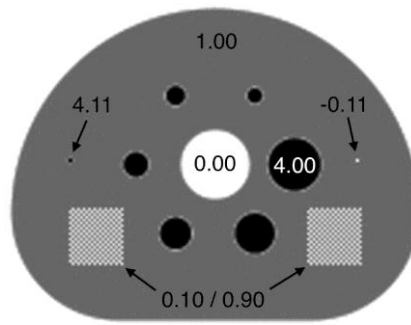
The primary goals and objectives of the PET/CT Digital Reference Object are to support the QIBA FDG-PET 'Technical Validation' efforts for Profile development. This will be done by (1) evaluation and validation of SUV calculations in PET images, (2) evaluation and validation of ROI calculations and (3) providing a common reference standard that can be adopted and modified by PET/CT scanner and display station manufacturers.

The PET and CT components of the Images of the DRO are each a set of DICOM format files, one file per image slice. Each set of files are typically grouped as a stack to form an image volume. Representative sections through the CT and PET image volumes are shown below.

The synthetic test object is based on, but is not identical to, the NEMA NU-2 PET test phantom [J Nucl Med, vol. 43 no. 10 1398-1409, 2002]. The PET object has added 'test voxels' together with 2D and 3D 'test patterns'. In each object, the thickness of the exterior shell is 3 mm, the thickness of the hot sphere walls is 1 mm, and the thickness of the lung insert wall is 2mm.



The CT DRO showing Hounsfield Units for each structure.



The PET DRO with the SUVbw values of each structure.

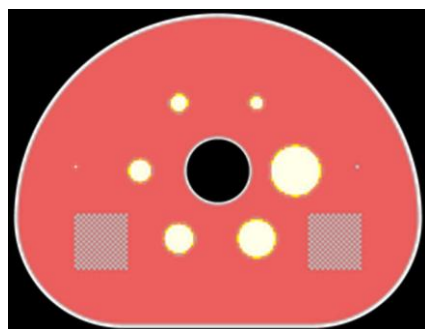


Image fusion of the CT and PET DROs showing perfect alignment



Coronal view of the PET DRO showing the 2D test pattern in slice 40 (left) as well as the 3D cubic test pattern (right)

1405

1406

Structure of the CT and PET DROs.

1407

The CT Object

1408

The CT object is $512 \times 512 \times 110$ voxels, and is stored in 110 DICOM files named 000001.dcm through 000110.dcm, numerically ordered so that 000001.dcm corresponds to slice 1 in the image volume.

1409

1410

The CT object has a reconstruction diameter of 500 millimeters and an axial extent of 220 millimeters, resulting in a voxel size of $500/512 \times 500/512 \times 2$ ($0.9765625 \times 0.9765625 \times 2.0$) millimeters³.

1411

1412

The interior of the phantom body and the interiors of the hot spheres have voxels with values of 0 Hounsfield Units (HU), simulating water in the body and the interior of the hot spheres. The shell of the body, lung insert wall, and hot sphere walls have voxels set to 120 HU, simulating polymethylmethacrylate. The voxels interior to the lung insert are set to -650 HU, simulating lung attenuation material. The voxels exterior of the phantom body are set to -1000 HU, simulating air. These values are indicated in the above figure. NOTE: Partial volume effects will alter the voxel values near the borders of different regions.

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1417

1418

1419

The PET Object

1420

The PET object consists of a $256 \times 256 \times 110$ voxel image volume stored in 110 DICOM files named 000001.dcm through 000110.dcm, similar to the CT object described above.

1421

1422

The PET object has a reconstruction diameter of 500 millimeters and an axial extent of 220 millimeters, resulting in a voxel size of $500/256 \times 500/256 \times 2$ ($1.953125 \times 1.953125 \times 2.0$) millimeters³.

1423

1424

The voxels interior to the phantom body are set to an SUV value of 1.00. The voxels interior to the six hot spheres are set to an SUVbw value of 4.00. The voxels corresponding to the polymethylmethacrylate shell and the exterior of the phantom body and interior to the lung insert are set to an SUVbw value of 0.00. NOTE: Partial volume effects will alter the voxel values near the borders of different regions.

1425

1426

1427

1428

There are two test voxels in slice 40 of the DRO. The test voxel furthest from the largest hot sphere in slice 40 is set to an SUVbw value of 4.11. The test voxel closest to the largest hot sphere in slice 40 is set to an SUVbw value of -0.11. NOTE: There is no polymethylmethacrylate shell surrounding the test voxels in the PET object, and no partial volume effects surrounding the test voxels.

1429

1430

1431

1432

There are two test patterns in the PET DRO, a square (2D) checkerboard pattern in slice 40, and a cubic (3D) checkerboard pattern centered in slice 40. The 3D cubic test pattern appears closest to the largest hot

1433

1434 sphere in an axial view of slice 40.

1435 Each test pattern consists of a checkerboard of voxels with alternating SUVbw values of 0.10 and 0.90 Both
1436 the 2D square and 3D cubic test patterns have edge measurements of 40 mm. The SUVbw values of each
1437 region of the PET DRO are shown in the above figure.

1438 Users of the DRO are asked to download the package, import the PET and CT objects into their viewing
1439 software, perform region of interest (ROI) analyses, and submit the results back to this website.

1440

1441 **Procedure**

1442 Users of the Digital Reference Object are requested to:

- 1443 1. Download the DRO (or import from CD) and the user report form.
- 1444 2. Verify the DRO files are present.
- 1445 3. Import the DRO into the viewing software.
- 1446 4. Perform ROI analysis of the DRO.
- 1447 5. Submit the completed report and store a copy locally.

1448

Digital Reference Object Analysis Sheet - Version 10/31/2011

You may record your answers directly on this form or by filling out the accompanying Excel spreadsheet. The numbers on each line indicate the corresponding rows and columns of the Excel spreadsheet.

1 Basic Information

Fill out the basic information for the test. Include a brief description of the workstation and its hardware, the software being tested, and the makes and models of the primary scanners that supply the images viewed on the workstation used for this test.

ROW	Item	Value
6	Name of Institution	
7	Name of person testing software	
8	Email or Phone contact	
9	Date of test	
10	Workstation used for test (Serial #)	
11	Description of hardware (Hardware Version)	
12	Make and model of monitor	
13	Software Manufacturer	
14	Name of software being tested	
15	Version of software	
16	Makes and models of primary scanners	

Load the DRO into your viewing software. Using an axial view, advance to **slice 40**, which contains the two test voxels and both test patterns as shown in Figure 1. Record the type of SUV that you are measuring (or 'Unknown') and the number of decimal places that the software reports for the SUV value. Record the type of ROI that your software uses (2D or 3D). Record the ROI measurement units and indicate if it is a diameter, an area, a volume, etc..

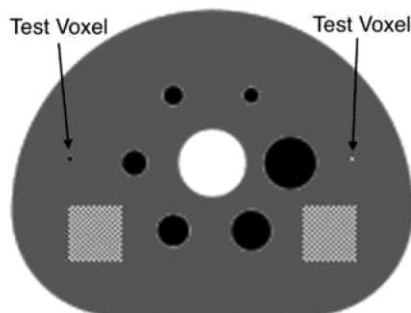


Figure 1: You should see both the hot and cold test voxels and the two square test patterns in slice 40.

ROW	Item	Value
20	SUV Type (BW, LBM, BSA)	
21	Number of decimal places	
22	ROI Type (2D, 3D)	
23	Recording ROI Area or Diameter?	

2 ROI Analysis of the DRO

For each of the following six ROIs (shown in Figure 2), record the maximum, minimum, mean, standard deviation for the voxel SUV values. Also record either the diameter or area of each ROI (if recording area, record the volume for ROI 6).

- (1) Draw a circular ROI with an area of 490 mm² (diameter=25 mm), concentric with the smallest hot sphere.
- (2) Draw a circular ROI with an area of 490 mm² (diameter 25 mm), concentric with largest hot sphere.
- (3) Draw a circular ROI with an area of 490 mm² (diameter 25 mm), concentric with the hot test voxel.
- (4) Draw a circular ROI with an area of 490 mm² (diameter 25 mm), concentric with the cold test voxel.
- (5) Draw a circular ROI with an area of 490 mm² (diameter 25 mm), centered within the single plane test pattern nearest the hot test voxel.
- (6) Draw a spherical (3D) ROI with a volume of 2,600 mm³ (diameter 25 mm), centered within the 3D block test pattern nearest the cold test voxel.

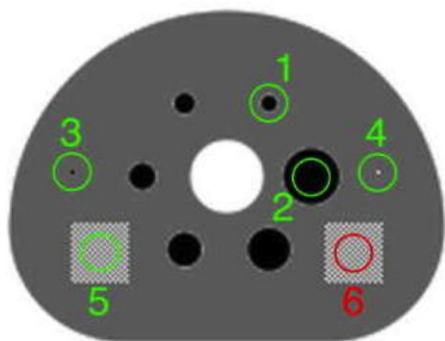


Figure 2: ROIs for the DRO analysis. The cross-section of the sphere in the 3D test pattern (on the right) is shown in red.

COL:		C	D	E	F	G
ROW	ROI	Max	Min	Mean	STD	Diam or Area
28	ROI 1					
29	ROI 2					
30	ROI 3					
31	ROI 4					
32	ROI 5					
33	ROI 6					

Appendix G: Vendor-neutral pseudo-codes for SUV calculation

G.1 Generic version

This appendix contains the consensus opinion on the generic form of SUV calculation from PET DICOM images. A generic pseudo-code is used with "//" signifying the beginning of a comment field to the end of the line. This version assumes: units are BQML, no private data elements required, series time is OK. Updated as of September 28, 2012. The most up to date version is maintained on the QIBA FDG-PET Wiki page (http://qibawiki.rsna.org/index.php?title=Standardized_Uptake_Value_SUV).

// SUV cannot be calculated if any of the specified DICOM attributes are missing or empty or zero

if Corrected Image (0x0028,0x0051) contains ATTN and DECAy and Decay Correction (0x0054,0x1102) is START {

 if Units (0x0054,0x1001) are BQML {

 half life = Radionuclide Half Life (0x0018,0x1075) in Radiopharmaceutical Information Sequence (0x0054,0x0016) // seconds

 if Series Date (0x0008,0x0021) and Time (0x0008,0x0031) are not after Acquisition Date (0x0008,0x0022) and Time (0x0008,0x0032) {

 scan Date and Time = Series Date and Time

 start Time = Radiopharmaceutical Start Time (0x0018,0x1072) in Radiopharmaceutical Information Sequence (0x0054,0x0016)

```

1469 // start Date is not explicit ... assume same as Series Date; but consider spanning midnight
1470 decay Time = scan Time – start Time // seconds
1471 // Radionuclide Total Dose is NOT corrected for residual dose in syringe, which is ignored here ...
1472 injected Dose = Radionuclide Total Dose (0x0018,0x1074) in Radiopharmaceutical Information Sequence (0x0054,0x0016) // Bq
1473 decayed Dose = injected Dose * pow (2, -decay Time / half life)
1474 weight = Patient's Weight (0x0010,0x1030) // in kg
1475 SUVbwScaleFactor = (weight * 1000 / decayed Dose)
1476 // Rescale Intercept is required to be 0 for PET, but use it just in case
1477 // Rescale slope may vary per slice (GE), and cannot be assumed to be constant for the entire volume
1478 SUVbw = (stored pixel value in Pixel Data (0x7FE0,0x0010) + Rescale Intercept (0x0028,0x1052))* Rescale Slope (0x0028,0x1053)
1479 * SUVbwScaleFactor // g/ml
1480 }
1481 }
1482 }

```

1483

1484 G.2 Robust version

1485 This appendix contains the consensus opinion on the most robust form of SUV calculation from PET DICOM
 1486 images. Updated as of September 28, 2012. The most up to date version is maintained on the QIBA FDG-
 1487 PET Wiki page (http://qibawiki.rsna.org/index.php?title=Standardized_Uptake_Value_SUV).

1488

```

1489 // SUV cannot be calculated if any of the specified DICOM attributes are missing or empty or zero
1490 if Corrected Image (0x0028,0x0051) contains ATTN and DECAy and Decay Correction (0x0054,0x1102) is START {
1491     if Units (0x0054,0x1001) are BQML {
1492         half life = Radionuclide Half Life (0x0018,0x1075) in Radiopharmaceutical Information Sequence (0x0054,0x0016) // seconds
1493         if Series Date (0x0008,0x0021) and Time (0x0008,0x0031) are not after Acquisition Date (0x0008,0x0022) and Time (0x0008,0x0032) {
1494             scan Date and Time = Series Date and Time
1495         }
1496     else { // may be post-processed series in which Series Date and Time are date of series creation unrelated to acquisition
1497         if GE private scan Date and Time (0x0009,0x100d,"GEMS_PETD_01") present {
1498             scan Date and Time = GE private scan Date and Time (0x0009,0x100d,"GEMS_PETD_01")
1499         }
1500     else {
1501         // else may be Siemens series with altered Series Date and Time
1502         // either check earliest of all images in series (for all bed positions) (wrong for case of PETSyngo 3.x multi-injection)
1503         scan Date and Time = earliest Acquisition Date (0x0008,0x0022) and Time (0x0008,0x0032) in all images of series
1504         or
1505         // back compute from center (average count rate ) of time window for bed position (frame) in series (reliable in all
1506         cases)
1507         // Acquisition Date (0x0008,0x0022) and Time (0x0008,0x0032) are the start of the bed position (frame)
1508         // Frame Reference Time (0x0054,0x1300) is the offset (ms) from the scan Date and Time we want to the average
1509         count rate time
1510         if (Frame Reference Time (0x0054,0x1300) > 0 && Actual Frame Duration (0018,1242) > 0) {
1511             frame duration = Actual Frame Duration (0018,1242) / 1000 // DICOM is in ms; want seconds

```

```

1512         decay constant = ln(2) / half life
1513         decay during frame = decay constant * frame duration
1514         average count rate time within frame = 1/decay constant * ln(decay during frame / (1 - exp(-decay during
1515         frame)))
1516         scan Date and Time = Acquisition Date (0x0008,0x0022) and Time (0x0008,0x0032)
1517         - Frame Reference Time (0x0054,0x1300) /1000 + average count rate time within frame
1518     }
1519 }
1520 }
1521 start Time = Radiopharmaceutical Start Time (0x0018,0x1072) in Radiopharmaceutical Information Sequence (0x0054,0x0016)
1522 // start Date is not explicit ... assume same as Series Date; but consider spanning midnight
1523 decay Time = scan Time - start Time // seconds
1524 // Radionuclide Total Dose is NOT corrected for residual dose in syringe, which is ignored here ...
1525 injected Dose = Radionuclide Total Dose (0x0018,0x1074) in Radiopharmaceutical Information Sequence (0x0054,0x0016) // Bq
1526 decayed Dose = injected Dose * pow (2, -decay Time / half life)
1527 weight = Patient's Weight (0x0010,0x1030) // in kg
1528 SUVbwScaleFactor = (weight * 1000 / decayed Dose)
1529 }
1530 else if Units (0x0054,0x1001) are CNTS {
1531     SUVbwScaleFactor = Philips private scale factor (0x7053,0x1000, " Philips PET Private Group")
1532     // if (0x7053,0x1000) not present, but (0x7053,0x1009) is present, then (0x7053,0x1009) * Rescale Slope
1533     // scales pixels to Bq/ml, and proceed as if Units are BQML
1534 }
1535 else if Units (0x0054,0x1001) are GML {
1536     SUVbwScaleFactor = 1.0 // assumes that GML indicates SUVbw instead of SUVlBm
1537 }
1538 }
1539 // Rescale Intercept is required to be 0 for PET, but use it just in case
1540 // Rescale slope may vary per slice (GE), and cannot be assumed to be constant for the entire volume
1541 SUVbw = (stored pixel value in Pixel Data (0x7FE0,0x0010) + Rescale Intercept (0x0028,0x1052))* Rescale Slope (0x0028,0x1053) * SUVbwScaleFactor // g/ml
1542

```

1543 Appendix H: Consensus formula for computing lean-body-mass normalization 1544 for SUVs

1545 It is important that the PET community is consistent in its computation of SUV_{LBM} , particularly in light of the
1546 recent article by Wahl et al. (1) that proposes using SUV_{LBM} as part of the PERCIST criteria to monitor
1547 treatment response.

1548 Two different formulas for estimating male Lean Body Mass-normalized SUV (SUV_{LBM}) are currently being
1549 used in the PET community. The two variations of the formula for estimating LBM for males are as follows:

$$1550 \quad LBM(\text{male}) = (1.10 \times \text{Weight}) - 128 \times (\text{Weight} / \text{Height})^2 \quad [1]$$

$$1551 \quad LBM(\text{male}) = (1.10 \times \text{Weight}) - 120 \times (\text{Weight} / \text{Height})^2 \quad [2]$$

1552 Where the units for weight are kg, and the units for height are cm. Only one formula is being used for the
1553 calculation of female LBM (2,3):

$$1554 \quad \text{LBM}(\text{female}) = (1.07 \times \text{Weight}) - 148 \times (\text{Weight} / \text{Height})^2 \quad [3]$$

1555 Both versions for estimating male lean body mass (equation 1 from Hallynck et al. (2) and equation 2 from
1556 Morgan and Bray (3)) are based on the original work of James (4), which in turn were derived from a fit of
1557 (weight/height²) to percentage body fat as measured by skin fold measurements. Equation 1 is the version
1558 widely used by the pharmacology community and can be considered the 'correct' version (5-7).

1559 The second version of the equation [2] can be traced back to an article by Morgan and Bray (3), in which
1560 the formula presented by Hallynck et al. (2) is likely misquoted, since the article (2) is referenced elsewhere
1561 in Morgan and Bray (3) without discussion of the difference in formulas where 120 was substituted for 128
1562 as a coefficient. The first incorporation of this formula for computing LBM into SUV calculations was
1563 described in Sugawara et al (8), which cites the Morgan and Bray paper (3). It is this version of the formula
1564 for males, with 120 as the coefficient, that has been sometimes quoted in the PET literature. Sugawara et al
1565 (8) used only data for female patients, which cites the formula for estimating female LBM by Morgan and
1566 Bray (3), which in turn matches the Hallynck et al. (2) paper.

1567 Although the impact of this difference in coefficient is relatively minor for patients with a normal body mass
1568 index ($\text{BMI} (\text{kg}/\text{m}^2) = (\text{weight}/\text{height}^2)$), it does vary as a function of the patient's weight / height ratio. For
1569 example, for a patient of height 180 cm and weight 75 kg (BMI: 23) the value of SUV_{LBM} as computed by the
1570 two formula would differ by less than 1.5 % for regions with an SUV_{LBM} of ~ 1 . However, for a male patient
1571 of the same height but weighing 150 kg (BMI: 46), the difference in SUV_{LBM} for the same regions would be
1572 ~ 7 %.

1573 In comparing equations [1] and [2], it is recommended that equation [1] be used in preference to equation
1574 [2]. However, although the James (2) is the most commonly used data source for equations estimating
1575 LBM, it is well known that it is incorrect for extreme BMI values (5-7). Janmahasatian et. al (5) have
1576 proposed alternative equations for LBM:

$$1577 \quad \text{LBM}(\text{male}) (\text{kg}) = \frac{9270 \times \text{Weight}}{6680 + (216 \times \text{BMI})} \quad [4]$$

$$1578 \quad \text{LBM}(\text{female}) (\text{kg}) = \frac{9270 \times \text{Weight}}{8780 + (244 \times \text{BMI})} \quad [5]$$

1579 These revised formulas for LBM have achieved some acceptance in the pharmacology community (6,7), and
1580 future versions of this Profile may recommend equations [4] and [5] instead of equations [1] and [3]. There
1581 are also continuing efforts to come up with more accurate methods for estimating LBM, through direct
1582 measurement on a per-patient basis using CT (9). However, the different methods providing estimates of
1583 LBM typically have unknown levels of bias and variance. Thus consistency and standardization are likely to
1584 yield larger improvements in study power for clinical trials, when compared to potential improvements in
1585 accuracy of LBM estimation.

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1604
1605