1 **QIBA-UPICT Protocol, Version for Public Comment**
2 **FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy, v1.0** (06.07.2013)
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4
5 Executive Summary
6
7 The FDG-PET/CT subgroup of the Uniform Protocol in Clinical Trial (UPICT) Working Group (now part of
8 QIBA initiative), consisting of imaging physicians and medical physicists worldwide with expertise in
9 early drug development from academic research organizations, government and industry, together with
10 imaging specialists has met regularly through in-person meetings and weekly conference calls over the
11 last 4 years to develop these evidence-based consensus guidelines for the use of FDG-PET/CT in
12 oncology clinical trials. A critical component of the development process was to extract 'verbatim'
13 information from acknowledged key scientific publications on FDG-PET in clinical trials (references) into
14 the appropriate section of the UPICT template; consolidate the information and from the consolidated
15 material, develop consensus statements (where appropriate), identify gaps in scientific knowledge and
16 suggest areas where future investigation may be warranted. The process of conversion from
17 consolidated to consensus was accomplished by the UPICT group in conjunction with input from the
18 SNM FDG-PET Global Harmonization Summit held in Salt Lake City in 2010.
19
20 This UPICT Protocol is intended to guide the performance of <u>whole-body FDG-PET/CT</u> within the context
21 of <u>single- and multi-center clinical trials</u> of <u>oncologic therapies</u> by providing *acceptable (minimum),*
22 *target, and ideal standards for all phases of the imaging examination as defined by the UPICT Template*
23 *V1.0* with the aim of minimizing intra- and inter-subject, intra- and inter-platform, inter-examination,
24 and inter-institutional variability of primary and/or derived data that might be attributable to factors
25 other than the index intervention under investigation. The specific potential utilities for the FDG-PET/CT
26 study(ies) as performed in accordance with this Protocol within any particular clinical trial could be to
27 utilize qualitative, semi-quantitative, and/or quantitative data for <u>single time point assessments (e.g.,</u>
28 <u>diagnosis, staging, eligibility assessment, investigation of predictive and/or prognostic biomarker(s))</u>
29 <u>and/or for multi-time point comparative assessments (e.g., response assessment, investigation of</u>
30 <u>predictive and/or prognostic biomarker(s))</u>. More generally, such standardization of FDG-PET/CT within
31 the conduct of clinical trials should 1) support internal decision-making in drug, biologic, and device
32 development, 2) provide data to support registration and market-label indications, and 3) support the
33 qualification of FDG-PET as an imaging biomarker (including as a surrogate for clinical endpoints) by
34 supporting meta-analyses of multiple clinical trials.
35
36 This document includes specifications for the performance of CT for the purposes of attenuation
37 correction and/or localization, but does not address the performance of diagnostic CT within the context
38 of FDG-PET/CT; although the integration of diagnostic CT in conjunction with FDG-PET/CT for oncology is
39 acknowledged as potentially useful and appropriate. When the integration of diagnostic CT is desired as
40 part of the imaging protocol within the clinical trial, specifications for the CT portion of the imaging
41 protocol may be derived from other UPICT protocol(s).
42
43 While focused primarily on the use of FDG-PET/CT in the conduct of oncologic clinical trials, this protocol
44 also may have utility for guiding the performance of high quality imaging studies in clinical practice.
45
46
47

48   1   Context of the Imaging Protocol within the Clinical Trial
49
50   1.1   Utilities and Endpoints of the Imaging Protocol
51
52   The specific utilities for the FDG-PET/CT imaging include:
53
54   • diagnosis and staging of tumors[1,2 3 4]
55   • prognostic stratification / biomarker[2,5 4]
56   • treatment planning or triage [4]
57   • edge detection of tumors in radiotherapy planning[1]
58   • lesion localization and characterization[1 4 3]
59   • evaluate and quantify tumor response / predictive stratification / biomarker[1,2,5-7 8]
60   • correlation between imaging and tissue biomarkers and/or pathway activity [8]
61
62   1.2.   Timing of Imaging within the Clinical Trial Calendar
63
64   The study protocol should specifically define an acceptable time interval that should
65   separate the performance of FDG-PET/CT image acquisition from both (1) the index
66   intervention and (2) other interventions (e.g. chemotherapy, radiotherapy or prior
67   treatment). If response assessment will be based on serial FDG-PET/CT imaging studies,
68   the time interval between the baseline study and the initiation of treatment should also
69   be specified as well as the time intervals between subsequent FDG-PET studies and
70   cycles of treatment. *Additionally, the study protocol should specifically define an*
71   *acceptable timing variance for performance of FDG-PET/CT around each time point at*
72   *which imaging is specified (i.e., the acceptable window of time during which the imaging*
73   *may be obtained "on schedule."* The timing interval and window are entirely dependent
74   upon 1) the utility for the FDG-PET/CT imaging within the clinical trial, 2) the clinical
75   question that is being investigated, and 3) the specific intervention under investigation.
76   There is some difference of opinion based on the reference source and the specific
77   index intervention. Suggested parameters for timing of FDG-PET/CT within oncologic
78   trials include:
79
80   • *When results of FDG-PET/CT are a study entry criterion, the baseline (eligibility)*
81   *scan(s) ideally should be performed within 21 days before initiation of the*
82   *therapeutic intervention. It should be noted that tumors with low FDG uptake (also*
83   *see Sections 9 and 10) may not be suitable for follow-up studies of treatment*
84   *response with PET.*[9]
85   • *For FDG-avid and evaluable tumors,* the minimum interval between the last dose of
86   chemotherapy *or biologic therapy* and FDG-PET ideally should be 10 days[1], with an
87   acceptable interval of up to 14 days[2,6];
88   • As an alternative if FDG-PET/CT is being used during an ongoing treatment schedule
89   (perhaps as an early predictor of response), the test should be performed at an
90   interval within the treatment schedule that is determined by factors including, but
91   not limited to, the type of treatment, specific cancer diagnosis, specific treatment
92   target, and details of the treatment schedule itself. For example, if the FDG-PET/CT
93   will be performed between cycles that have no "break," the scan might be

94	performed as close to the start of the next cycle as possible.[1] *However, if the FDG-*
95	*PET/CT will be performed within a treatment plan that incorporates periodic*
96	*"breaks" between sets of treatment cycles, the scan might be performed shortly*
97	*after the completion of the preceding cycle rather than after the "break" and*
98	*therefore prior to the next cycle.*
99	• In trials of or including radiation treatment, an interval of up to 4 months may be
100	required[2], although many investigators recommend a minimum delay after radiation
101	therapy of 6-8 weeks or longer before performing the post-treatment FDG-PET
102	study.[6] *Studies evaluating completeness of response should be performed later,*
103	*however investigational studies used to modify therapy or predict outcome may be*
104	*performed during therapy.*
105	• When FDG-PET/CT is used for post-treatment response assessment in lymphoma,
106	imaging should not be performed before at least 3 weeks after chemotherapy and
107	preferably 8 – 12 weeks after completion of radiotherapy per the consensus
108	statement of the Imaging Subcommittee of the IHP in Lymphoma[10].[1] For intra-
109	therapy evaluation please see bullet #3 above.
110	• *An issue that must be addressed in the study-specific clinical trial protocol is the*
111	*specific windows about each time point that would constitute an appropriate*
112	*variance for that specific clinical trial*
113	
114	1.3. Management of Pre-enrollment Imaging
115	
116	The imaging protocol must contain documentation as to how pre-enrollment imaging
117	should be managed; specifically 1) whether imaging obtained prior to enrollment be
118	used as baseline imaging, and 2) if so, under what specific conditions. *It is suggested*
119	*that the specific conditions should take into account technical factors related to the*
120	*imaging platforms (PET and CT) as well as the biology of the disease and the specific*
121	*interventions used in the trial. In general, scans performed as standard clinical care on*
122	*PET/CT scanners that have not been previously qualified for the clinical trial and/or not*
123	*in conformance with the imaging protocol would not be acceptable for the clinical trial.*
124	One reference suggests that PET/CT scanning performed within eight weeks prior to
125	initiation of drug therapy could be used as the baseline study[7]. While another source
126	states that if the pre-enrollment PET/CT was performed on an imaging platform not
127	approved for use in the trial or otherwise does not meet trial requirements, the scan
128	should be repeated, if feasible within the trial budget; however studies that are
129	performed on approved scanners and otherwise conforming to all trial specification will
130	be accepted as baseline studies and will be subjected to the same QA as studies
131	performed after registration. [3] [7]
132	
133	1.4. Management of Protocol Imaging Performed Off-schedule
134	
135	Acceptable: The clinical trial protocol should explicitly state the management of FDG-
136	PET/CT (and all other imaging tests) performed on qualified platforms and in accordance
137	with the specifications of the imaging test (see Sections 2.2, and 3 - 7) but outside of the
138	specified time window(s) of scheduled imaging (see Sections 1.2 and 1.3). The inclusion
139	of data from these off-schedule time points might have significant impact on the data
140	analysis for the clinical trial. Therefore, a priori the study design should state how such

141   off-schedule data points will be managed. Potential options include, but are not limited
142   to, 1) using all of these data in addition to the imaging data obtained on-schedule, 2)
143   using only some of these off-schedule data (e.g., FDG-PET/CT obtained as confirmatory
144   to other non-imaging evidence of disease status) in addition to the imaging obtained on-
145   schedule, and 3) ignoring all imaging data obtained off-schedule. Unless specifically
146   allowed by the clinical trial protocol, off-schedule imaging should not be allowed to
147   substitute for on-schedule imaging. The clinical protocol, the informed consent
148   document, and the clinical trial budget should address the management of off-schedule
149   imaging that was obtained for clinical purposes in temporal proximity to the necessary
150   on-schedule research imaging.

152   The clinical trial protocol should also specifically address how off-schedule scans will be
153   managed in the analysis of the clinical trial overall (e.g., will the sample size be inflated
154   to allow for post hoc exclusion of subjects who drop out secondary to findings noted on
155   off-schedule imaging studies).

157   1.5.   Management of Protocol Imaging Performed Off-specification

159   Criteria should be included in the protocol that define acceptable, target, and ideal FDG-
160   PET/CT imaging specifications and parameters. Imaging studies judged to be sub-
161   optimal, if performed for "standard of care" could be repeated at the discretion of the
162   site if the site deems the scan clinically unacceptable [3]. If the scan is judged
163   unacceptable for research purposes, the study may be repeated as dictated by the
164   protocol and informed consent. The protocol should then state how the cost of such
165   repeated studies should be managed within the trial budget [7]

167   1.6.   Management of Off-protocol Imaging

169   Acceptable: This UPICT protocol only addresses the performance of FDG-PET/CT in the
170   context of a clinical trial. However, since imaging studies other than FDG-PET/CT might
171   influence the conduct of the clinical trial including, but not limited to, the timing and
172   performance of the FDG-PET/CT study(ies), the clinical trial protocol should explicitly
173   state how all imaging tests, whether contemplated and/or obtained as part of the
174   clinical trial or clinical care, should be managed with regard to the conduct of the trial.
175   For the management of FDG-PET/CT studies performed off-schedule and/or outside of
176   specifications please see Sections 1.2 – 1.5.

178   1.7.   Subject Selection Criteria Related to Imaging

180   Acceptable:
181   Fasting Blood Glucose: If quantitative FDG-PET/CT is to be used towards either primary,
182   secondary, or exploratory aims, the study should include specific directions as to the
183   management of subjects with abnormal fasting blood glucose measurements, whether
184   known to be diabetic or not. While there is a paucity of scientific data to suggest the
185   appropriate cutoff of blood glucose measurements that should be excluded from clinical
186   trials that use FDG-PET/CT scan data, it is important to define how such subjects and the
187   data from their imaging studies are managed to ensure comparability of imaging data

4

188 within and among clinical trials. Specifically when quantitative FDG-PET/CT is being
189 used as the study's primary endpoint, the acceptable blood glucose range should be
190 specified, as well as consideration and explanation as to the inclusion or exclusion of
191 subjects with abnormal fasting blood glucose.
192
193 Lesion Conspicuity: It should be noted that tumors with low FDG uptake at baseline
194 (also see Sections 9 and 10) may not be suitable for follow-up studies of treatment
195 response with FDG-PET/CT (e.g., most FDG-avid tumor activity should be greater than
196 1.5 times hepatic mean +2 SD, see Section 10.2.1.1.1). Minimal lesion size and
197 multiplicity may also be necessary as baseline inclusion criteria and if so those
198 thresholds should be stated in the clinical trial protocol.
199
200 1.7.1.   Relative Contraindications and Remediations
201
202 Inability to comply with or tolerate the performance of FDG-PET/CT imaging
203 may be a relative exclusion criterion for subjects in a clinical trial that depends
204 upon FDG-PET/CT for a primary or secondary endpoint. Examples of such
205 relative contraindications include inability to remain motionless for the duration
206 of the scan time or to lie flat for any number of reasons (e.g., severe congestive
207 heart failure). However, such relative exclusion criteria are not unique to FDG-
208 PET/CT. A plasma glucose level above the threshold as defined in Section 4.2.2
209 may necessitate the rescheduling of the FDG-PET/CT test to another day when
210 the plasma glucose level is less than the defined threshold. For this reason,
211 subjects at risk for elevated plasma glucose levels should be scheduled early
212 during the timing interval as specified in Section 1.2 so that if the test must be
213 rescheduled the test date will still fall within the acceptable timing interval (See
214 Section 1.2) so as to avoid a protocol deviation. In addition, it is suggested that
215 for subjects who are known diabetics that three serial morning fasting blood
216 glucose determinations (using home test kits) with values of less than 200 mg/dl
217 (≈11.1 mmol/L) be obtained prior to scheduling the FDG-PET/CT test in order to
218 assure that the test results may be valid within the context of the trial (see
219 Sections 1.7.2, 3 and 4.2.2). Relative contraindications become absolute (i.e.,
220 Imaging Exclusion Criteria) when they cannot be remediated. When the FDG-
221 PET/CT imaging endpoint is a trial endpoint, the subject would then be excluded
222 from the trial.
223
224 1.7.2.   Absolute Contraindications and Alternatives
225
226 The protocol should specifically define a threshold plasma glucose level that
227 should represent an absolute exclusion criterion for participation in any clinical
228 trial that depends on FDG-PET/CT imaging for any primary or a quantitative
229 secondary endpoint if the plasma glucose level cannot be maintained below
230 that threshold level using the diabetic management procedures as described in
231 Section 4.2.2. Threshold plasma glucose levels for inclusion as suggested by
232 referenced standards documents and publicly listed clinical trials include:
233
234 • A plasma glucose level: ≤126 mg/dl (≈7.0 mmol/L)[1]

235   •   Blood glucose levels: ≤150 mg/dl (≈8.3 mmol/L) [7]
236   •   Blood glucose levels: ≤200 mg/dl (≈11.1 mmol/L) [2,3]
237   •   Subjects known to be diabetic who have three serial fasting morning blood
238   glucose levels of >200 mg/dl (despite adequate medical management)
239   prior to the baseline or initial FDG-PET/CT study should be excluded from a
240   clinical trial in which quantitative FDG-PET/CT is used for a primary
241   endpoint. [11] When FDG-PET/CT is used towards secondary and/or
242   exploratory endpoints the trial should specifically state whether subjects
243   with fasting blood glucose levels >200 mg/dl (≈11.1 mmol/L) will be
244   included or excluded; and if included how the data from such subjects will
245   be managed. Furthermore, there are specific clinical trial purposes (e.g.,
246   pD determination) for which fasting blood glucose levels >200 mg/dl (≈11.1
247   mmol/L) are acceptable. Finally, there is a scientific gap in knowledge
248   regarding the relationship between fasting blood glucose level and the
249   effect on quantitative and qualitative FDG-PET/CT. It is recommended that
250   investigators utilize pooled data from studies performed under rigorous
251   protocols (such as the UPICT Oncologic FDG-PET/CT protocol) to investigate
252   this relationship – including data from subjects with fasting blood glucose
253   levels >200 mg/dl (≈11.1 mmol/L). [11]
254
255   Many clinical trials exclude subjects who are pregnant (or suspect they are
256   pregnant) or breastfeeding when FDG-PET/CT is being used as a primary or
257   secondary endpoint. However, such potential subjects may already be excluded
258   on the basis of the index intervention under investigation without regard to the
259   use of FDG-PET/CT.
260
261   Additional suggested exclusion criteria include weight exceeding table limits
262   (300 - 450 lb or 136 – 205 kg for most current PET/CT scanners) and subjects
263   with a history of life-threatening allergic / anaphylactoid reactions to any
264   contrast media if contrast is being used in the study. [3]
265
266   Relative contraindications become absolute (i.e. Imaging Exclusion Criteria)
267   when they can no longer be remediated. When the FDG-PET/CT imaging
268   endpoint is a trial endpoint, the subject would then be excluded from the trial.
269
270
271   1.7.3.   Imaging-specific Inclusion Criteria
272
273   *One source states that for clinical trials with longitudinal FDG-PET*
274   *measurements as a primary endpoint might require a minimum tumor FDG-*
275   *avidity based on the SUV (e.g., tumor SUV of > 1.5 x hepatic mean + 2 SD of*
276   *hepatic mean using a 3 cm ROI to determine the mean) at baseline in order to*
277   *remain on or to be eligible for participation on the study and have subsequent*
278   *follow-up FDG-PET/CT scans [7,12] . There may also be lesion "size" threshold*
279   *(RECIST, WHO, volume) and/or lesion multiplicity (stage) threshold for eligibility*
280   *(See also sections 9 and 10).*
281

282 2 Site Selection, Qualification and Training (See also Section 12 relative to QC)
283
284 2.1 Personnel Qualifications
285
286 Acceptable: Each site shall have technical, physics, radiochemistry, and physician
287 personnel trained in the use of FDG-PET/CT in the conduct of oncologic clinical trials
288 prior to trial activation and subject accrual (or for **Target** Performance prior to site
289 qualification). In lieu of an on-site physicist, a consulting physicist or vendor-qualified
290 service support personnel is acceptable.
291
292 2.1.1 Technical
293
294 Appropriate education, training, and certification of technologists is required to
295 perform PET/CT. Representatives from the Society of Nuclear Medicine
296 Technologist Section (SNMTS) and the American Society of Radiologic
297 Technologists (ASRT) met in 2002 and published specific recommendations [13]
298
299 2.1.2. Physics
300
301 The SNM considers certification and continuing education in the appropriate
302 sub- field(s) to demonstrate that an individual is competent to practice one or
303 more of the subfield(s) of medical physics and to be a qualified medical
304 physicist. The SNM recommends that the individual be certified in the
305 appropriate subfield(s) by the American Board of Radiology (ABR) or the
306 American Board of Science in Nuclear Medicine (ABSNM). [13]
307
308 2.1.3. Physician
309
310 Imaging experts interpreting PET/CT scans should have appropriate training in
311 both PET and CT. A working group of representatives from the American College
312 of Radiology, the Society of Nuclear Medicine (SNM), and the Society of
313 Computed Body Tomography and Magnetic Resonance agree only appropriately
314 trained, qualified physicians should interpret PET/CT.[14] This working group has
315 also recommended the number of continuing medical education credits earned
316 and the number of cases interpreted that would demonstrate adequate
317 training. [13]
318
319 2.1.4. Other (e.g., radiochemistry, radiobiologist, pharmacist, etc.)
320
321 Acceptable: For oncologic FDG-PET/CT the qualifications of the personnel
322 involved in the preparation of the FDG should be appropriate to comply with
323 the FDA part 212 specifications or the international equivalent, as appropriate
324 to the regulatory jurisdiction within which the FDG will be administered.
325
326 2.2 Imaging Equipment
327

328   Each site needs to have contemporary PET/CT system(s).[11] Multiple references suggest
329   that integrated PET/CT scanners are preferable to be used for imaging based on
330   increased accuracy for lesion localization and characterization than that obtained from
331   the results obtained from PET and CT separately and interpreted sided by side or
332   following software based fusion of the PET and CT datasets.[1] PET scanners that utilize
333   NaI detectors are excluded. [6][15]

335   An important aspect of quantitative multi-center PET imaging studies and therefore
336   integral to the qualification of imaging platforms is the cross-calibration of scanner
337   performance across various imaging sites. Several societies, organizations and clinical
338   trials networks, such as the NCI, ACRIN, EORTC, EANM and SNMMI, etc. have developed
339   multi-center clinical trials imaging guidelines and have set up or are setting up PET/CT
340   system validation and site accreditation programs to ensure that data collected using
341   these systems are comparable, i.e. can be exchanged. These site accreditation
342   programs use different phantoms for this purpose, among the performance
343   characteristics that are tested are: (1) the verification of a correct (cross-) calibration of
344   the PET/CT system (against a dose calibrator) [1,2,15,16], (2) scanner normalization and
345   uniformity[15] and (3) the assessment of 2D or 3D SUV recovery coefficients (thereby
346   essentially assessing contrast recovery and/or partial volume effects as a function of
347   sphere size or rod diameter).[1,2,16] Despite the differences in the implementation of
348   scanner validations, all site accreditation programs aim to assess image quality on some
349   or all of these main image characteristics. Future work should focus on further aligning
350   the activities of these societies, either by harmonizing the scanner validation
351   platforms/phantoms and development of a equivalent scanner multi-center QC
352   program. The latter should be feasible considering the good agreement between the
353   societies regarding the image characteristics to be verified. At present there is a strong
354   interest from all groups in establishing a common FDG PET standard.

356   Site qualification by a standardized method (including, but not limited to,
357   documentation of a rigorous quality control program incorporating the use of a uniform
358   phantom to verify scanner normalization and calibration) is the minimum acceptable for
359   clinical trials[15] and use of a standardized multi-compartmental phantom (to additionally
360   evaluate detectability, resolution and contrast recovery) at all sites for this purpose is
361   the target. [11] For a detailed discussion with materials and methods see Section 12.1.1

363   Initial and ongoing periodic QC for CT as used for attenuation correction and localization
364   is included within the scope of this document (see 12.1.1 for detail). However, QC for
365   diagnostic CT performed in conjunction with oncologic FDG-PET/CT is not included
366   within the scope of this document. Documentation for diagnostic CT may be obtained
367   from other UPICT documents.

369   The sites also need to have all the ancillary equipment for conduct of the trial including,
370   but not limited to, appropriately calibrated glucose measuring device, dose calibrators,
371   stadiometer to measure height, and scales to weigh subjects. See Section 12.1.1 for
372   quality control.

373
374

375   2.3   Infrastructure
376
377   Acceptable: All sites participating in the conduct of an oncologic clinical trial utilizing
378   FDG-PET/CT must have oversight by an Institutional Review Board, Ethics Committee, or
379   equivalent group that oversees and is permitted to review and approve experimental
380   studies involving human subjects; a Radiation Safety Committee or equivalent body; and
381   an entity designated to oversee the privacy of personal healthcare information (e.g.,
382   HIPAA Board or equivalent; n.b. in many United States institutions the IRB serves as the
383   Privacy Board for research matters). The participating site must also have the
384   prerequisite infrastructure to perform the specified acquisition, archival, de-
385   identification, and transfer of imaging data as required by the clinical trial protocol in a
386   matter compliant with the protocol and all local, regional, and national regulatory
387   requirements.   Sufficient infrastructure must be demonstrated and documented to
388   perform and report the quality control procedures specified within the clinical trial
389   protocol with expectations enumerated in the clinical trial within the appropriate
390   documentation.
391
392
393   3   Subject Scheduling
394
395   Prior to scheduling potential and/or already accrued subjects for FDG-PET/CT with its inherent
396   (albeit minimal) risks, confirmation of appropriateness for imaging (e.g., history, physical
397   examination, staging, biopsy for diagnosis, etc.) should be performed and documented.
398   Scheduling diabetic subjects may require special attention (please see Section 4.2.2 for
399   additional details) and therefore this should be specifically queried at the time of scheduling. At
400   the time of scheduling, the study team should determine that inclusion of the subject does not
401   violate any of the study-specific inclusion and exclusion criteria pertinent to the FDG-PET/CT
402   study. (SNM GHS) For considerations related to the scheduling of subjects who are known to be
403   diabetic please also see Sections 1.7.2 and 4.2.2.
404
405   • Additional scheduling recommendations for diabetic subjects are suggested by two
406   references.[1,2] These include the following:
407   o For type I diabetes:
408   ▪ Ideal to achieve euglycemia prior to PET study
409   ▪ Schedule study for late morning by eating normal breakfast at 7 am and
410   taking normal amount of insulin; then fast for at least 4 hours till exam
411   o For type II diabetes:
412   ▪ Schedule study for late morning
413   ▪ Comply with at least 4 hour fast till exam
414   ▪ Continue oral medication (hypoglycemic) as usual
415   • One reference suggests the following for diabetic management:
416   o Diabetic subjects should be scanned early in the morning before the first meal, and
417   doses of insulin and/or hypoglycemic medication should be titrated appropriately in
418   consultation with the subject's referring physician. [17]
419

420   Before scheduling an FDG-PET study, diabetic subjects should test their ability to maintain
421   reasonable plasma glucose levels after fasting, while avoiding insulin close to the time that FDG
422   would be administered.
423
424   • For known diabetic subjects with anticipated fasting blood glucose (FBG) measurements for
425   the day of the examination between 126 mg/dl (≈7.0 mmol/L) and 200mg/dl (≈11.1
426   mmol/L), the following scheduling recommendations apply:
427   o Ideal / Target: Type I and Type II diabetic subjects should be scanned early in the
428   morning before the first meal, and doses of insulin and/or hypoglycemic medication
429   should be withheld if glucose levels remain in the acceptable range. This should be
430   established from morning blood glucose levels prior to the study.
431   o Acceptable: Type I and Type II diabetic subjects, who cannot reliably attain
432   acceptable glucose levels early in the morning, should be scheduled for late
433   morning, and should eat a normal breakfast at 7 am and take their normal morning
434   diabetic drugs; then fast for at least 4 hours till exam. This strategy is acceptable
435   only for:
436   ▪ Non-quantitative PET/CT, or
437   ▪ Endpoints that are not for the primary aim, or
438   ▪ Subjects whose baseline study was performed with a FBG <200 mg/dl (≈11.1
439   mmol/L), but who have become uncontrolled hyperglycemics secondary to
440   treatment effect, disease progression, or are being evaluated for
441   exploratory endpoints
442   o In each case, the goal is to achieve a fasting blood glucose with the prescribed range
443   (e.g., ≤126 (≈7.0 mmol/L), ≤150 (≈8.3 mmol/L), or ≤200 mg/dl (≈11.1 mmol/L)
444   dependent on the clinical status of the subject, mechanism of therapy, and the
445   utility of the FDG-PET/CT test in the clinical trial) [11]
446
447   3.1   Timing Relative to Index Intervention Activity
448   Acceptable: Please see Section 1.2
449
450   3.2   Timing Relative to confounding Activities *(to minimize "impact")*
451
452   Activities, tests, and interventions that might increase the chances for false positive
453   and/or false negative FDG-PET/CT studies should be avoided prior to scans. The
454   allowable interval between the potentially confounding event and the imaging test will
455   be dependent on the nature of the confounder. For example, a percutaneous or
456   excisional biopsy of a suspicious mass may cause focally increased FDG-PET activity or
457   might lead to the appearance of a non-malignant mass (e.g., hematoma) on the CT
458   portion of the study. A percutaneous ablation procedure of a known malignant focus
459   may cause focally increased FDG-PET activity and/or an immediate post-ablation
460   increase in the apparent volume of the ablation target lesion. The time of onset and the
461   duration of the increased FDG-PET activity and/or the change in lesion volume might be
462   different for these two different confounding factors.
463
464   If iodinated contrast is to be used for the CT portion of the PET/CT study, conflict with
465   other tests and treatments should be avoided congruous with community standards of
466   care (e.g., thyroid scan).

467
468   3.3   Scheduling Ancillary Testing
469
470   Avoid scheduling tests that might confound the qualitative or quantitative results of the
471   FDG-PET/CT study within the time period prior to the scan. For example, a glucose
472   tolerance test should not be scheduled during the 24 hours prior to the performance of
473   FDG-PET/CT. Similarly, other tests that might involve increasing plasma glucose, insulin,
474   or corticosteroid levels should also be avoided. Exercise cardiac stress testing should be
475   avoided during the twenty-four (24) hours prior to the performance of FDG-PET/CT.
476   Similarly, other tests that might involve vigorous exercise and thereby increase muscle
477   metabolic function should also be avoided.
478
479   4   Subject Preparation
480
481   4.1   Prior to Arrival
482
483   The main purpose of subject preparation is to reduce background tracer uptake in
484   normal tissue (kidneys, bladder, skeletal muscle, myocardium, brown fat) while
485   maintaining and optimizing tracer uptake in the target structures (tumor tissue).[18]
486   Below is a generally applicable protocol to address (1) Dietary, (2) Fluid Intake, and (3)
487   Other activities that may impact the FDG-PET/CT procedure or results.
488
489   (1) Dietary (for the management of previously known or unknown diabetic subjects
490   please see section 4.2.2):
491
492   •   According to two sources, subjects should fast for an absolute minimum (acceptable
493   level) of 4 hours prior to start of FDG-PET study, [17] although the target pre-test fasting
494   period is recommend as a 6 hour minimum [1,2]. This can be achieved as follows:
495   o   Subjects scheduled to undergo the PET study in the morning should not eat
496   after midnight and preferably have a light meal during the evening prior to the
497   PET study.
498   o   Subjects scheduled for an afternoon PET study may have a light breakfast before
499   8 am.
500   o   Medication can be taken as prescribed (see Section 4.2.2 for diabetic
501   management)
502   •   Two sources have stated that a low carbohydrate diet should be followed for 24
503   hours before the study, culminating with fasting for the final six hours. [6 17]
504   •   Enteral nutrition is at least six (6) hours prior to the anticipated time of FDG
505   administration. [11]
506   •   One study has suggested that a high-fat, low-carbohydrate meal is preferred for the
507   last meal prior to commencing the period of fasting; [19 20] Although there are
508   insufficient data to recommend these strategies as routine at this time[11]
509
510   (2) Fluid Intake:
511   Adequate hydration (before and after FDG administration) is important (both to ensure
512   a sufficiently low FDG concentration in urine (less artifacts) and for radiation safety

513   reasons). Whichever hydration strategy is used (how much and when to administer), the
514   protocol should be uniform among sites during a trial.   Specific hydration
515   recommendations include: oral intake of at least 710-1665 ml of water while fasting [6],
516   consumption of two to three 8-12 oz water (710-1065 ml) while fasting[17], and 1 liter
517   during 2 hours prior to FDG administration[1,2].

518

519   If IV contrast is to be injected as part of the study, subjects should be asked to drink
520   more fluid (total of 1 liter) during the two hours prior to the study. The fluid
521   administered should not contain glucose or caffeine. It is acceptable for subjects to
522   receive non-glucose containing IV solutions such as normal or dilute saline. Lactated
523   Ringer's solution is not acceptable and should be discontinued. This hydration strategy
524   should be modulated as clinically appropriate in subjects with certain medical conditions
525   including, but not limited to congestive heart failure, renal failure and fluid retention for
526   example. [11]

527

528   Parenteral nutrition and intravenous fluids containing glucose should be discontinued at
529   least 4 (acceptable) - 6 (target) hours before the PET examination[1 11 17]. The infusion
530   used to administer intravenous pre-procedural hydration must not contain any glucose.

531

532   (3) Other Activities:
533   To minimize uptake of radiotracer into muscle, the subject should avoid strenuous
534   exercise, or cold exposure before the PET exam for a minimum acceptable period of at
535   least 6 hours but preferably for a target time period of 24 hours prior to the PET exam [6]
536   [1,17].

537

538   Other activities that might be avoided are contained in sections 3 and 3.2.

539

540   Performing FDG-PET scanning in the context of recent (within 24 hour) steroid
541   administration may affect the subject's glucose control and hence SUV
542   quantitation. Consequently, if intravenous contrast enhanced CT is required by the
543   protocol in addition to the PET/CT exam, then special consideration is needed for
544   subjects with iodinated contrast allergy who will require steroid premedication for the
545   contrast enhanced CT. In this situation it is preferable that the contrast enhanced CT
546   scan (with appropriate steroid administration) is performed at least one to two days
547   following the 'non-contrast' PET/CT exam. If steroid premedication is given prior to
548   PET/CT exam, then the quantitative assessment obtained from the PET exam may be
549   adversely affected. In cases where premedication is needed for the contrast enhanced
550   CT, the local imaging facility's premedication strategy should be followed and used
551   consistently for the subject across all time points

552

553

554

555   4.2   Upon Arrival

556

557   4.2.1   Confirmation of subject compliance with instructions

558

559 Upon arrival 1) confirmation of subject compliance with pre-procedure instructions and
560 2) the occurrence of potentially confounding events should be documented on the
561 appropriate case report forms. The documentation should include some or all of the
562 following:
563 • timing, character, and amount of the most recent previous oral and/or intravenous
564 intake of fluid and nutrients
565 • timing and dosages of relevant non-prescription and prescription medications taken
566 prior to the PET/CT scan (e.g., the last cycle of chemotherapy or non-cytotoxic
567 pharmacotherapy, administration of growth factors, cytokines, steroids, beta
568 blockers, etc.)
569 • extent of physical activity and most recent exposure to cold temperature for the
570 preceding 24 hours
571 • timing and description of medical procedures performed prior to the PET/CT scan
572 (e.g., radiation therapy, biopsy, surgery)
573 • timing and description of relevant medical tests performed prior to the PET/CT scan
574 (e.g., invasive tests and/or tests that involve the administration of exogenous
575 substances and/or tests that involve vigorous physical activities)
576 • timing of iodinated contrast reaction prophylaxis if appropriate
577 • confirmation that the subject has completed the trial Informed Consent Document.
578
579 The FDG-PET/CT procedure should be explained to the subject and exam-specific
580 consent should be obtained if that is the standard of care for the site or the standard
581 established for the specific clinical trial. There should be documentation of subject-
582 specific risk factors including, but not limited to, previous contrast reactions (if iodinated
583 contrast is to be used) and the presence of implanted electronic devices (e.g.
584 pacemakers, neural stimulators, cochlear implants). [17]
585
586 4.2.2 Ancillary Testing To Be Performed Upon Arrival
587
588 Subject height and body weight must be measured precisely with standardized
589 measurement devices and with the subject in a gown or light clothing and
590 recorded as the minimum acceptable standard.[1,2,6,17] The target standard would
591 add that for serial studies in the same subject, weight should be measured
592 directly prior to each PET study since body weight often changes during the
593 course of the study.[1,11]
594
595 Blood glucose monitoring, measurement and documentation and the
596 appropriate management/disposition of hyperglycemic/ diabetic subjects are
597 addressed by all references and should be included as a minimum acceptable
598 standard of performance.
599
600 • It is important to measure and document subject blood glucose level shortly
601 prior to and target within the 2 hours prior to (ideally within 1 hour for all
602 subjects and target within 1 hour for insulin-requiring diabetic subjects) FDG
603 administration (all, SNM GHS).

604   • Ideal: fasting blood glucose level < 126 mg/dL (≈7.0 mmol/L).in the absence
605   of recent insulin therapy. This may have the effect of excluding diabetic
606   subjects, including those who are undiagnosed at the time of the scan.
607   • Target: fasting blood glucose level < 150 mg/dL (≈8.3 mmol/L).
608   • Acceptable: Subjects with blood glucose measurements between 126 mg/dL
609   (≈7.0 mmol/L) and 200mg/dL (≈11.1 mmol/L) can be imaged.[1 17 2 6], there
610   are varying actions suggested by the different references.
611   • There is no consensus from these references for diabetic or non-
612   diabetic subject management in the glucose range of 126 - 200 mg/dL
613   (≈7.0 - 11.1 mmol/L). The imaging protocol for each individual clinical
614   trial should indicate the glucose cut-off thresholds and the exact
615   management for diabetic and non-diabetic subjects with plasma glucose
616   levels between 126 - 200 mg/dl (≈7.0 - 11.1 mmol/L), especially if the
617   quantitative data from the FDG-PET/CT examination will be used
618   towards a primary or secondary endpoint and/or will be compared in a
619   serial manner over the course of the protocol.
620   • Subjects with blood glucose level > 200 mg/dL (≈11.1 mmol/L) should be
621   rescheduled. Adjustments to diet, medications, and exercise made if
622   necessary, so that the fasting blood glucose concentration can be
623   brought down to the acceptable range at the time of FDG injection, or
624   excluded depending on the subject circumstances and the trial being
625   conducted. (EU, ACRIN)
626
627   • Secondary to recognized problems with administration of insulin (due to
628   alteration of FDG biodistribution and diminished accuracy of SUV
629   determination-NCI), insulin must not be given to reduce pre-FDG-
630   administration glucose levels, unless the interval between administration of
631   insulin and FDG is more that 4 hours.[1,6]
632
633   4.2.3   Preparation for Exam
634
635   In order to avoid artifactual distribution of the FDG, it is critical that subject
636   preparation after arrival and prior to imaging are standardized among all sites
637   and subjects throughout the conduct of the clinical trial. [1,2,5,6,17]
638   • The waiting and preparation rooms should be relaxing and warm (> 75° F or
639   22° C) during the entire uptake period (and for as long as reasonably
640   practicable prior to injection, at least 15 minutes is suggested as
641   acceptable). Blankets should be provided if necessary.[11]
642   ▪ In addition to a warm room, several studies have shown that one option to
643   reduce brown fat uptake is beta blockade such as the administration of
644   propranolol.[21,22] More recent studies have shown that for patients 21 and
645   under, a lower dose of 0.33 mg/kg with a maximum of 20 mg administered
646   one hour before FDG injection has been effective.(add ref) For adult
647   patients with a history of brown fat uptake, 20 mg has also been used.
648   • The subject should remain recumbent or may be comfortably seated;
649   activity and conversation should be kept to an absolute minimum. For

14

650   example, the subject should be asked to refrain from speaking, chewing, or
651   reading during the uptake period.[11] For brain imaging the subject should be
652   in a room that is dimly lit and quiet for FDG administration and subsequent
653   uptake period.[17]

654   •   The subject may use the rest room and should void immediately (5 – 10
655   minutes) prior to the FDG-PET/CT image acquisition phase of the
656   examination.
657   •   Bladder catheterization is not routinely necessary; but if necessary the
658   catheter should be placed prior to injection of FDG. Bladder catheterization
659   may be important for the evaluation of pelvic tumors (e.g., cervix or
660   prostate cancer).
661   •   Following the administration of FDG, the subject should drink 500 ml (or 8 –
662   12 oz, 237-354 ml per ACRIN) of water (or receive by intravenous
663   administration 250 - 500 ml of non-glucose containing fluid). Fluid intake
664   may need to be modified for those subjects on fluid restriction.
665   •   For specific areas of anatomic interest (e.g., tumors located in the lower
666   abdomen, pelvis or kidney) intravenous diuretic agents may be used (e.g.,
667   20 – 40 mg of furosemide given nearly contemporaneously (within 10 – 15
668   minutes) with the administration of FDG). Per the SNM harmonization
669   summit if bladder catheterization is performed IV diuretics should be
670   administered as described herein so as to ensure that the concentration of
671   activity in the renal collecting systems and bladder is relatively dilute.
672   •   Sedation is not routinely required, but is not contraindicated provided that
673   the sedative used does not interfere with the uptake of FDG. If sedation
674   might be used, the subject should be instructed in advance that operation
675   of a motorized vehicle will be prohibited after the FDG-PET/CT test.
676   Sedation may have utility in specific clinical circumstances such as brain or
677   head and neck tumors, claustrophobic subjects, or children.
678   •   The amount of fluid intake and use of all medications (e.g., diuretic,
679   sedative) must be documented on the appropriate case report form.
680   •   Subjects undergoing a CT scan should empty their pockets and remove any
681   clothing containing metal and any metallic jewelry from the body parts to
682   be scanned, changing into a hospital gown if necessary.[17]
683
684
685
686   5   Imaging-related Substance Preparation and Administration
687
688   IV and oral iodinated contrast is not discussed as part of this document as its utility is related to
689   the diagnostic CT examination.
690
691   The FDG must meet USP specifications or meet other current specifications as defined by the
692   FDA or other appropriate regulatory agency for the pertinent regulatory jurisdiction where
693   testing is to be performed. The quality control should be consistent with Section 12.2. If IV
694   and/or oral iodinated contrast is to be used in the study, the density, quantity, and composition
695   (if pertinent) should be specified in the protocol.

696
697   5.1   Substance Description and Purpose
698
699   A brief statement regarding FDG as the imaging agent should be included in the clinical
700   trial protocol where appropriate; for example: FDG is a glucose analogue. Its use in
701   oncology is based on the fact that most types of tumors utilize more glucose than most
702   other types of normal tissue.
703
704   5.2.   Dose Calculation and/or Schedule
705
706   The ^{18}F - FDG dose is usually around 5mCi in Europe and between 10mCi (=370 MBq)[5]
707   and 20 mCi (=740 MBq)[17] in the United States. Further FDG dose refinement and/or
708   dose reduction can be achieved by taking into account: (1) patient weight, for example
709   by applying a dose of 5 – 8 MBq/kg; (2) 2D versus 3D scanning mode; (3) acquisition
710   time per bed position and; (4) percentage bed overlap of subsequent bed positions. The
711   exact dose and the time at which dose is calibrated should be recorded. Residual dose
712   remaining in the tubing, syringe or automated administration system and any dose
713   spilled during injection should be recorded.[1,2,5,17]
714
715   • In the case of using an automated system, the administered FDG activity should be
716   within 3% accuracy (this must be ensured by manufacturer and verified by the user);
717   i.e., the actual administered activity may not deviate more than 3% from that
718   indicated by the reading of that device or dose calibrator following instructions
719   given by the manufacturer of the automated administration system .
720   • Residual activity as determined by the above methods should be used to correct the
721   administered dose for any quantitative results reported.
722
723   Any upper dose limits related to dead time/count rate limitations, as recommended by
724   the tomograph manufacturer should be taken into account. Moreover, (upper) dose
725   limits may apply because of national or local legislation . In case upper dose limits apply,
726   consistent image quality across sites should be accomplished by increasing scanning
727   time. For pediatric studies, other guidelines may apply, such as the EANM pediatric dose
728   card. [23,24]
729
730   5.3.   Timing, Subject Activity Level, and Factors Relevant to Initiation of Image Data
731   Acquisition
732
733   FDG uptake into both tumors and other body tissues is a dynamic process that peaks
734   and plateaus at various time points dependent upon multiple variables.[25,26]   Therefore,
735   it is extremely important that (1) the time interval between FDG administration and the
736   start of emission scan acquisition is consistent and (2) when repeating a scan on the
737   same subject, it is essential to use the same interval after injection for scans performed
738   at different times.
739
740   The suggested consensus time (from all references) between FDG administration and
741   scan acquisition is 60 minutes based on historical use of this test; assuming this is the
742   target window, an acceptable window is often cited as +/- 5 minutes (55-65 minutes).

743   Two references allow the acceptable window to be +/- 10 minutes (50-70 minutes),
744   which is considered the absolute minimum of acceptability.[6,17,27]
745

746   However, on the basis of the SNM harmonization summit while the "target" tracer
747   uptake time should be 60 minutes, there was consensus that the "acceptable" window
748   should be from 55 to 75 minutes so as to ensure that imaging does not begin
749   prematurely so as to allow adequate tumor uptake of FDG and to account for the
750   practicality of work flow which often does not accommodate imaging at exactly 60
751   minutes after FDG injection.[11] The exact time of injection must be recorded; the time of
752   injection initiation should be used as the time to be recorded. Ideally, the injection and
753   flush should be completed within one minute with the rate of injection appropriate to
754   the quality of the vein accessed for FDG administration so as to avoid compromising the
755   integrity of the injection vein*.
756

757   More recent evidence might justify a target interval of greater than 60 minutes for a
758   particular trial. If a target time greater than 60 minutes is chosen for a specific trial, the
759   imaging protocol should justify the specific time chosen, as well as the acceptable
760   window about this target time. Furthermore, as routine clinical practice might not allow
761   the use of pre-recruitment scan for the study, the protocol should include a plan for
762   repeating the baseline scan if necessary to allow appropriate inter-time-point
763   comparisons.[7,11]
764

765

766   When repeating a scan on the same subject, especially in the context of therapy
767   response assessment, it is essential to apply the same time interval with target window
768   of +/- 10 minutes (with an acceptable window of +/- 15 minutes) provided that the scan
769   must not begin prior to 55 minutes after the injection of FDG.[11] If a limited or targeted
770   scan is obtained at follow-up after a whole body scan was performed at baseline, one
771   should consider adjusting the timing of the follow up scan to be congruent with the
772   timing for the same anatomic region as achieved during the baseline study.
773

774   If, for scientific reasons, an alternate time (between dose administration and scan
775   acquisition) is targeted for a specific protocol, then the rationale for this deviation
776   should be stated; inter-time point consistency must still be followed.[6]
777

778   5.4.   Administration Route
779

780   FDG should be administered intravenously through a large bore (≥21 gauge) indwelling
781   catheter placed anatomically remote (e.g., contralateral extremity to site of disease if at
782   all possible) to any site(s) of suspected pathology, preferably in an antecubital vein.
783   Intravenous ports should not be used, unless no other venous access is available. If a
784   port is used additional flush volume should be used. As reproducible and correct
785   administration of FDG is required for quantitation purposes, extravasation or
786   paravenous administration should be avoided.[1,2 6 17] If an infiltration is suspected, the
787   fact should be recorded and if the study is quantitative, i.e. SUVs will be measured, then
788   the infiltration site should be imaged and the approximate amount of infiltration should
789   be calculated. If the infiltration is greater than 5% of the administered dose and the

790 quantitative result from the FDG-PET/CT study is a primary or secondary endpoint, the
791 data point might be censored from review or the subject might not be included in
792 study.[11] The injection site should be documented on the appropriate case report form.[17]
793
794 Presuming that the IV access site is properly functioning, the same route of
795 administration may be used for iodinated contrast as is used for FDG.
796
797 5.5. Rate, Delay and Related Parameters / Apparatus
798
799 Either manual or automated injection systems may be used to administer the FDG.
800
801 • In the case of manual administration, a three-way valve system should be attached
802 to the previously placed intravenous cannula (See Section 5.4) so as to allow at least
803 a 10 cc normal (0.9% NaCl) saline flush following FDG injection. Residual activity
804 within the syringe, and as much of the administration system as is available
805 (including the needle cap) must be measured and the residual dose should be
806 documented (See Section 5.2).[1,17,28]
807 • In the case of an automated administration system, the manufacturer's instructions
808 should be followed. However, the automated system and administration
809 procedures must be ensured by the manufacturer and verified by the user to
810 perform within the characteristics specified in Section 5.2)
811
812 5.6. Required Visualization / Monitoring, if any – **NA**
813
814 5.7. Quality Control
815 See 12.2.
816
817 6 Individual Subject Imaging-related Quality Control
818 See 12.3.
819
820 7 Imaging Procedure
821
822   7.1   Required Characteristics of Resulting Data
823
824   7.1.1 Data Content
825
826 For most Oncology indications, anatomic coverage should include from the skull
827 base (external auditory meatus to the proximal to mid-thigh. This is considered
828 a 'whole body' scan. However, other ranges could be used as appropriate for
829 specific clinical trials. However, the clinical trial should then provide specific
830 instructions with justification. Usually the scanning direction should be
831 caudiocranial to minimize effect from increasing bladder activity during the scan.
832 Scanning direction should be protocol specified. It is critical that for a given
833 subject, scanning direction on baseline scans be duplicated at follow-up time
834 points. [6,11]
835

836	Any potential sources of artifact (e.g., urine collection bags, surgical drainage
837	bags, IV lines and related devices) should be managed or positioned so as to
838	eliminate or minimize degradation of the image and image-related data.
839	
840	Extended anatomic coverage (e.g. brain or extremities) may be performed for
841	tumors that show higher probability of metastasis or direct extension above the
842	skull base or below the mid-thigh. If extended anatomic coverage is performed,
843	this could be performed as a continuation of the skull base to mid-thigh exam or
844	be performed as a two-step protocol. Two-step exam may be preferable,
845	especially in the case of head and neck tumors. If a two-step or an anatomy
846	extended examination is performed, attention to scan timing is critical to
847	provide time relevant comparison with earlier time points (see section 5.3).
848	
849	Either one of the following two different scanning strategies can be used for
850	FDG-PET/CT acquisition. For the first strategy, there is no intent to obtain a
851	diagnostic CT scan at the FDG-PET imaging session; for the second strategy, a
852	diagnostic CT is obtained. Whichever strategy is used, it is recommended that all
853	FDG-PET/CT scans for an individual subject (**target for all subjects**) be
854	performed using the same strategy for all sequential time points. The workflow
855	chosen should be described in the protocol and should be tailored
856	commensurate to the level of expectation of the obtained data (e.g. qualitative
857	or quantitative SUV analysis).
858	
859	Strategy 1: For FDG-PET/CT in which the CT is used for attenuation correction
860	and localization only (no diagnostic CT intent):
861	• CT Scout (topogram), followed by
862	• CT for anatomic localization and attenuation correction, followed by
863	• Emission scan acquisition
864	
865	Strategy 2: For FDG-PET/CT in which a diagnostic CT is performed in conjunction
866	with FDG-PET, one of two strategies shall be used. Either (2a) follow Strategy 1
867	and then, with no or minimal patient motion after the PET Emission scan
868	acquisition, perform an additional IV contrast-enhanced diagnostic CT or (2b)
869	perform a contrast-enhanced diagnostic CT before following the workflow
870	described in Strategy 1.
871	
872	For both strategies, there are several common issues specific to the CT exam
873	that may have an impact on quantitative FDG-PET output, which need attention
874	and protocol specification. These include (1) contrast material administration,
875	(2) respiratory motion compensation instructions and (3) CT scanning technique
876	(kVp, mAs and pitch). Here is a summary of the acceptable level of
877	behavior/procedure for each of these three issues.
878	
879	All these issues should be addressed in the clinical trial protocol, **(with target of**
880	**consistency across all time points for each given subject and ideally with**
881	**consistency across all sites and all subjects (both inter-subject, and intra- and**
882	**inter-facility).** The actual details of imaging for each subject at each time point

19

883 should always be recorded. Any particular clinical trial should NOT allow some
884 sites to implement one strategy and other sites to implement the alternative.
885
886 For strategy 1 where the CT is used for attenuation correction and localization
887 only (no diagnostic CT intent), the following behavior levels apply:
888
889 • Contrast Material
890   The presence of a positive contrast agent (IV or oral), by affecting the CT
891   attenuation map, can result in a small variability of quantitative SUV
892   evaluation. If this was the only consideration, then ideal would be to
893   prohibit CT contrast administration. However, in some clinical situations
894   (dependent upon tumor type, tumor behavior or level of anatomic interest),
895   the benefit of oral CT contrast may outweigh the small errors induced in
896   SUV measurement that may include increased SUV variability.
897   Consequently, ideal and target approaches are grouped as below. Each
898   protocol should specify the desired approach for the given study. Most
899   importantly, for each subject, the same approach should be followed for all
900   imaging time points.
901
902   a. Acceptable
903   No IV contrast; dilute positive oral contrast is acceptable
904
905   a. Target/Ideal
906   No positive contrast agent (IV or oral) for FDG-PET/CT studies with a
907   predominant intent of quantitation at both baseline and follow-up
908
909   No IV contrast agent; negative or dilute positive oral contrast is allowed
910   for FDG-PET/CT studies with primary quantitative intent with additional
911   need for oral contrast to increase confidence of true positive disease
912   detection and/or additional qualitative assessment.
913
914 • Respiratory Motion Compensation
915   Respiratory motion causes SUV errors by two mechanisms: motion blurring
916   and attenuation correction mismatches between CT transmission map and
917   emission data.
918
919   a. Acceptable
920   Verbal instruction to the subject for shallow breathing during CT and
921   PET.
922
923   b. Target
924   Verbal instructions to subject for similar shallow breathing during both
925   the PET and CT acquisitions; respiratory gating if called for in a given
926   protocol specification
927
928   c. Ideal

929	Verbal instructions to subject for similar shallow breathing during both
930	the PET and CT acquisitions; respiratory gating if called for given
931	protocol specification; possibly with advanced methodologies for
932	respiratory synchronization if offered by manufacturer and appropriate
933	to the study. Respiratory gating on PET may require several CT
934	attenuation maps for optimal quantitation.
935	
936	• CT Technique
937	
938	a. Acceptable
939	Recording of actual kVp and exposure (CTDI, DLP) for each subject at
940	each time point. CT dose exposure should be appropriately reduced in
941	smaller patients and children.
942	
943	b. Target
944	Consistency in use of kVp and low exposure (CTDI, DLP) for all time
945	points for a given subject in addition to the Acceptable conditions
946	stated below. CT dose exposure should be appropriately reduced in
947	smaller patients and children.
948	
949	c. Ideal
950	Use of manufacturer recommended kVp and exposure CT Dose Index
951	(CTDI) or Dose Length Product (DLP) settings for low dose exam in
952	addition to the Target and Acceptable conditions stated below. CT dose
953	exposure should be appropriately reduced in smaller patients and
954	children.
955	
956	Regarding CT radiation exposure, rules of "As Low as Reasonably
957	Achievable" (ALARA) should be followed. For a given protocol, the
958	purpose of performing the CT scan (attenuation correction only or
959	attenuation correction and anatomic localization) should be
960	determined. The CT technique (mAs, pitch, collimation, kVp, and slice
961	thickness) used should result in as low as reasonably achievable
962	exposure needed to achieve the intended goal of imaging working with
963	the scanner manufacturer to achieve this objective. The technique used
964	for an imaging session should be repeated for that subject for all
965	subsequent time points assuming it was properly performed on the first
966	study.
967	
968	Strategy 2: For FDG-PET/CT in which a diagnostic CT is performed in
969	conjunction with FDG-PET, since there may be variability introduced
970	into the SUV calculations by the presence of even dilute intravascular
971	iodinated contrast. Consequently, each clinical trial should choose
972	either the Acceptable or the Target/Ideal strategy as described below
973	for use at all sites, for all time points, and for all subjects. Any particular
974	clinical trials should NOT allow some sites to implement one strategy
975	and other sites to implement the alternative.

976		
977		
978	a.	Acceptable
979		Perform a contrast enhanced (IV and dilute or negative oral contrast)
980		diagnostic CT before step 1 of Strategy 1, then with no or minimal
981		patient motion between the diagnostic CT and the PET/CT complete
982		steps 1-3 (including a separate tidal-breathing AC / localization CT) of
983		Strategy 1 ensuring that the diagnostic CT acquisition is performed
984		consistently for a given subject across all time points. The IV contrast
985		would then be in equilibrium phase during the emission scan acquisition
986		and the AC / localization CT scan. (note – since there are no data as to
987		the magnitude of variance in SUV calculation between the IDEAL /
988		Target strategy and the Acceptable strategy, perhaps QIBA should
989		investigate if the Acceptable strategy is indeed truly acceptable for
990		quantitative FDG-PET/CT in the conduct of a clinical trial.)
991		
992	b.	Target / Ideal
993		Follow Strategy 1 (steps 1-3 above) and then with no or minimal patient
994		motion between the diagnostic CT and the PET/CT perform an
995		additional IV contrast-enhanced diagnostic CT after the emission PET
996		scan acquisition. Ensure that the diagnostic CT acquisition is performed
997		consistently for a given subject across all time points. Note that for this
998		case, use negative or dilute positive oral contrast for the non-
999		attenuation CT scan.
1000		In some instances, such as head and neck cancer, a separate dedicated
1001		PET and CT acquisition may be appropriate with the arms in a different
1002		position (down) than would be used for the remainder of the whole
1003		body study (see also Section 7.2.1 "Subject Positioning").
1004		
1005	c.	Unacceptable
1006		Performance of a single diagnostic quality CT study prior to or after the
1007		emission scan for all purposes (i.e., anatomic localization, attenuation
1008		correction, and diagnostic CT information) is considered unacceptable
1009		for clinical trial use.
1010		The major negatives for this strategy are due to misregistration and
1011		incorrect attenuation correction application (especially around the level
1012		of the diaphragm) due to differential diaphragmatic position between
1013		optimal diagnostic CT (typically full breath hold inspiration) and
1014		emission (tidal breathing) FDG-PET scan acquisitions.[29] This is believed
1015		to strongly outweigh the benefit of radiation dose reduction achieved
1016		by eliminating the low-dose CT for anatomic localization / attenuation
1017		correction map. A dose reduction can be achieved in cases in which a
1018		diagnostic IV contrast CT is required, by limiting the CT with contrast to
1019		the most relevant regions of the body, which may be a smaller extent
1020		than the area imaged on PET.
1021		
1022	7.1.2	Data Structure

22

1023
1024   Acceptable / Target: The matrix size, slice thickness, and reconstruction zoom
1025   should yield a target reconstructed voxel size of 3 – 4 mm in all three
1026   dimensions (i.e., not achieved through post-processing), although not
1027   necessarily isotropic. – for QC see section 12.1.1
1028
1029   Ideal : Reconstructed voxel size (i.e., not achieved through post-processing)
1030   should be as small as possible without introducing artifacts and also so as to be
1031   consistent across all trial sites; with current technology 2 – 3 mm in all three
1032   dimensions is achievable.
1033
1034   7.1.3   Data Quality
1035
1036   Image quality (as defined by SUV calibration, SUV Recovery Coefficient, and
1037   SNR) should be such that when applying the same acquisition and
1038   reconstruction protocol as used in subject scanning to the protocol specified
1039   phantom(s) the output should meet the QC standards as stated in Section
1040   12.1.1.
1041
1042   Treatment response assessment and classification (based on criteria) require
1043   several quantitative and qualitative assessments. For details see Sections 9 and
1044   10. In summary, however, the analysis and interpretation steps depend on
1045   several aspects including, but not limited to, assessment of lesion eligibility,
1046   percentage change in activity of specified lesions at each time point relative to
1047   baseline, and the appearance of new lesions that meet eligibility criteria.
1048
1049   For the first two aspects (lesion eligibility and measuring percentage change)
1050   standardization of quantitative image quality, e.g., by means of harmonizing
1051   recovery coefficients measured in specific dedicated phantoms, will result in
1052   more uniform lesion selection and response assessments across institutes.
1053   Consequently, harmonizing quantitative performance of PET/CT systems
1054   coupled with defining some minimum and/or optimum performance metrics
1055   should be a strong consideration in the design of a multicenter trial.
1056
1057   For the assessment of progression related to the appearance of one or more
1058   new lesion(s), it is important to set a minimal threshold for image quality with
1059   respect to lesion detectability. As such, scanners need to have a minimal image
1060   quality performance/lesion detectability/SNR in order to be suitable to be used
1061   in trials. It therefore is conceivable that two different sets of reconstruction
1062   algorithms and settings may be necessary to use in the trial; one for lesion
1063   detection and the other for lesion quantitation.
1064
1065   Both lesion detectability and quantitation must be carefully considered during
1066   study design so as to properly define minimum quality standards to be applied
1067   across all sites and scanner platforms (see Section 12.1.1).
1068
1069   7.2   Imaging Data Acquisition

1070
1071   All QC procedures should be followed and documented prior to the initiation of
1072   acquisition.
1073
1074   For serial scans of the same subject, every attempt should be made to use the same
1075   scanner, and the same scanner model throughout the trial.[27]
1076
1077   However, in some cases a different scanner that has been previously qualified and is the
1078   same platform as the scanner used at baseline can be used for a subject's follow-up scan
1079   in the instance of equipment malfunction.[7]
1080
1081   The ideal level of performance is that all serial scans on a subject should be performed
1082   on the same scanner with the same software version; acceptable / target performance
1083   is that all serial scans on a subject should be performed on equivalent scanners (i.e., the
1084   same model) but also with the same software version). [11]
1085
1086   Additionally, all scan acquisitions for a given subject should include identical
1087   transmission and emission scanning techniques and emission scan duration per bed
1088   position[27] There is no consensus provided on emission scan time range. The number of
1089   bed positions and the acquisition time per bed position will be scanner specific. Typical
1090   parameters are 6 bed positions and an acquisition of 2 – 5 min per bed position. The
1091   minimum acceptable time per bed position should be between 2 and 4 minutes for a 3D
1092   acquisition with 2D acquisitions typically requiring at least 1.5 - 2x longer depending on
1093   the administered FDG dose; although the absolute impact on image quality by scan time
1094   per bed position is currently undefined it is dependent on several pertinent factors
1095   including, but not limited to, administered dose, body weight and habitus, bed overlap,
1096   and specific model / version of the imaging platform used. In general, increased scan
1097   time per bed position will improve the SNR and thus it may be important to increase
1098   scan time when quantitative metrics are used towards a primary endpoint.
1099
1100   As new technology becomes available, it is important that acquisition parameters are
1101   implemented to ensure at least equivalent, if not superior, measurable image quality
1102   and output metrics.
1103
1104   Whole body acquisitions can be in either 2- or 3- dimensional mode with attenuation
1105   correction, but a consistent method should be chosen for all serial scanning of an
1106   individual subject throughout the trial.
1107
1108   A relationship has been described between applied FDG dose, acquisition time per bed
1109   position, percentage bed overlap and scanning mode (2D, 3D) in order to harmonize
1110   image quality (and avoid bias in quantification). [1,2] Using this relationship these
1111   parameters are directly linked, e.g. a higher FDG dose can be offset by shorter
1112   acquisition times per bed position etc.
1113
1114   Acceptable: All serial scans on any individual subject must be performed on the same
1115   previously qualified scanner for each time point if quantitative results are to be used for
1116   primary or secondary trial endpoints. If a site has more than one scanner of the same

1117 model with the same software version and those scanners have both been previously
1118 qualified and both scanners also have been previously demonstrated to be equivalent
1119 by periodic quality assurance testing, the serial scans could be performed on any of
1120 these equivalent scanners. If a subject has already been injected with the FDG dose and
1121 the previously used scanner is not available, a different previously qualified scanner may
1122 be used; but this should be noted on the case report form. This may result in restriction
1123 of data use to qualitative data only. If there has been a software version upgrade and
1124 pre- and post-upgrade quality assurance testing demonstrates equivalency, this is
1125 tantamount to using the same scanner. If there is difference in scanner performance
1126 after the software upgrade, this should be noted on the applicable case report forms.
1127 This may result in restriction of data use to qualitative data only. All serial scans on the
1128 same subject should use identical transmission and emission scanning techniques for all
1129 time points.
1130
1131 While there may be variance based on type of scanner, scanning algorithm, model, and
1132 software version, the following guidelines are meant to assist each site in achieving the
1133 desired data quality as specified in Sections 5.2, 7.1.3, and 12.1.1. Therefore, the
1134 determination of the exact scanning acquisition parameters should be guided by the
1135 following considerations and activities.
1136
1137 For a dose of 5 MBq/kg or higher (370 MBq or more for a 75 kg patient) the minimal
1138 time per bed position using the manufacturers' recommended bed overlap
1139 specifications. The time per bed position should be at least 2 mins for 3D systems
1140 showing ≥50% bed overlap and at least 4 min for 3D systems showing <50%. Time per
1141 bed position may be modified inversely proportional to alteration in injected dose per
1142 body weight within the limits of the scanner performance as determined by the
1143 manufacturer or an appropriately qualified independent standard-setting organization
1144 or peer-reviewed publication.
1145
1146 For 2D systems these times per bed should be at least 1.5 times longer for the same
1147 injected dose based on body weight. Time per bed position may be modified inversely
1148 proportional to alteration in injected dose per body weight within the limits of the
1149 scanner performance as determined by the manufacturer or an appropriately qualified
1150 independent standard-setting organization or peer-reviewed publication.
1151
1152 In general, increased scan time per bed position will improve the SNR and thus it may be
1153 important to increase scan time when quantitative metrics are used towards a primary
1154 endpoint.
1155
1156 Whatever scan acquisition parameters are determined on the basis of the
1157 recommendations (Acceptable, Target, and Ideal) in this document, efforts should be
1158 made to maintain consistency throughout the course of the clinical trial allowing for
1159 optional adjustments based on body weight. Specifically, when scan acquisition
1160 parameters are determined by quality assessment and control procedures performed
1161 for site qualification, those parameters should be implemented for all subjects and all
1162 time points, with subject-specific adjustments only as specified and allowed by the
1163 imaging protocol embedded within the clinical trial documents. This may require

1164 periodic measurement of quality assessment and control parameters and potential
1165 subsequent adjustments to scan acquisition parameters after upgrades and major
1166 service. All such quality assessment and control procedures should be documented and
1167 any resultant adjustments to scan acquisition parameters should also be documented.

1168

1169 Target: Image noise levels are measured using an anthropomorphic phantom (e.g.
1170 NEMA, ACR, SNM, EANM) with a uniform area to assess image 'noise' by means of the
1171 coefficient of variation (COV), which is expressed as a percentage and is defined as COV
1172 = (SD / Mean) x 100, for the voxel values within a specified volume of interest (VOI).

1173

1174 The phantom should be filled such that the activity concentration in the uniform area is
1175 (approximately 0.1 to 0.2 uC/ml), similar to the expected average normal tissue
1176 concentration at the time of imaging in an average weight (70-80 kg) subject in
1177 combination with the intended FDG dosage. The phantom should be scanned using the
1178 minimal time per bed specified in the trial protocol or using the routinely applied time
1179 per bed in the local clinical setting. Moreover, image reconstruction methods and
1180 settings should equal those specified in the trial protocol or equal those routinely
1181 applied in the local clinical setting.

1182

1183 A volume of interest (VOI) should be positioned entirely within the phantom's uniform
1184 area and as much as possible centrally located within the phantom. The VOI should be a
1185 cubic or rectangular volume, with the length of each side as close as possible to, but no
1186 less than 3 cm. A sphere measuring no less than 3 cm. in diameter may also be used as
1187 the VOI on systems that have the capability to accommodate this strategy. The COV of
1188 the voxel values thus determined should be recorded and should also be below 15%.

1189

1190 Ideal: Using the methods described immediately above, the phantom should be
1191 scanned at the proposed time per bed position and reconstructed using the acceptable
1192 reconstruction methods and settings (e.g. minimal and/or harmonized resolution
1193 criteria). The COV within the VOI should be calculated and should yield a COV of 10% or
1194 better.   If the ideal COV is not achieved, the time per bed position could be increased so
1195 as to achieve the desired COV.

1196

1197 7.2.1   Subject Positioning

1198

1199 During PET-CT, subjects should be positioned in the center of the field of view
1200 (FOV), preferably with the subjects' arms to be positioned overhead (to
1201 minimize beam hardening and FOV truncation artifacts). Alternatively, the arms
1202 can be positioned along the side for head and neck imaging (for two-step
1203 procedure – see section 7.1.1). Subjects may be unable to maintain arms above
1204 head for the examination, in which case protocol specific handling needs to be
1205 defined. Arm positioning in a particular subject should be consistent as possible
1206 across all time points.

1207

1208 If PET-CT data are used for radiation planning, the examination should be
1209 carried out in the radiation position using the same dedicated radio-opaque
1210 positioning devices as used in the radiotherapy department. Support devices,

1211   under the back and/or the legs, may be used to enable the subject to
1212   comfortably maintain his/her position throughout the exam.[27]
1213
1214   7.2.2   Instructions to Subject During Acquisition
1215
1216   The diagnostic CT is usually performed in maximal inspiration breath-hold which
1217   could result in image artifacts due to mis-registration of the lung-liver interface
1218   between emission and CT images if the diagnostic CT is being used for
1219   attenuation correction (i.e., there is only one CT scan performed for both
1220   diagnosis and attenuation correction which is not the UPICT recommended
1221   method per section 7.1.1). Therefore, the CT acquisition for attenuation
1222   correction should be done with shallow breathing without regard to the CT
1223   technology used (acceptable / target / ideal).
1224
1225
1226   7.2.4   Model-Specific Parameters
1227   The vendor model-specific and software version-specific parameters that would
1228   reproducibly produce image data meeting the requirements as stated in Section
1229   7.1 while also complying with the radiation dosimetry as specified in Section 12
1230   and 13 is not known at this time. Optimally, the vendors will, over time,
1231   produce such operating instructions for some if not all of their platforms. For
1232   the present, this document specifies certain performance criteria and image
1233   quality specifications that must be met as described elsewhere in this section.
1234
1235
1236   7.3   Imaging Data Reconstruction
1237
1238   - PET emission data must be corrected for geometrical response and detector efficiency
1239   (normalization), system dead time, random coincidences, scatter and attenuation.[1,2,27]
1240   - Data acquired in the 3D mode can be reconstructed directly using a 3D reconstruction
1241   algorithm or re-binned into 2D data and subsequently be reconstructed with a 2D
1242   reconstruction algorithm.
1243   - Iterative reconstruction algorithms are current standard for PET (rather than filtered
1244   back projection), and should be used to reconstruct all PET images.
1245   - Reconstructions should be performed with and without attenuation correction.
1246   -Scanners must be properly normalized and calibrated to ensure uniformity and
1247   accuracy of SUV measurements within the limits of the spatial resolution
1248   - Standardization of reconstruction performance is necessary to obtain comparable
1249   resolution and SUV recoveries across the same subject and inter-subject across sites.
1250   This has not yet been achieved, but is actively being addressed by the major PET
1251   manufacturers.
1252
1253   7.3.1   Model-Specific Parameters
1254
1255   Acceptable: The current acceptable practice is to provide general
1256   reconstruction guidelines and allow individual sites to choose the specific
1257   parameters used for their particular scanner model/version, based in part on

1258   current clinical practice. If this approach is used, the parameters should be
1259   reviewed for appropriateness and consistency and the resulting image quality
1260   should be assessed with phantom imaging performed as part of the PET/CT
1261   scanner qualification.
1262
1263   Target/Ideal: If warranted by the particular trial endpoints (and specifically if an
1264   endpoint is based on absolute quantitative PET measures), acquisition and
1265   reconstruction parameters for each specific scanner model/version should be
1266   tailored to achieve comparable performance (i.e., harmonization across
1267   platforms and sites) in terms of spatial resolution or SUV contrast recovery and
1268   noise.
1269
1270   7.3.2 Archival Requirements for Reconstructed Imaging Data
1271   See 11.4.
1272
1273
1274   7.3.2 Quality Control
1275   See 12.4.
1276
1277 8 Image Post-processing
1278
1279 8.1 Input Data to Be Used
1280
1281   Input data can be either Reconstructed Data, or Post-Processed Image Data as defined
1282   below.
1283
1284   8.1.1. Definitions
1285
1286   Raw Data: This is an ambiguous term as it can refer to scanner raw data (i.e.,
1287   sinograms or list-mode) or image raw data. This term should not be used.
1288   Raw Projection Data: This term refers to the data as acquired by the scanner
1289   before reconstruction (i.e., sinograms or list-mode). When this term is used, the
1290   user should specify the exact type of Raw Projection Data.
1291
1292   Reconstructed Image Data: This is the image data exactly as produced by the
1293   reconstruction process on the PET or PET/CT scanner. i.e., a stack of DICOM
1294   slices/files constituting a PET image volume with no processing other than that
1295   occurring during image reconstruction. This is always a stack of DICOM
1296   slices/files constituting a PET image volume that can be analyzed on one or
1297   more of the following: PET scanner console, PET image display workstation,
1298   PACS system, etc.
1299
1300   Post-Processed Image Data: An image that has been transformed after
1301   reconstruction in some manner, including but not limited to: smoothing,
1302   sharpening, image zoom, rotation/translation, resampling, interpolation, slice
1303   averaging, MIP, etc.. This is typically a stack of DICOM slices/files constituting a

1304   PET image volume that can still be analyzed on one or more of the following:
1305   PET scanner console, PET image display workstation, PACS system, etc.
1306
1307   Secondary Image: This is an ambiguous term as it can refer to either Post-
1308   Processed Image Data or a DICOM secondary capture image (akin to a
1309   photograph). This term should not be used. Instead please see Post-Processed
1310   Image Data above.
1311
1312   8.2   Methods to Be Used
1313
1314   After data collection and image reconstruction as detailed in Section 7, Reconstructed
1315   Image Data (PET images) are generated that meet the image characteristics defined the
1316   by the trial.
1317
1318   For both visualization/interpretation and quantification, no unintended additional image
1319   processing (interpolation, re-binning, reorientation, zooming etc) should be applied to
1320   the originally reconstructed PET data.
1321
1322   8.2.1.   Definitions
1323
1324   Image Processing: Transformations applied to an entire image or a region of an
1325   image. These transformations include, but are not limited to: smoothing,
1326   resolution recovery, image zoom, rotation/translation, re-sampling,
1327   interpolation, slice averaging, de-identification, etc.. The output of this process
1328   is itself an image, often intended for visual or quantitative analysis.
1329
1330   8.2.2.   Processing affecting quantification
1331
1332   Acceptable: Image Post-Processing methods and parameters that are used
1333   should be recorded and applied to all images in a consistent manner following
1334   methods specified in the clinical trial. For example all images might be
1335   smoothed to the same overall resolution and/or reconstructed with the same
1336   voxel size (or in a defined range of voxel sizes). Quantitation should be applied
1337   consistently across all time points and all subjects within a given site.
1338
1339   The originally reconstructed PET data set should always be preserved. In case
1340   processed PET datasets are required, they should be saved as separate
1341   secondary datasets.
1342
1343   Target: No Image Post-Processing is used for quantitation and all analyses are
1344   applied to the Reconstructed Image Data.   Post-Processed Data may be used for
1345   visualization and to facilitate identifying the ROI / VOI. However, the underlying
1346   Reconstructed Image Data should be used for all quantitative purposes. The ROI
1347   / VOI derived from the Post-Processing should be transferred to the
1348   Reconstructed Image Data for quantitation. Quantitation should be applied
1349   consistently across all time points and all subjects within a given site.
1350

29

Ideal: No Image Processing is used for quantitation. Instead the analysis software for ROIs and VOIs always applies the analysis to the Reconstructed Image Data, regardless of the appearance of the image on the display station (which may be Post-processed). This is also a component of the QIBA FDG-PET Profile. The Ideal level of performance is equivalent to the Target level of performance, but in addition to being applied consistently across all time points and all subjects within a given site the consistency is also across all subjects, all time points, and all sites within a given trial.

8.2.3. Processing affecting visualization

Addition image processing may be performed for specific applications or use cases. For visualization most of the image viewing software or platforms will 'automatically' apply some kind of image interpolation (on screen) and image zoom to enhance visual image quality, i.e., almost all viewing and data analysis SW application will perform online image interpolation while displaying PET images on screen. Additional image processing may be applied upon user input, such as zooming, re-binning, reorientation, adjustment of slice thickness or summing of slices and image filtering. When automatic interpolation is applied, it would be desirable that the user has accessibility to replicated zoomed image data at its original matrix size.

Acceptable/Target/Ideal: For visual inspection/interpretation of PET/CT data the by the viewing software or platform default online interpolation and zooming may be used. In addition, so-called maximum intensity projections (MIP) may be generated as they may facilitate localization and detection of lesions. Additional processing, such as zooming, re-binning, reorientation and filtering may be applied upon user request only. User should be able to manipulate color scale settings (window/level and color table). It should always be possible to revert to the default orientation, zoom and binsize (preferably a 'revert to default' button is available).

8.2.4. Image de-identification (See also Section 11.2)

Acceptable: If images are de-identified to remove PHI, no information that affects quantitation should be removed.

Target/Ideal: Only the minimal required PHI should be removed; i.e., all information that is not required to be removed should be retained.

8.3 Required Characteristics of Resulting Data

Acceptable: After visual post-processing is completed, the original data subjected to the post-processing must be retained in its original state. The transformation between the post-processed and original data must be described so as to allow subsequent reproduction by a third party. Any annotations and/or mark-ups performed on the

1397   post-processed dataset must be transformed to a copy of the original dataset (but still
1398   leaving one copy of the original dataset without alteration).
1399
1400   After PHI is removed, all information that affects quantitation should remain intact and
1401   unchanged.
1402
1403   8.4   Platform-specific Instructions
1404
1405   Currently there are no specific instructions that have been compiled for various
1406   platforms. Post-processing should be performed in accordance with vendor
1407   recommendations for the given model and/or specific user manuals.
1408
1409
1410   8.5   Archival Requirements
1411   See 0.
1412
1413   8.6   Quality Control
1414   See 12.5.
1415
1416   9   Image Analysis
1417
1418   For quantitation to be most robustly applied, images must meet the image acquisition
1419   guidelines as stated within the UPICT Protocol, including, but not limited to, similar tracer
1420   uptake times (see Section 5.3), same scanner and reconstruction algorithm (see Section 7) and
1421   similar injected dose (see Section 5.2). Additionally, the same software and workstation model
1422   and version should be used for a given subject across all time points (and for central analysis for
1423   all sites and all subjects and all time points) for the analyses described in this section. Stability
1424   and acceptability guidelines have been articulated in the PERCIST 1.0 guidelines (Wahl et al., J
1425   Nucl Med. 2009 May;50 Suppl 1:122S-50S).
1426
1427   Image analysis and interpretation also presumes that the image datasets to be used are
1428   reconstructed and attenuation corrected as per 7.3 of this UPICT Protocol.
1429
1430   9.1   Input Data to Be Used and Covariates Necessary for Analysis
1431
1432   Image quantitation is typically performed by determining a Standardized Uptake Value
1433   (SUV) in tumor and, ideally, in a reference normal organ. The SUV measure to be
1434   utilized needs to be specified for each protocol and needs to be used consistently at all
1435   sites and across all subjects and all time points for all lesion measurements.
1436
1437   9.1.1 The SUV Statistic
1438
1439   Nomenclature relevant to the SUV statistic shall be defined to address the (1)
1440   subject relevant versus (2) statistical sampling relevant issues. Regardless the
1441   SUV statistic(s) used, it is recommended that the SUV value is recorded at least
1442   to the tenths place (e.g. 4.7) whether used as an absolute value or as a change
1443   metric. As an exploratory metric, it is suggested that some measure (e.g., SD) of

1444   heterogeneity within measured multi-voxel VOIs be expressed along with the
1445   SUV metric (e.g., 4.7 ± 0.2). However, it should be recognized that the utility of
1446   reporting this variance in is unknown at this time and is likely highly dependent
1447   on the standardization of the imaging and reconstruction processes.
1448
1449   9.1.1.1. Subject indices (bw, lbm, bsa, other)
1450
1451   The subject relevant issue is whether to use body weight (bw),lean body mass
1452   (lbm) or body surface area (bsa).
1453   •   SUL = SUVlbm = reference to lean body mass
1454   •   SUV = SUVbw = reference to body weight
1455   •   SUVbsa = reference to body surface area (rarely used)
1456
1457   From the SNM GHS*, there was consensus that SUV normalized to lean body
1458   mass (SUL) is an appealing concept for correcting the radiotracer distribution
1459   based on differences in body habitus in order to obtain absolute values and
1460   changes. It was acknowledged that the requirement of SUL may be limiting at
1461   this time due to either vendor platform software limitations, and limitations in
1462   the formula for characterizing the obese patient population. Target/acceptable
1463   is SUV reporting with inclusion of measurement and reporting of subject height
1464   and weight (see separate section 4.2.2.) and reporting to allow for other
1465   normalizations.
1466
1467   If lean-body-mass (LBM) normalization is used for SUV calculation, the
1468   consensus recommendation is to use the formulae developed by James,[30] which
1469   is:
1470
1471   LBM(male) = (1.10 x Weight) - 128 x (Weight / Height)^2
1472   LBM(female) = (1.07 x Weight) - 148 x (Weight / Height)^2
1473
1474   Where the units for weight are kg, and the units for height are cm.
1475
1476   An alternative form for males is sometimes used, which can be traced back to
1477   an article by Morgan and Bray [31] in which the formula presented by James is
1478   likely misquoted, using 120 instead of 128 as a coefficient. This form was
1479   mentioned, but not used, in an article by Sugawara et al, [32] as a method for LBM
1480   normalization of SUV calculations, with subsequent adoption by some
1481   practitioners. However the pharmacology community does not use the
1482   alternative version. [33]
1483
1484   The above formulae are recognized as inaccurate for patients with extremely
1485   high body mass index (BMI) values (Han 2007), and alternative methods have
1486   been proposed [34] that are for these cases (e.g. BMI > 35 kg/m^2 or men > 300 lbs
1487   and women > 250 lbs). In addition there are continuing efforts to come up with
1488   improved methods for estimating LBM, including direct measurement on a per-
1489   patient basis using CT. [35] However, as noted in the QIBA FDG-PET/CT profile
1490   (Appendix H), the different methods provide estimates of LBM typically have

1491   unknown levels of bias and variance. Thus consistency and standardization are
1492   currently considered as important as potential improvements in accuracy.
1493
1494
1495   9.1.2.   Statistical sampling – including report-out values
1496
1497   9.1.2.1. single voxel
1498   9.1.2.2. multiple voxel
1499
1500   Each of the SUV statistics defined above may be measured by one of
1501   three statistical sampling methods. That is the SUL, SUV, and SUVbsa
1502   may each be measured using a single voxel measure (max) or multi-
1503   voxel measures (mean or peak). There are known issues with the use of
1504   the SUVmax in the presence of low counts, which result in positive
1505   bias,[36] specifically there is an upward bias of the single voxel SUV max at
1506   low count rates. In addition, multiple voxel methods have shown
1507   improved repeatability.[36,37] [12] Despite these issues, the SUVmax has
1508   demonstrated utility as a prognostic and predictive indicator in both
1509   clinical use and research studies, even though it may not be as
1510   reproducible from study to study as the SUV of larger regions. The
1511   following discussion (and the remainder of Sections 9 and 10) will use
1512   SUV as the generic example. However, the discussions are generally
1513   applicable to SUL and SUVbsa (when appropriate and necessary
1514   discussion differentiating among these statistics will be included in
1515   various sections of this document).
1516
1517   SUVmax = single voxel (most FDG-avid voxel in tumor ROI)
1518   SUVmean = mean SUV value for ROI with more than one voxel
1519   SUVpeak = subcategory of SUVmean where volume (SUVpeak-3D) or
1520   area (SUVpeak-2D) is defined specifically. In PERCIST, the SULpeak is a
1521   3D ROI obtained from a 1 cc volume sphere (measuring approximately
1522   1.2 cm in diameter) and defines the most metabolically active 1 cc
1523   volume in a tumor. An approximation of the SUL peak can be the value
1524   obtained by measuring the SUVpeak of an area which is 1.2 cm in
1525   diameter and which usually subtends only a single slice, but which might
1526   also be defined on multiple (most usually three) slices (for further
1527   discussion on the methods to be used for defining the 3D volume and
1528   the 2D area please see Section 9.2) ACRIN defines the 2D SUVpeak as a
1529   circular ROI centered on the SUVmax with a 0.75-1.75 cm diameter (1.0
1530   cm is preferred). Some PET workstations do not have automated
1531   methods to define the SUV peak. There are alternate approaches for
1532   determining the region to be used for the SUVpeak metric. One involves
1533   moving the VOI/ROI throughout the tumor and measuring multiple
1534   SUVpeaks (one for each VOI/ROI) until the highest intratumoral
1535   SUVpeak measurement is located.   Another involves locating the
1536   SUVmax and then centering the SUVpeak VOI/ROI on the SUVmax pixel.
1537   However, this method may not result in measuring the most FDG-avid

1538	portion of the tumor. An automated search mechanism to find the most
1539	FDG-avid SUVpeak has been developed as a computer code in some
1540	systems. It is often, though not always, the case that SUVpeak is
1541	centered on the SUVmax pixel in a tumor. It would be ideal to achieve
1542	consistency in the peak method that is used. However, it is unclear at
1543	this time which method is optimal.
1544	
1545	All references indicate that SUVmax (maximum voxel value or most
1546	FDG-avid voxel) is required for each lesion that is reported as specified
1547	in the study protocol and/or considered clinically relevant.
1548	
1549	Multiple references also indicate that SUVmean of the VOI/ROI
1550	obtained be reported. [1,6,38] The SUVpeak equals the SUVmean only
1551	when the VOI is a sphere with a specified diameter, which is also
1552	indicated as a reportable statistic (EU, ACRIN) and the SUVpeak *is the*
1553	most intense region of the tumor. PERCIST requires the use of SULpeak.
1554	(PERCIST article, Wahl). The SUV mean may be operator and ROI
1555	placement dependent if defined manually. While it has been used in
1556	many studies, it is not required by PERCIST as is SUV max. More
1557	objective methods are preferred for segmenting the tumor to define
1558	SUV mean (see sec 9.2).
1559	
1560	Nearly all PET systems will allow determination and reporting of a single
1561	voxel SUVmax. However, several reproducibility studies have shown
1562	somewhat greater variance for single voxel measurements (SUVmax) on
1563	test/re-test than for somewhat larger regions of interest (SUVmean)
1564	(Ref: AJ de Langen, JNM 2012) . Newer PET scanners offer PET
1565	reconstructions including matrix sizes of 256 x 256 and larger and slice
1566	thicknesses in the 1-2 mm range. These single voxels are much smaller
1567	than the single voxels used in earlier determinations of PET precision
1568	and are more subject to noise related variance. At low count levels
1569	these single voxel measurements are subject to systematic errors
1570	including possible overestimation of SUVmax as compared with truth. In
1571	addition, point spread function/resolution recovery methods have been
1572	implemented which may variably drive single voxel quantification.
1573	While these methods have been used to improve lesion detection, there
1574	are changes in quantitative values that may impact response
1575	assessment. At this time, It is preferred that studies with quantitative
1576	response assessment not use resolution recovery methods due to the
1577	unknown impact and lack of standardization. For this reason, while
1578	single voxel values can be reported and are typically highly correlated
1579	(though higher) with an SUVmean from larger VOI (such as the 1.2 cm
1580	diameter volume recommended in PERCIST, SUVpeak), caution must be
1581	given to modest changes in values in single voxel SUVmax from test to
1582	test, especially in newer PET scanners with short acquisitions, large
1583	matrix sizes, low injected tracer doses and thin slice thicknesses
1584	(resulting in small voxels). Most contemporary PET workstations allow

1585	for determination of a VOI of a fixed volume larger than a single voxel.
1586	At present, variance of the SUV in a larger VOI is not reported, but it
1587	may be explored.
1588	
1589	The optimal method of assessing a biologically relevant tumor response
1590	may vary depending on the tumor type, therapy, and timing of scans vs.
1591	the therapy, and is not yet fully resolved. Furthermore, the underlying
1592	tasks of choosing and prioritizing the optimal statistical metric to use
1593	and the optimal methodology to define lesion VOI/ROI (section 9.2.a) is
1594	challenging given the lack of rigorous comparative studies to date on
1595	which to rely. It is clear that the differing metrics are strongly
1596	correlated with one another. Methods with a single voxel are
1597	statistically more variable than those with slightly larger numbers of
1598	voxels included; meaning that changes in single voxel SUV measure (i.e.,
1599	SUL, SUV, SUVbsa) between studies may have to be larger to be
1600	statistically different. Intuitively, the most accurate representation of a
1601	lesions cellular tumor burden should include a combination of tumor
1602	burden volume and the metabolic activity of that burden as proposed
1603	with the Total Lesion Glycolysis (TLG).[39] For very small tumors, the
1604	SUVpeak values may include some tissue that is non-tumor, lowering
1605	apparent tumor activity. It is also possible tumor volume from PET may
1606	be informative.
1607	Note that by combining strategies of body habitus normalization and
1608	ROI peak averaging using the PERCIST example of SULpeak, this is an
1609	SUV measurement using lbm as patient size normalization and mean
1610	value of specific size (1.2cm diameter sphere) VOI/ROI as statistical
1611	sampling method. Furthermore, SUVpeak can be provided which uses
1612	bw as subject distribution "unit" and mean value of specific size VOI/ROI
1613	as statistical sampling method.
1614	
1615	
1616	
1617	Acceptable: SUVmax (normalized by body weight or lean body mass) -
1618	single voxel (must specify and should be the same across all subjects
1619	and time points); x,y, and z dimensions of a single voxel should be
1620	known and recorded (e.g. within the DICOM header). Input parameters
1621	for calculating SUV should be recorded (section 9.1.ii.b).
1622	
1623	Target: SUVpeak in addition to SUVmax (must specify and should be the
1624	same across all subjects and time points). For discussion of how partial
1625	or fractional pixel / voxel data could and should be managed, see
1626	Section 9.2.2.
1627	
1628	Ideal: In addition to recording the Target metrics, additional metrics for
1629	body habitus correction and/or voxel averaging should be included such
1630	as the SULpeak (SULpeak-3D more desirable than SULpeak-2D) and

1631   SULmax- both in the most FDG-avid region of each particular target
1632   tumor should be captured - size of single pixel should be known (;
1633
1634   Exploratory: it is recommended but not required to supplement Ideal,
1635   Target, and Acceptable performance with an exploratory measures of
1636   Total Lesion Glycolytic (TLG) activity (Larson et al, Clin Positron Imaging.
1637   1999 May;2(3):159-171) and Metabolic Tumor Volume (MTV)
1638
1639   9.1.3.   Covariate inputs (e.g. glucose uptake time, height, weight, FDG-dose)
1640   Please see Section 4.2.2 on obtaining and recording covariate inputs and
1641   Section 10.2.1 regarding glucose correction
1642
1643

1644   9.2   Methods to Be Used
1645   9.2.1   Methodology for defining ROI/VOI
1646
1647   ROI (or VOI) tool to be utilized to define either fixed symmetrical size object or
1648   lesion constraint condition and strategy to define edge detection needs to be
1649   prescribed. Note that the methods for extracting metrics from ROI/VOIs are
1650   described above in section 9.1. To follow is a catalogue of potential strategies,
1651   but the UPICT Protocol does not stipulate any one as preferred. However, the
1652   trial design should stipulate which of the strategies is to be used uniformly
1653   across all subjects and time points during the course of the trial. These
1654   strategies can be summarized as below:
1655
1656   Manual: Requires the intervention of an expert reader to define anatomic
1657   and/or metabolic ROI/VOIs. While this method does not represent ground truth
1658   it may be used as a standard for the apparent tumor boundaries, it is observer
1659   dependent and may have substantial inter- and intra-reader variability. 3D
1660   manual approaches require defining ROIs on multiple planes to generate VOIs.
1661   Likewise, a 3D measurement such as SUVmax requires evaluating multiple 2D
1662   ROIs to identify the plane containing the maximum SUV within the tumor
1663   volume. Shapes can either be irregular polygons or fixed geometric shapes such
1664   as circles, rectangles, etc..
1665
1666   Semi-automated: Requires some user intervention such as defining target
1667   lesions or masking neighboring healthy structures with physiologic FDG-uptake
1668   and uses computer algorithms to define tumor boundaries. A common
1669   approach is to use either a pre-defined or user-defined relative threshold based
1670   on the maximum value (e.g. 70% of SUVmax). Another approach is to use an
1671   absolute threshold (e.g. SUV liver mean + 2SD). More sophisticated approaches
1672   have also been implemented such as using gradient-based segmentation.
1673
1674   Automated: Requires no user intervention and is fully automated. However,
1675   algorithms must be validated against ROI/VOIs defined by expert readers.
1676

1677　　　　　　　　　　　By way of an example, the threshold for definition of an evaluable lesion for
1678　　　　　　　　　　　tumor volume articulated by PERCIST is mean liver SUL in a 3 cm. diameter
1679　　　　　　　　　　　sphere in the right lobe of the liver + 2 SD of liver noise. This threshold is
1680　　　　　　　　　　　defined at baseline so that lesions can be "hot enough" to have a measurable
1681　　　　　　　　　　　decline in F18 activity on subsequent studies with therapy. For relative
1682　　　　　　　　　　　threshold as the constraint definition, SNM GHS notes that tumor ROI's
1683　　　　　　　　　　　reflecting the metabolic volume of the tumors are desirable. For simplicity,
1684　　　　　　　　　　　volumes based on a 70% threshold of the peak tumor SUV should be produced.
1685　　　　　　　　　　　This(ese) are viewed as exploratory reports but recognize the tumor volume
1686　　　　　　　　　　　may provide data beyond that of the peak or max SUV in a tumor.
1687
1688　　　　　9.2.2　　　Geometric issues (e.g. handling partial pixel/voxel)
1689
1690　　　　　　　　　　　The SNM GHS suggested that appropriate use of partial pixel values to secure a
1691　　　　　　　　　　　1.2cm diameter (≈1 cc volume) ROI was appropriate and desirable, since
1692　　　　　　　　　　　standard pixel sizes would not allow selection of a 1 cc volume precisely in most
1693　　　　　　　　　　　cases. [11]
1694
1695　　　　　　　　　　　Acceptable: Any regular 2D area for peak activity measurement (e.g., SUVpeak-
1696　　　　　　　　　　　2D) ROI would be defined as a circular ROI on a single axial slice with a diameter
1697　　　　　　　　　　　of 1.2 cm within the limits of the voxel size (with a minimum diameter of 3
1698　　　　　　　　　　　voxels without using partial voxels). It also acceptable to use a 1.2 cm circular
1699　　　　　　　　　　　ROI with interpolated voxel values.
1700
1701　　　　　　　　　　　Target: Any regular 3D volume for peak activity measurement (e.g., SUVpeak-
1702　　　　　　　　　　　3D) VOI would be defined as an isotropic spherical VOI with a diameter of 1.2
1703　　　　　　　　　　　cm within the limits of the voxel size (with a minimum diameter of 3 voxels
1704　　　　　　　　　　　without using partial voxels).
1705
1706　　　　　　　　　　　Ideal: Any regular 3D volume for peak activity measurement (e.g., SUVpeak-3D)
1707　　　　　　　　　　　VOI would be defined as an isotropic spherical VOI with a diameter of 1.2 cm
1708　　　　　　　　　　　(achieved using interpolated voxel values).
1709
1710　　　　　　　　　　　Exploratory: For irregular VOI (TLG, MTV) no single method is specified as Ideal
1711　　　　　　　　　　　or Target. However, Acceptable performance of this Exploratory metric is
1712　　　　　　　　　　　defined as specifying which method is used and using the same method
1713　　　　　　　　　　　consistently across all time points for a all subjects and sites, and providing the
1714　　　　　　　　　　　data as stated in Section 9.1.
1715
1716　　　9.3　　　　　Required Characteristics of Resulting Data
1717　　　　　9.3.1　　　Tumor assessment – See Sections 9.1, 9.2, and 10.
1718　　　　　9.3.2　　　Internal normalization / Comparator tissue(s)
1719
1720　　　　　The stability of normal tissue SUV (e.g. liver, blood pool) in tests performed at differing
1721　　　　　times in the same patient is considered to be a reasonable and practical indicator of the
1722　　　　　use of similar techniques of performance of PET (see 12.3.2) when quantitative FDG-
1723　　　　　PET/CT is used as a primary or secondary endpoint.[40] Such stability can suggest it

1724   appropriate to use the tumor SUV data for response assessment. Measurement of the
1725   normal liver mean was suggested using a 3 cm diameter spherical VOI that should be
1726   reported at each time point. An alternate method is use of blood pool activity
1727   (especially if the liver is adversely affected by metastatic disease) (as described
1728   separately -reference section 10.2.1.1.1.).
1729
1730   It is possible that a subject's liver SUV may change during the course of the trial
1731   (perhaps as a consequence of disease progression or the therapeutic intervention). The
1732   study protocol should specify how quantitative measurements in subjects with "out of
1733   range" liver (blood pool) SUL measurements will be managed. One potential
1734   mechanism would be to analyze the data both including and excluding subjects with
1735   "out of range" liver (blood pool) SUL measurements.
1736
1737   Acceptable: SUV of the liver and/or blood pool should be reported for all subjects and all
1738   time points. Large deviations in SUVs between the baseline and follow-up time points
1739   should be investigated for technical errors (e.g. incorrect dose or calibration issues).
1740
1741   Target: If the SUV of the liver and/or blood pool are not within 30% of the comparator
1742   (either baseline or immediate previous as dictated by the study protocol) study then the
1743   data receive additional level of review and scrutiny to determine if it should be included
1744   in the study.. PERCIST proposed the following: Normal liver SUL must be within 20%
1745   (and 0.3 SUL mean units) for baseline and follow-up study to be assessable. If liver is
1746   abnormal, blood pool SUL must be within 20% (and 0.3 SUL mean units) for baseline and
1747   follow-up study to be assessable.
1748
1749   Ideal: Unknown
1750   Exploratory: The ratio of tumor SULpeak to liver (blood pool) SULmean could be
1751   reported as an exploratory metric to correct for global variations.
1752
1753   Liver (or blood pool) SULmean and SD are important to report, but not a full substitute
1754   for quality control (see Section 9.6). Liver (or blood pool if liver is replaced with disease)
1755   ROI/VOIs are considered a reasonable method to assess noise, although acceptable
1756   noise level in PET has not yet been determined.
1757
1758   Acceptable: Qualitative visual assessment should be performed to confirm the overall
1759   image quality and noise are acceptable.
1760
1761   Target: SD of liver or blood pool recorded at baseline and all subsequent time points.
1762
1763   Ideal: Normal tissue SD such as liver or blood pool would ideally be used to assess
1764   image noise and define quality control procedures..
1765
1766   9.5   Archival Requirements
1767
1768   Any annotations and/or mark-ups performed during post-processing and/or analysis
1769   must be transformed to a copy of the original dataset (but still leaving one copy of the
1770   original dataset without alteration); also please see 0.

1771
1772
1773   9.6 Quality Control
1774   See 12.6.
1775
1776   9.6.1. Statistical Quality of measurement(s) (e.g. noise)
1777
1778   Quality control of the required inputs (imaging data acquisition and
1779   reconstruction and covariates) has been described elsewhere in this document
1780   and must be satisfied prior to analysis and interpretation. Additional QC metrics
1781   should include:
1782
1783   9.6.1.1. Subjective assessment of image quality. For example, movement or
1784   mis-registration can lead to invalid AC, poor quality / unreliable
1785   quantitative data. Some images may be too poor in quality (e.g.,
1786   inadequate counts per field) to quantify. All necessary data available to
1787   determine if quality is acceptable or not; (e.g., both AC and non-AC
1788   images should be generated routinely and must be available). Specific
1789   sources of degradation in quality that should be assessed include, but
1790   are not limited to:
1791
1792   •   Artifacts secondary to implants in area of concern
1793   •   Patient motion
1794   •   Extraneous activity (e.g., IV tubing or urine) in field.
1795   •   Extravasation of FDG
1796
1797   The output of this subjective QC assessment must include the
1798   judgments to whether the study, despite artifacts, still has utility in
1799   analysis (e.g., quantitative, semi-quantitative, and/or qualitative).
1800
1801   9.6.1.2. Objective Assessment
1802
1803   Ideal: Use of a digital reference object is necessary to assess the
1804   performance characteristics (e.g., accuracy, precision, etc.) of the
1805   software tool, the user interface, and the "user" during the SUV
1806   determination workflow including, but not limited to, the determination
1807   of the most FDG-avid pixel / voxel and the creation of the standardized
1808   ROI / VOI.
1809
1810   Acceptable / Target: Document the workstation and software models
1811   and versions used and ensure that for each subject the same
1812   workstation and software model and version is used across all time
1813   points; should hardware and/or software upgrades occur during the
1814   course of the trial, testing should verify the comparability of
1815   quantitative metrics used in the trial (with comparability defined by the
1816   specifications in the clinical trial documentation) also see Section 12.1.1.

1817   Document that the selected parameters used for analysis were achieved
1818   in actual practice. All workstations and software tools should have gone
1819   through validation by the manufacturer with approval by the
1820   appropriate regulatory body(ies) or the validation should be publically
1821   and transparently available. The trial should include specific QC tasks to
1822   ensure QC of the users with documentation at the time of site
1823   qualification and periodically during the trial.

1824
1825
1826   10.   Image Interpretation

1827
1828   10.2 Methods to Be Used

1829
1830   The points listed serve to take the input data and then:
1831   (a) *discriminate* - qualify as either target or non-target lesion
1832   (b) *compare* - to baseline
1833   (c) *derive*- use combination of target / non-target / presence/absence of new disease to
1834   (d) *describe, stratify, and potentially classify or categorize into discrete classifications-*
1835   into response assessment category (responder, stable, progressive disease)to obtain
1836   Output data (which could also include SUL data of each lesion) from which an
1837   Interpretation (Section 10.3- Required Characteristics of Resulting Data) can be
1838   rendered (with incorporation of QC check).There are overlap issues (to Baseline and On-
1839   study time points), but there are also time-point specific issues which discriminate
1840   Baseline from On-study.

1841
1842   10.2.1. Baseline Time Point Evaluation

1843
1844   10.2.1.1.   Qualification of Target Lesions

1845
1846   While target lesions require the most FDG-avidity, If the lesion cannot be
1847   reliably be measured on PET due to, for example, artifacts from nearby intense
1848   F18 containing structures (like the bladder), then an alternative the next most
1849   FDG-avid measurable lesion can be quantified. Similarly, if the most FDG-avid
1850   lesion is in a region where the quality of quantitation is suspect perhaps due to
1851   motion or attenuation artifacts (e.g. at the diaphragm/liver interface, or in the
1852   neck under the circumstance that the head has moved) then (an) alternative
1853   lesion(s) can be chosen, ideally nearly as intense in activity. The less easily
1854   measurable lesion would be a non-target lesion and would still be assessed for
1855   disappearance in the case of possible PR or clear increase in activity in the case
1856   of PD.   While PERCIST does not require a lesion to be measurable by CT or
1857   anatomic measures when choosing (a) target lesion(s), if two lesions are of
1858   similar FDG avidity (i.e., within 10-15% of one another), then the lesion which is
1859   more easily measurable anatomically might be preferable for analysis. Details
1860   are enumerated below.

1861
1862   10.2.1.1.1.   Minimum metabolic threshold

1863

1864	If using a single lesion paradigm for change assessment, the
1865	most FDG-avid lesion should be selected. However, if this lesion
1866	cannot be reliably measured on PET due to, for example,
1867	artifacts from nearby intense F18 containing structures (like the
1868	bladder), then the next most FDG-avid lesion should be
1869	measured. Similarly, if the candidate target lesion is in a region
1870	where the quality of quantitation is suspect, perhaps due to
1871	motion or attenuation artifacts (e.g. at the diaphragm/liver
1872	interface, or in the neck under the circumstance that the head
1873	has moved), then (an) alternative lesion(s) can be chosen,
1874	ideally nearly as intense in activity.
1875	
1876	If a multiple target lesion paradigm for change assessment is
1877	used, then the aforementioned considerations for target lesion
1878	selection should also be applied. In either case (single or
1879	multiple target lesion selection), the less easily measurable
1880	lesion(s) would be non-target lesion(s) and would still be
1881	assessed for disappearance in the case of possible PR or clear
1882	increase in activity in the case of PD. While PERCIST does not
1883	require a lesion to be measurable by CT or anatomic measures
1884	when choosing (a) target lesion(s), if two lesions are of similar
1885	FDG avidity (i.e., within 10-15% of one another), then the lesion
1886	which is more easily measurable anatomically might be
1887	preferable for analysis. PERCIST proposes 1.5 x liver mean SUL
1888	(3 cm diameter spherical ROI in the right lobe of normal liver) +
1889	2 X SD of liver noise as the minimum target lesion threshold at
1890	baseline. If the liver is not in the field of view or is abnormal to a
1891	degree that normal liver cannot be assessed, then the alternate
1892	comparator is to use a minimum threshold level of 2 times SUL
1893	mean of blood pool in a 3D object defined as a 1-cm diameter
1894	ROI in descending thoracic aorta extended over 2-cms tracking
1895	the long axis of the aorta; or by making this measurement in
1896	multiple 2D 1-cm diameter ROIs extending sequentially over 2-
1897	cm of the descending aorta. If the descending aorta is not
1898	evaluable a VOI of the same volume should be measured from
1899	elsewhere in the thoracic aorta.
1900	
1901	Given the absence of knowledge the general guidance is
1902	suggested below:
1903	
1904	Acceptable: A minimum FDG-avidity is required and should be
1905	specified in the clinical trial protocol. This can be determined by
1906	either a subject-specific threshold as proposed with PERCIST or
1907	as a general cutoff. For a general cutoff, an SUVmax of 4 is
1908	suggested for all target lesions, although in some settings a
1909	lower minimum SUVmax may be acceptable, such as in the lung
1910	or breast.

1911		
1912		
1913		Target/Ideal: The ideal minimum threshold above background
1914		is not known. Components of the ideal threshold could include
1915		both the mean and standard deviation of the SUV of a normal
1916		reference tissue.
1917		
1918		
1919		
1920		
1921	10.2.1.1.2.	Influence of anatomic measurability of lesion size; including
1922		reportability of lesion anatomic size
1923		
1924		In PERCIST 1.0, lesions selected as target lesions on the basis of
1925		meeting minimum metabolic activity thresholds as defined
1926		above (Section 10.2.1.1.1) need not meet minimum size
1927		requirements; although if multiple lesions with similar FDG
1928		activity are present, the most FDG-avid anatomically
1929		measurable lesion(s) are preferable to FDG-avid lesion(s) that
1930		are not anatomically measurable. This may be more valid for
1931		lesions that are markedly FDG-avid than for lesions that show
1932		relatively low-level FDG activity. Therefore by extension for
1933		lesions that have less FDG avidity, it may be reasonable to
1934		include a minimum lesion size threshold (or guideline) in
1935		addition to other minimum criteria for target lesion
1936		qualification. This is especially important for small lesions in
1937		anatomic areas subject to artifact from motion (e.g., lung base
1938		or hepatic dome) or for lesions difficult to separate from
1939		contiguous normal tissues showing metabolic activity (e.g.
1940		urinary bladder). The SNM GHS* suggests that tumors should
1941		typically be over 2 cm in diameter for target lesion inclusion at
1942		baseline, although a lesion meeting the appropriate FDG activity
1943		metrics need not meet this anatomic measurement threshold as
1944		a mandatory minimum. Practically, evaluation of lesion size
1945		(e.g., longest diameter) may be difficult especially if no
1946		dedicated CT was performed either in conjunction with or
1947		within an allowable temporal association with the FDG-PET
1948		scan. This may be due to intrinsic lesion characteristics (e.g.,
1949		infiltrative or CT lesion isodensity to surrounding tissue) or due
1950		to the anatomic location of tumor (e.g., bone marrow site). For
1951		lesions subject to partial volume effect of SUV measurement,
1952		notably due to anatomic location (e.g., peri-diaghragmatic
1953		lesions at either lung base or hepatic dome), a minimum size
1954		requirement may also be reasonable.
1955		
1956		If multiple candidate target lesions of similar FDG intensity are
1957		present, then the chosen target (or targets depending upon

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response assessment paradigm being used) should be the larger of the lesion(s) also taking into account the reproducibility of lesion measurement based on subjective factors described below (Section 10.2.1.1.3).

These issues should be addressed prospectively in the clinical trial protocol and protocol-specific guidelines should document whether or not minimum size criteria for target lesion qualifications are used and if so how such size criteria will be used.

Subjective assessment on reproducibility of measurement (e.g., contiguous structures, conglomerate lesions, hypometabolic lesions, fluid collections, etc.)

Given multiple lesions that qualify on the basis of threshold activity and minimum size, priority should be given to those lesions that are measurable in an accurate and reproducible way. Therefore, lesions with a problematic anatomic location or configuration might not be chosen for measurement if there are other lesions that may be measured with more accuracy and reproducibility. If a lesion is not chosen at baseline secondary to difficulty in accurate measurement, but on subsequent scans the lesion is assessed as dominant or progressive then hindsight review may be appropriate. The analysis and interpretation should explain the interscan discrepancy (see section 10.3) and such a lesion may have to be assessed as a "non-target" lesion.

10.2.1.1   Use of Non-target lesions

Non-target lesions can be considered as disease that is quantifiable or disease that is assessable qualitatively but does not meet requirements for target disease. The presence of non-target lesions should be noted; this can be done either by noting the presence/absence of non-target disease or by identifying sites of non-target disease by organ or anatomic location (e.g., liver or abdominal nodes). Non-target disease should be qualitatively evaluated at each time point. Furthermore, changes in the status of the non-target lesions may be noted if only in a qualitative manner (see section 10.2.1.3). However, if a non-target lesion becomes a target lesion on a later scan, hindsight quantitative review may be appropriate. The analysis and interpretation should explain the interscan discrepancy (see section 10.3). Note that in PERCIST, non-target lesion(s) can become target if the lesion increases in intensity beyond the original target lesion, such that the previously defined non-target lesion is the most FDG-avid lesion on the subsequent scan performed on-study. This would typically be considered disease progression if PERCIST criteria are met.

10.2.1.2   Use of Qualitative lesion assessment

2004   Incorporation of a visual assessment in the analysis and interpretation with
2005   documentation in the CRF may have utility especially in certain oncologic
2006   conditions (e.g., Cheson criteria in lymphoma).
2007
2008   10.2.1.3   Other Observations and reporting methods
2009
2010   The assessment should include commentary related to false positive and false
2011   negative (e.g. disease mimics/variants/QC) activity as not all foci that meet the
2012   preceding criteria may be indicative of disease (e.g., infection, inflammation,
2013   fracture, post-radiation changes). Similarly, there may be artifacts that mimic or
2014   obscure reportable disease (e.g., metallic orthopaedic and/or dental implants).
2015   The trial case report forms should include a mechanism for ensuring the capture
2016   of these data.
2017
2018   10.2.1.4   Covariate & Normalization Strategies
2019
2020   10.2.1.4.1   What to use and what not to use (e.g., glucose correction)
2021
2022   Glucose normalization (both for SUV and SUL): not discussed at
2023   SNMGHS, but discussion needs to be included in UPICT
2024   protocol. Proposal for discussion: Acceptable – collect glucose
2025   data on everyone shortly before radiotracer is injected Target –
2026   use properly specified glucometer and collect glucose data;
2027   Ideal – It is not clear yet if corrections for glucose levels enhance
2028   the ability of PET to predict treatment response. It is suggested
2029   this can be explored prospectively to help determine if the
2030   actual corrections of SUL are appropriate / necessary / possible.
2031   It is possible the "corrections" may add additional errors to
2032   assessments so it is not viewed as appropriate to routinely
2033   apply "corrections" in this setting. [41]
2034
2035   Correction for the timing of image acquisition relative to the
2036   time of FDG injection outside the prescribed window has been
2037   suggested by some references. However, this is not universally
2038   accepted and considered exploratory at this time.
2039
2040   10.2.2   On-study Evaluation
2041
2042   10.2.2.1   Strategy dependent upon the analysis and interpretation paradigm
2043
2044   The workflow for the analysis and interpretation of the non-baseline
2045   imaging examinations (i.e., "on-study" evaluations) is based on the
2046   response assessment paradigm that has been chosen for the specific
2047   clinical trial; and therefore the baseline requirements.
2048

A reviewer's approach to performing target lesion inter-time point FDG-PET assessment depends primarily upon the interpretation strategy, distinguished by two considerations:

- By using either one target lesion or up to five target lesions and
- By using the most FDG-avid lesion(s) for each time point versus comparing the same lesion(s) across time points

The imaging review charter should define the approach prospectively. Currently, the literature is not conclusive on which approach best correlates with clinical outcomes. In order to obtain data consistently across multiple studies that can eventually undergo meta-analysis, it is recommended to perform quantitative analysis on up to five of the most metabolically active lesions, to include **the most** metabolically active lesion at each time point. The details of how to perform this analysis are included in the target lesion section below. The case report form (and subsequent data capture) should be structured in a manner to allow both cross time point same lesion assessment as well as cross time point hottest lesion assessment.

There are 3 basic methods as follows:

1) Single most FDG-avid lesion: The most FDG-avid lesion at baseline that meets previously stated minimum requirements is defined on all time points. Relative change in this single lesion is calculated at each follow-up time point compared to baseline as follows :

$$\frac{SUV(TL_{BL}, FU)-SUV(TL_{BL}, BL)}{SUV(TL_{BL}, FU)}$$

Where

BL = Baseline scan
FU = Follow-Up scan
TL_{BL} = Target Lesion with greatest SUV at baseline

2) Single most FDG-avid lesion at each time-point: The most FDG-avid single lesion meeting minimum requirements is selected at baseline as well as each time point. The follow-up lesion is not necessarily the same lesion as the baseline lesion or other follow-up time points. The relative difference between the baseline target lesion (TL_{BL}) and the follow-up target lesion (TL_{FU}) is calculated as follows where the target lesions are not necessarily the same:

$$\frac{SUV(TL_{FU}, FU)-SUV(TL_{BL}, BL)}{SUV(TL_{BL}, BL)}$$

Where

TL_{FU} = Target Lesion with greatest SUV at follow-up

2095 The workflow for the on-study evaluations is based on determining the
2096 most FDG-avid tumor lesion on each individual study independent of
2097 the baseline or any previous studies and performing the analysis and
2098 interpretation of the most FDG-avid single lesion; thereafter finding the
2099 non-target lesions (lesions other than the most FDG-avid lesion) and
2100 performing the analysis and interpretation on those that are pertinent,
2101 if any; and finally performing the summary statistical interpretation on
2102 the per subject basis (as opposed to the per lesion basis).

2103

2104 3) Summed target lesions: Up to five most FDG-avid lesions are defined
2105 on the baseline examination (with no more than two per organ and all
2106 lesions meeting the defined metabolic threshold). The same target
2107 lesions are defined at each follow-up time point. For each time-point
2108 the sum of all target lesions is calculated. The change in the summed
2109 target lesions is calculated at each follow-up time point relative to
2110 baseline as follows:

2111 $$\frac{SUM (SUV(TL_i, FU) - SUM(SUV(TL_i, BL)}{SUM(SUV(TL_i, BL)}$$

2112

2113

2114 Where TL_i = from 1 to 5 target lesions

2115

2116 The workflow for the on-study evaluations begins with finding the same
2117 lesions that were chosen as the target lesions on the baseline
2118 examination and performing the analysis and interpretation on each of
2119 them; thereafter finding the non-target lesions from the baseline
2120 examination and performing the analysis and interpretation on each of
2121 them; and thereafter finding any new lesions that meet the minimum
2122 threshold requirements and performing the analysis and interpretation
2123 on each of them; and finally performing the summary statistical
2124 interpretation on the per subject basis (as opposed to the per lesion
2125 basis).

2126

2127 The preceding workflow is contrasted with the workflow in the
2128 paradigm that depends on using the five most FDG-avid lesions as
2129 defined on each examination independently from one another (with no
2130 more than two per organ and all lesions meeting the defined minimum
2131 threshold), the workflow for the on-study evaluations begins with
2132 defining the five most FDG-avid lesions as previously defined without
2133 regard to the lesions chosen at baseline or any preceding studies and
2134 performing the analysis and interpretation of those five lesions;
2135 thereafter finding any pertinent non-target lesions (lesions other than
2136 the five most FDG-avid lesions) and performing the analysis and
2137 interpretation on those that are pertinent, if any; and finally performing
2138 the summary statistical interpretation on the per subject basis (as
2139 opposed to the per lesion basis).

2140

2141   The details for response assessment within each of these paradigms are
2142   specified in the subsequent Section 10.3. The definition of "the target
2143   lesion" should be based on the preceding criteria that include SUV
2144   measurement, reproducibility, measurability, motion, etc. The use of
2145   the response assessment paradigms is categorized by performance level
2146   as:
2147
2148   Acceptable –
2149
2150   Option 1: Single target lesion at baseline followed over all subsequent
2151   studies (i.e., generally the most FDG-avid single lesion but defined as
2152   the same lesion from time point to time point).
2153
2154   Option 2: Single target lesion (generally the most FDG-avid single lesion
2155   but potentially a different lesion from time point to time point provided
2156   that the lesions were both present on both studies – i.e., not a new
2157   lesion on the subsequent study(ies)).
2158
2159   Whichever option is chosen as the primary metric for the specific clinical
2160   trial, it is strongly suggested that data derived by both methods would
2161   be archived to allow post-hoc analysis of the clinical trial data.
2162
2163   Target –
2164   Option 1: In addition to the acceptable performance, sum of the most
2165   FDG-avid five target lesions with no more than two per organ
2166   (potentially different lesions from time point to time point) with all
2167   lesions meeting the minimum threshold requirements.
2168
2169   Option 2: Most FDG-avid five target lesions at baseline followed over all
2170   subsequent studies (i.e., defined as the same lesions from time point to
2171   time point). This option may have utility when lesion selection is
2172   performed in the context of RECIST 1.1 anatomic response assessment
2173   criteria.
2174
2175   Whichever option is chosen as the primary metric for the specific clinical
2176   trial, it is strongly suggested that data derived by both methods would
2177   be archived to allow post-hoc analysis of the clinical trial data.
2178
2179   Ideal (exploratory) -
2180   In addition to the acceptable and target (either Option 1 or Option 2)
2181   level of performance one would also determine the TLG activity across
2182   lesions included in the paradigm's dataset meeting the PERCIST
2183   minimum threshold (either only the five target lesions or all lesions, to
2184   be specified in the protocol). The use of TLG activity has not yet been
2185   validated across multiple tumor types in a multi-institutional setting.
2186   Hence, while this level of performance may be categorized as ideal, it is
2187   at this point in time exploratory in nature.

2188
2189   There may be alternative trial designs for specific clinical trial endpoints
2190   (e.g., targeting specific lesions based on local-regional therapies or
2191   correlation with biopsy).
2192
2193   10.2.2.2   Definition and Management of "New Lesions"
2194
2195   A new lesion is defined as either 1) an anatomic area that had no
2196   evidence of disease at baseline by FDG activity but with FDG activity on
2197   the follow up study AND a confirmatory anatomic lesion that is not
2198   related to a false positive cause (e.g., infection, treatment effect) or 2)
2199   an anatomic area that had no evidence of disease at baseline by FDG
2200   activity but with FDG activity on follow up study but without a
2201   confirmatory anatomic lesion that is not related to a false positive cause
2202   (e.g., infection, treatment effect) that is confirmed as persistent at one-
2203   month follow up (by FDG and/or CT and/or biopsy). In the case of the
2204   latter definition, the dating of the new lesion should be the time of first
2205   appearance that met the previously defined minimum FDG-activity
2206   threshold. Some tumors might be anatomically new lesions without
2207   FDG activity. Non-FDG avid lesions should be assessed by RECIST 1.1
2208   criteria. For non-target lesions please see Section 10.2.1.2.
2209
2210   10.3.   Required Characteristics of Resulting Data – Summary Output Data (Response
2211   Assessment)
2212
2213   **Objective response**
2214   Description of response should preserve the intrinsically continuous and
2215   quantitative nature of PET SUV. Determination if a response has occurred at all
2216   (i.e., if the quantitative alteration is greater than expected due to intrinsic
2217   biological variability and measurement error) is critical. It may also be
2218   convenient to further classify or categorize response (e.g., CMR, PMR, SMD,
2219   PD). Quantitative response metrics should be determined with consideration of
2220   multiple factors including, but not limited to, the purpose of the trial, the
2221   precise timing of the PET/CT scans within the imaging and treatment schedule
2222   (including the allowable window around each time point), the tumor type, the
2223   treatment paradigm employed, and the type(s) of decision(s) that will be based
2224   on the response assessment. In particular, the choice of absolute or relative
2225   threshold for determining response category may depend on the context (e.g. %
2226   change may depend on tumor type and treatment). In addition, the utility and
2227   purpose of the response assessment will impact the appropriate threshold. For
2228   example, a larger threshold (e.g. => 30%) may be appropriate for predicting
2229   therapeutic efficacy and/or clinical evaluation of an individual patient, while a
2230   lower threshold (e.g. <=15%) may be appropriate for determining statistically
2231   significant change in a population of patients. Typically a larger change at the
2232   end of effective therapy is expected while smaller changes early after initiation
2233   of treatment may be indicative of response. There are a number of proposed
2234   schemas (EORTC, PERCIST) available to guide the categorization of quantitative

2235   response metrics (as derived by methods described previously in Section 10 of
2236   this document), which are otherwise a continuous variable.
2237
2238   Should the proposed schema include confirmatory imaging studies, the type and
2239   timing of such confirmatory imaging should be specified in the protocol.
2240
2241   The proposed response assessment schema references two comparator imaging
2242   timepoint scans: baseline scan and "best response" scan. The baseline scan
2243   timepoint is defined as the scan timepoint performed prior to initiation of the
2244   focused intervention under investigation. Thus, often the baseline scan is done
2245   prior to any therapy. However, when there has been prior therapy or there is a
2246   change in therapy, sufficient time should elapse following the prior therapy to
2247   ensure that the patient is in a stable state at the time of the baseline scan. The
2248   best response scan timepoint is defined as the scan timepoint at which the
2249   lowest level of disease (or maximal response to the therapeutic intervention) is
2250   identified. The best response timepoint may be the same as the baseline
2251   timepoint if there is no interval (on-study) timepoint that shows improvement.
2252   If progressive disease is determined using comparison to a nadir scan, then a
2253   follow-up confirmatory PET/CT scan is suggested. There is limited literature on
2254   progression and the zuse of comparisons to nadir, partially due to the small
2255   number of imaging time points.
2256
2257   Although RECIST criteria uses comparison to the best response or nadir of tumor
2258   size response, it is not clear that this approach should be used in assessing
2259   response using metabolic imaging. In some cases it may be appropriate, but at
2260   this time it is not clear that the concept of change compared to nadir response
2261   should be used with FDG imaging. The current recommendation is that
2262   comparison should be done compared to the baseline scan, which is obtained
2263   prior to any therapy, or to a baseline scan that is done once any acute response
2264   to prior therapy has resolved.
2265
2266   In some cases, particularly relatively early after start of therapy, FDG uptake in
2267   tumor can increase without reflecting true disease progression. This has been
2268   termed "pseudo-progression" [42-45] This only occurs in some settings, but must
2269   be considered in data interpretation in the design of a new clinical trial.
2270
2271   For assessment of a responder (CMR or PMR), comparison is made to the
2272   baseline timepoint. For assessment of progression (PMD), comparison can be
2273   made to either the baseline timepoint or the nadir timepoint. See section
2274   below on PMD for further discussion. If the nadir timepoint is used as the
2275   comparator for PMD and time to progression is being evaluated as a reportable
2276   value, then time zero should be defined as the time of the baseline timepoint.
2277   This calculation would then capture the time interval between initiation of
2278   focused intervention and time of progression.
2279

2280	One potential categorization schema is presented for consideration in this
2281	document (PERCIST). This schema also does capture the essence of the EORTC
2282	criteria.
2283	
2284	Objective response reporting should be provided based on the following
2285	performance thresholds:
2286	
2287	Acceptable:
2288	
2289	The categorization schema used for a particular clinical trial should be clearly
2290	outlined in the clinical trial protocol prior to activation and data analysis. The
2291	rationale for the categorization schema used should be provided in the clinical
2292	trial design (which may be accomplished by reference to a societal standard or a
2293	publication in the peer-reviewed literature). Whichever categorization schema
2294	is used, the continuous un-categorized quantitative data as derived by methods
2295	described previously in Section 10 of this document should be retained and
2296	made available for post hoc analysis. Furthermore in cases of disease
2297	progression and/or response, data should be retained and made available
2298	regarding the quantitative and qualitative behavior of target, non-target, and
2299	new lesions including both PET and concomitant / follow-up CT-derived
2300	information.
2301	
2302	Target and Ideal: While total lesion glycolysis and tumor burden may provide
2303	additional information, there are insufficient data at this time to suggest the
2304	ideal method for assessing response.
2305	
2306	An example categorization schema follows.
2307	
2308	**PMD (Progressive Metabolic Disease):**
2309	
2310	In a clinical trial that includes only a pre-intervention scan and a post-
2311	intervention scan, PMD is defined as significant increase in tumor uptake
2312	compared to baseline. Note that, particularly when imaging is done relatively
2313	early after treatment, increased uptake may indicate a good response (pseudo-
2314	progression).
2315	
2316	In a clinical trial that includes multiple post-intervention scans (perhaps in trials
2317	with longer term follow up after completion of therapy) it is useful to compare
2318	tumor uptake to "best response" uptake values. In this case, PMD is defined as
2319	a significant increase in tumor uptake compared to "best response". It is
2320	acknowledged that progression from the baseline is a very conservative
2321	approach that may undercall the date of PMD. If the best response timepoint is
2322	prospectively defined as the comparator for PMD assessment in a protocol, then
2323	it is strongly suggested that a confirmatory follow-up time point be performed
2324	at least when progression is defined ONLY in terms of a rise in SUV (and not new
2325	lesions).
2326	

2327   Progressive disease can be assigned based on progression of target lesions,
2328   identification of one or more new lesions or unequivocal progression of non-
2329   target lesions as further defined:
2330
2331   1) Target Lesion Assessment: It is proposed in PERCIST for the single most FDG-
2332   avid lesion at each time point (not necessarily the same lesion) that at least a
2333   30% increase in 18F-FDG uptake, with ≥1.0 increase in SUV unit (or ≥0.8 increase
2334   in tumor SUL peak) be used as the threshold for PMD, given assurance of
2335   technical quality of scan. If more than one target lesion option is chosen, the
2336   sum of all target lesions (up to 5) at baseline and follow-up should be calculated
2337   and then this increase will be calculated as sum change of all qualifying target
2338   lesions identified, not based on any one of the target lesions; and/or
2339
2340   2) Non-target Lesion Assessment: Unequivocal progression of 18F-FDG-avid
2341   non-target lesion(s). There is currently no literature-based threshold defined to
2342   qualify the unequivocal requirement. Intuitively, the level of increase should
2343   probably be larger than that required for target lesion PMD to avoid
2344   overweighting of non-target assessment in PMD categorization. If PMD is based
2345   on non-target lesion assessment ONLY or primarily, then progression should be
2346   verified by confirmatory contemporaneous and/or follow-up imaging (which
2347   should be performed within 1 month) and/or biopsy unless PMD also is clearly
2348   associated with progressive disease by RECIST1.1; and/or
2349
2350   3) New Lesion Assessment: One or more new 18F-FDG-avid lesion(s) that are
2351   typical of cancer and not related to treatment effect, infection or inflammation;
2352   this typification may also require confirmatory studies in some circumstances.
2353   (See Section 10.2.2.2).
2354
2355   PMD should be reported to include percentage change in SUV units, (including,
2356   time after treatment, in weeks) and whether new lesion(s) are present/absent
2357   and their number. For example, rather than merely reporting PMD, the
2358   categorization should be specified to state that the SUV has increased by some
2359   value (e.g., +35%) as measured at some specific time point (e.g., week four) and
2360   the number if new lesions present at this time point if any (e.g., "in addition
2361   there are five new lesions). Because SUV is continuous variable, dividing
2362   response criteria into limited number of somewhat arbitrary response
2363   categories may result in loss of data. For this reason, PERCIST preserves
2364   percentage changes in SUV units in each reported category. Because rapidity
2365   with which the scan normalizes may be important (faster appears to be better),
2366   PERCIST asks for time from start of treatment as part of reporting. For example,
2367   a CMR with a change in SUV of -90%, at one week, is probably superior to a CMR
2368   with a change in SUV of -90%, at ten weeks; especially if the latter subject was
2369   previously evaluated as SMD with a percentage change of SUV of -20% at the
2370   one-week post treatment evaluation.
2371

2372	As analysis of TLG volume is being proposed as an exploratory endpoint, this
2373	metric should not be used in isolation to determine PMD at this time. However,
2374	the data should be made available as previously stated (see Section 10.2.2.1).
2375	
2376	**CMR:**
2377	1. Complete resolution of 18F-FDG uptake within measurable target lesion(s) so
2378	that the uptake is less than or indistinguishable from blood-pool levels (When
2379	liver activity is available for evaluation, this implies that the lesion uptake would
2380	be less than mean liver activity).
2381	2. Disappearance of all other (i.e., non-target lesions) lesions to background
2382	blood pool levels.
2383	3. Percentage change in FDG uptake should be recorded from the measurable
2384	region, as well as the time in weeks after treatment was begun. For example, in
2385	addition to reporting the CMR the report should also include the percentage
2386	change in SUV (e.g., -90%) and the time at which the evaluation is being made
2387	(e.g., four weeks). If there is both anatomic and functional complete response,
2388	there is no anatomic lesion to target for SUV measurement. Hence, a change in
2389	the SUV of the lesion is not possible to measure, especially if there is only one
2390	target lesion. Recording the background activity at the site of the previous
2391	lesion (provided there is no obvious artifact in the anatomic region) or the liver
2392	or blood background could be explored.
2393	4. No new 18F-FDG–avid lesions in pattern typical of cancer.
2394	5. If progression is noted by RECIST (anatomic measurement), but not by
2395	metabolic activity, verify with follow-up imaging.
2396	6. There may be "faint" activity in certain lesions that is greater than immediate
2397	background but that is less than or indistinguishable from blood-pool levels.
2398	The presence of such lesions and the absolute SUV measurement should be
2399	noted; however, their presence should not dissuade classification as CMR
2400	provided those lesions meet the aforementioned criteria.
2401	
2402	**PMR**:
2403	1) Reduction of minimum of 30% in target measurable tumor 18F-FDG uptake.
2404	2) Absolute drop in SUV must be at least 1.0 (the absolute drop in SUL must be
2405	at least 0.8 SUL units), as well. Measurement is commonly in same lesion(s) as
2406	baseline but can be (an)other lesion(s) if the lesion(s) was previously present
2407	and is currently the most active lesion after treatment (see Section 10.2.2.1).
2408	ROI/VOI does not have to be in precisely same area as the baseline scan, though
2409	typically it is.
2410	3) No increase equal to or greater than 30% in FDG uptake (must be at least 1.0
2411	SUV or 0.8 SUL units, as well) or size of target lesion(s) (i.e., no PD by RECIST 1.1
2412	or IWC) (if PD anatomically, must verify with follow-up). Reduction in extent of
2413	tumor 18F-FDG uptake is not requirement for PMR. Percentage change in SUL
2414	should be recorded, as well as the time in weeks after treatment was begun.
2415	For example the categorization as PMR should be further qualified by including
2416	the percentage decrease in SUV units (e.g., -40%) and the number of weeks
2417	after treatment initiation at which the observation is made (e.g., three weeks).
2418	4) No new lesions.

52

2419
2420 **SMD:**
2421 1)   Not CMR, PMR, or PMD.
2422 2)   SUVpeak in metabolic target lesion(s) should be recorded, change in
2423 SUVpeak of the target relative to the baseline , as well as the time from start of
2424 most recent therapy, in weeks. As has previously been suggested the
2425 categorization as SMD should be accompanied by the percentage change in SUV
2426 units (e.g., -15%) and the number of weeks after treatment initiation at which
2427 the measurement is made (e.g., seven weeks).
2428
2429 **Overall Best Response in a given subject (summation of time point**
2430 **determinations using the categorization schema above including target and**
2431 **non-target lesions; new lesion; etc.):**
2432 1. Best time-point response (e,g., CMR, PMR, SMD, PMD) that is noted during
2433 the time period defined as the time from treatment start to 1) CMR, or 2)
2434 disease progression / recurrence or 3) termination of the subject from the
2435 clinical trial.
2436 **Duration of Best Response in a given subject (summation of time point**
2437 **determinations using the categorization schema above including target and**
2438 **non-target lesions; new lesions; etc.):**
2439 **1.** Measured from the date Best Subject Response criteria are first met to date
2440 disease progression / recurrent disease is first noted or the date that the subject
2441 has completed the trial follow-up period (with some indication that the Best
2442 Response category (e.g., CMR, PMR/SMD) may still be ongoing). Note, CMR by
2443 RECIST 1.1 is not required. However, the criteria for CMR for the specific trial
2444 should be specified in the clinical trial documentation. Progression from PMR to
2445 PMD is suggested (i.e., the transition from PMR to SMD may be insufficient) to
2446 end the "Duration of Best Subject Response" for subjects with PMR as the
2447 transition from PMR to SMD may not be clinically relevant and/or statistically
2448 robust.
2449 **2. Duration of Overall Response in a given subject**: from date CMR and/or PMR
2450 criteria are first met (whichever status came first); to date PMD is first noted or
2451 the date that the subject has completed the trial follow-up period (with some
2452 indication that the best overall response category may still be ongoing).
2453 Progression from PMR to PMD is suggested (i.e., the transition from PMR to
2454 SMD may be insufficient) to end the "Duration of Best Subject Response" for
2455 subjects with PMR as the transition from PMR to SMD may not be clinically
2456 relevant and/or statistically robust.
2457 **3. Time to Progression:** from date of treatment start to date PMD is first noted
2458 by PET/CT.
2459 **4. Duration of SMD**: In subjects that do not achieve an observed CMR or PMR,
2460 the Duration of SMD is defined as the time from initiation of therapy to the time
2461 of PMD.
2462 **5. Progression Free Survival**: defined as the time from the initiation of therapy
2463 to the time of PMD or death. Progression Free Cancer-specific Survival is
2464 measured from the time of therapy initiation to the time of PMD or death due
2465 to cancer.

53

2466   Note: If PMD must be confirmed on a follow up scan for any of these measures
2467   of duration, PMD would be timed to the date when PMD was FIRST noted by
2468   PET/CT criteria, not the date of confirmation.
2469
2470
2471
2472   10.3.   Reader Training
2473   Reader training should be specified in the clinical trial documentation for the
2474   specific clinical trial or reference may be made to generic reader training
2475   documents when appropriate.
2476
2477
2478 11. Archival and Distribution of Data
2479
2480   11.1 Central Management of Imaging Data
2481
2482   Two sources (EANM, ACRIN) mention use of DICOM formatted data. One source (EANM)
2483   indicates that data should be stored in DICOM format Part 10: Media Storage and File Format
2484   for Media Interchange. DICOM format should meet the Conformance Statement written by
2485   manufacturer of the PET/CT system (EU).
2486
2487   Acceptable: Data should be stored and transmitted in compliance with pertinent DICOM
2488   standards (which for CD and DVD storage and transmission is DICOM format Part 10: Media
2489   Storage and File Format for Media Interchange). When data are transmitted using ftp or other
2490   Internet-based systems, the archival and transfer method used must allow transmission of all
2491   data necessary for qualitative and quantitative assessments without alteration of the data from
2492   the acquisition state. All data transfer should be secure and HIPAA-compliant. When a central
2493   archival and review facility is used in a clinical trial, the individual trial design should explicitly
2494   state what types of data (e.g., raw data, reconstructed data, post-processed data, etc.) are to be
2495   transmitted to the central facility in addition to being archived at the participating site.
2496
2497   11.2 De-identification / Anonymization Schema(s) to Be Used
2498
2499   Two sources (EU, ACRIN) indicate that DICOM image data need to be de-identified/anonymized.
2500   The header of the DICOM formatted images may contain information that identifies the patient
2501   and these tags should be scrubbed or these tags may be replaced by information about study ID,
2502   randomization or case IDs as indicated by the image core lab. De-identification must be
2503   performed prior to transmittal of the data from the local site to the image core lab. Both sources
2504   indicate use of (s)FTP as means of transmittal. One source (EU) indicate storing de-identified
2505   DICOM formatted images on media (CD, DVD) and sending it by regular mail.
2506
2507   Acceptable: Data de-identification / anonymization is performed on a third-party or PACS
2508   workstation in a manner that is HIPAA-compliant and compliant with the directions of the
2509   clinical trial. However, all data necessary to perform qualitative and quantitative assessments
2510   must remain available and unaltered. Hence, removal of PHI should not affect the underlying
2511   imaging data. Specifically all data necessary for reconstruction, post-processing, interpretation,
2512   and analysis should not be affected by the removal of PHI during the de-identification process.

2513   And any algorithms used for de-identification should not remove prerequisite imaging data
2514   when PHI is removed. There needs to be a mechanism to perform quality control to ensure that
2515   the de-identified / anonymized imaging data correctly correspond to a specific subject ID.
2516
2517   Target / Ideal: In addition to the acceptable performance level, data de-identification /
2518   anonymization is performed on the image acquisition platform in a manner that is HIPAA-
2519   compliant and compliant with the directions of the clinical trial. There is no admixture of PHI
2520   and imaging data within the same DICOM fields. There should be no PHI in private fields (i.e.,
2521   DICOM tags). There should be no imaging data necessary for qualitative or quantitative
2522   assessments in private fields (i.e., DICOM tags).
2523
2524   11.3 Primary Source Imaging Data
2525
2526   Acceptable: All FDG-PET/CT studies used within the context of the clinical trial should be
2527   archived as primary source data and should be subjected to the quality assurance mechanism
2528   for imaging obtained within the context of the clinical trial. Archival of raw projection data is
2529   optional. If raw projection data are of interest for a particular trial, the trial protocol should
2530   state explicitly the standards for the format and storage (including the duration of storage) of
2531   such data. All archives and archival processes should be secure and should include disaster
2532   recovery.
2533
2534   Target / Ideal: In addition to the acceptable level of performance, archival of raw projection
2535   data is also mandated in a secure and redundant manner for a duration the same as for all other
2536   archived trial data.
2537
2538   11.4 Reconstructed Imaging Data
2539
2540   Acceptable: Archival of reconstructed image data either by DICOM format Part 10-compatible
2541   media storage or local PACS / server-based storage by both the sites and the central review
2542   entity (if any). Archival of raw projection data is optional. If raw projection data are of interest
2543   for a particular trial, the trial protocol should state explicitly the standards for the format and
2544   storage (including the duration of storage) of such data. All archives and archival processes
2545   should be secure and should include disaster recovery.
2546
2547   Target / Ideal: In addition to the acceptable level of performance, archival of raw projection
2548   data is also mandated in a secure and redundant manner for a duration the same as for all other
2549   archived trial data.
2550
2551   11.5 Post-Processed Image Data
2552
2553   Acceptable: If post-processed image data is included in the clinical trial imaging
2554   protocol or is used during the analysis and interpretation steps whether specified in the
2555   trial protocol or not, such post-processed image data should be archived at the time and
2556   by the site at which the post-processing is performed, inclusive of all data that was used
2557   in the post-processing.
2558
2559   11.6 Analysis Results

2560
2561 Acceptable: Archival of the analysis is performed at the time and by the site at which
2562 the analysis is performed by use of a clinical trial-specific case report form that
2563 references the specific slices and lesions and provides all pertinent qualitative and
2564 quantitative data as required by the clinical trial protocol. DICOM secondary image
2565 capture may be optionally included for clarification.
2566
2567 Target: In addition to the acceptable level of performance, archival of the analysis is
2568 performed at the time and by the site at which the analysis is performed by use of
2569 annotations and/or mark-ups on the reconstructed (or post-processed) image data and
2570 saved as a new series so that the original reconstructed (or post-processed) image data
2571 are retained without alteration. Theses annotations and/or mark-ups may be archived
2572 either as a "screen save" or DICOM secondary image capture.
2573
2574 Ideal: As per Target, except the ROI / VOI data are captured as true primary data in
2575 DICOM format rather than as a representation of the ROI / VOI data captured as an
2576 image.
2577
2578 11.7 Interpretation Results
2579
2580 Acceptable: All site interpretation results (see Section 10) should be archived at the
2581 time and at the site that such data output is generated. When a central facility is
2582 included in the trial design, the site interpretation results and the central facility
2583 interpretation results should be archived at the central facility. These results include,
2584 but are not limited to, the interpretation and analysis data output as described in detail
2585 within Sections 9 and 10 of this UPICT Oncologic FDG-PET/CT protocol pertinent to the
2586 clinical trial design. Merely archiving the summary statistics at the subject level over all
2587 time points is considered insufficient for QA and reproducibility assurance. The duration
2588 of archive for the imaging data should be the same as for all other trial-related data
2589 unless otherwise stipulated by the sponsor and/or regulatory oversight agencies.
2590
2591 12.   Quality Control
2592
2593   12.2.   QC Associated with the Site
2594
2595   12.2.1. Quality Control Procedures
2596
2597   The Imaging QC section of the clinical trial protocol should specify how site
2598   compliance should be verified and documented. There should be specific site
2599   report forms and checklists to facilitate the verification and documentation of
2600   QC.
2601
2602   If exceptions to any of the performance standards stated below occur and
2603   cannot be remediated on site, the site should promptly communicate the issue
2604   to the appropriate internal overseer / coordinating center / core lab for advice
2605   as to how the irregularity should be managed; if possible this communication
2606   should occur prior to acquisition of any subject data.

2607
2608   All **Target** performance specifications are in addition to those stated for the
2609   **Acceptable** level of performance. Similarly, all **Ideal** performance specifications
2610   are in addition to those stated for both the **Target and Acceptable** levels of
2611   performance.
2612
2613   All auxiliary equipment (e.g., clocks, scales, stadiometer, glucmter, and dose
2614   calibrators) are calibrated and/or synchronized and/or periodically monitored
2615   and documented as part of an ongoing QC program as follows:
2616
2617   12.1.1.1.   Clock Calibration and Synchronization:
2618
2619   **Acceptable**: Checks for internal consistency daily and after
2620   service events. Synchronization of all clocks used in the conduct
2621   of the FDG-PET/CT study should be performed monthly or as
2622   needed based on consistency checks. Dose calibrator and
2623   scanner computer clocks and all clocks used in the conduct of
2624   the imaging study are synchronized within +/- 60 seconds.
2625   **Target**: Checked weekly against an external reference standard
2626   (e.g., NTP or equivalent appropriate standard at the site of
2627   acquisition).
2628   **Ideal**: Dose calibrator and scanner computers are synchronized
2629   daily through an vendor-supported automated process against
2630   the reference standard and therefore within +/- 5 seconds of
2631   reference standard.
2632
2633   12.1.1.2.   Scales and Stadiometer Calibration and Performance:
2634   **Acceptable**: Verified at the time of installation/comissioning
2635   and checked on a regular basis (no less frequently than
2636   annually) by assigned institutional staff.
2637   **Ideal**: Required data is transferred directly from measurement
2638   device into scanner by electronic, HIS/RIS, or other means
2639   bypassing operator entry but still requiring operator
2640   verification.
2641
2642   12.1.1.3.   Glucometer Calibration:
2643   **Acceptable**: Glucose measurements should be made using a
2644   CLIA approved, CLIA cleared, or equivalent (outside the US)
2645   glucose measurement technique.
2646   **Ideal**: Required data is transferred directly from measurement
2647   device into scanner by electronic, HIS/RIS, or other means
2648   bypassing operator entry but still requiring operator
2649   verification.
2650
2651   12.1.1.4.   Dose Calibrator(s) QC:
2652   **Acceptable**: All calibration tests are performed per the
2653   manufacturer's directions and as defined by the applicable

2654		regional and national regulatory bodies using acceptable
2655		reference standards (e.g., NIST). The most recent
2656		manufacturer-specific F18 gain settings are used during these
2657		calibration tests. Accuracy, linearity, and geometry tests should
2658		be performed at installation and after service events. Linearity
2659		testing should be performed at least quarterly. Accuracy testing
2660		should be performed at least annually using the appropriate
2661		reference standard. Daily constancy should be measured with a
2662		long-lived isotope in the range of 500-650 keV and net
2663		measured activity should be within +/- 5% of expected value.
2664		Manufacturer-recommended QC should be performed on dose
2665		calibrators that are part of an automated injection system.
2666		Cross calibration between manual dose calibrators that are used
2667		for scanner QC and/or manual injections and automated
2668		injection systems should be confirmed to be within 5%. Careful
2669		attention should be made to ensure consistent injection
2670		technique including tubing length and diameter. It should also
2671		be confirmed that all of the activity is injected into patients
2672		following the designated flush.
2673		

Target: QC procedures should incorporate the use of traceable
NIST (or equivalent) Ge68-calibration source to perform
accuracy test at least annually to verify the F-18 calibration with
deviation <+/-3%. Linearity testing should be performed
quarterly using decay or attenuating sleeve method. Dose
calibrators should be adjusted

Ideal: An NIST-traceable (Ge68 or other equivalent source) F18-
simulation source is used to calibrate the dose calibrator
calibration setting for F18 to match the reading to the actual
activity of the NIST source. Required data is transferred directly
from measurement device into scanner by electronic, HIS/RIS,
or other means bypassing operator entry but still requiring
operator verification.

12.1.1.5.   CT component of PET/CT scanner

Acceptable: CT scanners require rigorous acceptance testing
and routine QC to ensure appropriate image quality and
radiation exposure. As these devices administer radiation, there
are additional regulatory requirements at the national and/or
state level. In addition, specific QC procedures should be
performed according vendor recommendations. Examples or
vendor-recommended CT QC procedures are shown . As an
example of general procedures that should be formed on all
scanners, the NCIE CQIE guidelines of CT QC are listed as
follows.

2700		Daily QC: At a minimum, daily QC should be performed prior
2701		scanning and include air calibrations, measurements of water
2702		CT numbers and standard deviations, and check for absence of
2703		artifacts.
2704		
2705		Annual QC: The following tests should be performed at
2706		installation, after tube replacement, and annually:

2707 • Scout Prescription & Alignment Light Accuracy
2708 • Imaged Slice Thickness
2709 (slice sensitivity profile, SSP)
2710 • Table Travel/Slice Positioning Accuracy
2711 • Radiation Beam Width
2712 • High-Contrast (Spatial) Resolution
2713 • Low-Contrast Sensitivity and Resolution
2714 • Image Uniformity & Noise
2715 • CT Number Accuracy
2716 • Artifact Evaluation
2717 • Dosimetry/CTDI
2718 •

2719 **Ideal**: The results of QC testing should be exported in a file
2720 format that is readily accessible along acceptable ranges of
2721 performance.
2722

2723 12.1.1.6. PET Scanner or PET component of PET/CT scanner (General QC
2724 Procedures including Calibration)
2725

2726 **Acceptable**: Scanner is cross-calibrated with same dose
2727 calibrator used to assay patient injections. The cross calibration
2728 should be reviewed/performed at least every 3 months, after
2729 scanner upgrades , after new setups, and after modifications to
2730 the dose calibrator (per ACRIN CQIE guidelines).
2731

2732 The same scanner with the same acquisition/reconstruction
2733 protocol, software and settings should be used for each subject
2734 study. Only if the primary scanner is unavailable, a scanner
2735 demonstrated as having equivalent output (as predefined by
2736 the clinical trial site qualification and QC documentation and
2737 supported by accepted international standards) and qualified
2738 through the protocol's site qualification process may be used
2739 (ideally the second scanner should be of the same make, model,
2740 and software version as the primary scanner). The same
2741 scanner acquisition and reconstruction parameters should be
2742 used for QC as are being used for subject image acquisition
2743 (except for scan duration which may be extended for QC
2744 purposes).
2745

2746 Scanner calibration factors (as defined by each manufacturer
2747 specific to each scanner model) should be recorded and
2748 monitored. Variances of more than 3-5% are potentially due to
2749 mis-calibration and therefore should result in verification of
2750 correct calibration and/or recalibration as necessary.
2751
2752 At a minimum, phantom calibration should be performed
2753 annually using acceptable standards as enumerated below. The
2754 same method should be used by each site for the duration of
2755 the trial (not necessary for every site to use the same method).
2756
2757 A) ACRIN / EANM criteria for uniform cylinder[1,46]
2758 　　　1. overall Mean Bkgd. SUV = 1.0 ± 0.1
2759
2760 B) Modified ACR phantom criteria (note the modification of SUV
2761 Bkgd criterion)
2762 　　　1. Mean Bkgd SUV: 0.9 – 1.1
2763 　　　2. 25 mm cylinder: > 1.8 – < 2.8
2764 　　　3. 16 mm / 25 mm ratio: > 0.7
2765
2766 C) SNM CTN criteria
2767 　　　1. SUV = 1.0 ± 0.1 as assessed in the standard
2768 　　　uniform portion of the standard CTN oncology
2769 　　　phantom.
2770 　　　2. Visualization of all simulated lesions
2771 　　　=>10mm.
2772 　　　3. SUVmax of simulated lesions 15mm or 20mm
2773 　　　>= 2.2.
2774
2775 D) NCI CQIE
2776 　　　1. Volume-averaged SUV in phantom between
2777 　　　0.90 and 1.10
2778 　　　2. Axial variation in phantom < 10%
2779 　　　3. Dynamic studies: Volume-averaged SUV of
2780 　　　each time frame varies by < 10% over the
2781 　　　course of the 25-minute acquisition.
2782
2783 Manufacturer specific Image registration calibration between
2784 the PET and CT scanner should be performed at installation and
2785 after service events that involve moving either device. The
2786 image registration should be evaluated annually or after any
2787 suspicion of misregistration. Registration calibration should be
2788 performed after any confirmed misregistration that exceeds the
2789 manufacturer's specified tolerance
2790
2791 **Target**: Scanner calibration, uniformity and recovery coeficient
2792 versus sphere or cylinder diameter should be assessed quarterly

2793		or after any major service or upgrades that may affect
2794		quantitative accuracy.
2795		
2796		**Ideal**: Each site shall perform and document the full range of
2797		the QC tests listed below (as specified by the **Ideal** performance
2798		characteristics) using automated, standardized methods and
2799		phantoms (i.e., those listed above) to document compliance.
2800		This should be part of site qualification and then should be
2801		repeated periodically, at least annually and after any major
2802		service and after any scanner recalibration related to software
2803		upgrades. Vendors should implement daily quality control
2804		reports that can be exported and submitted along with patient
2805		studies for clinical trials.
2806		
2807		SUV measurements for a standardized phantom should have an
2808		overall mean SUV = 1.0 ± 0.05. ROIs (approximately 4 cm or
2809		greater but not including portions subject to partial volume
2810		effects) appropriate to the use instructions for the particular
2811		phantom employed.
2812		
2813		Cross calibration with dose calibrator is accomplished with
2814		paired NIST-traceable sources for the dose calibrator and PET
2815		scanner. This calibration is checked weekly.
2816		
2817		Image registration between PET and CT images should be
2818		evaluated periodically including the effect of patient weight and
2819		bed deflection.
2820		
2821	12.1.1.7	Syringes and tubing used during QC processes:
2822		
2823		**Acceptable**: Syringes and injection tubing are assayed pre- and
2824		post-injection and pertinent information (i.e., time of
2825		measurement and amount of residual activity) is recorded
2826		routinely if applicable to the specific scanner QC routine and
2827		capabilities. The injection technique should be standardized by
2828		ensuring that the same specification of syringes and tubing are
2829		used.
2830		
2831		
2832	12.1.1.8.	Normalization:
2833		
2834		**Acceptable**: Normalization of detector response should be
2835		performed according to vendor recommendations at least every
2836		3 months, after relevant service events, after appearance of
2837		software/hardware upgrades, and appearance of artifacts in
2838		uniformity check. Vendor-specific quality daily control checks
2839		should be performed and confirmed to be acceptable.

2840
2841   **Target**: Documentation of the normalization and results should
2842   be provided in a readily accessible format.
2843
2844   **Ideal**: For some systems, more frequent normalization may be
2845   preferred (e.g. monthly) provided that this is done in an
2846   automated manner with minimal risk of human error.
2847
2848   12.1.1.9.   Uniformity:
2849
2850   **Acceptable**: In addition during the normalization and
2851   calibration methods outlined above, transverse and axial
2852   uniformity should be assessed with a uniform phantom using a
2853   water phantom with F18 at least every 3 months, after new
2854   scanner calibrations, and after software upgrades. Qualitative
2855   review should be performed (i.e., by visual inspection) to ensure
2856   that there are no artifactual variations within or between axial
2857   slices.
2858   Uniformity should be assessed with a uniform cylinder with an
2859   F-18 compound in water. For uniformity tests the cylinder can
2860   also use Ge-68/Ga-68 in epoxy as a sealed solid source, but only
2861   if the uniformity has been verified by other means. The ROI
2862   employed should conform with the use instructions for the
2863   particular phantom employed. Phantom quantitative
2864   measurements with overall mean SUV = 1.0 ± 0.10 should be
2865   made with an ROI (approximately 3 cm or greater but not
2866   including portions subject to partial volume effects) appropriate
2867   to the use instructions for the particular phantom employed.
2868
2869   By ACRIN/EANM/SNM criteria axial slice uniformity does not
2870   vary more than 10% from one end of the axial FOV to the other.
2871
2872   By SNM CTN criteria, phantom sections of uniformity do not
2873   vary more than 10% from one another.
2874
2875
2876   **Target**: The overall mean SUV = 1.0 ± 0.05 should be made with
2877   an ROI (approximately 3 cm or greater but not including
2878   portions subject to partial volume effects) appropriate to the
2879   use instructions for the particular phantom employed.
2880
2881
2882   **Ideal**: Daily uniformity measurements are performed and
2883   recorded in an accessible manner that can be exported and
2884   distributed with individual patient studies.
2885
2886   12.1.1.10.   Image Quality:

2887
2888 **Acceptable**: A standardized image quality phantom scan should
2889 be performed at least annually to check hot and cold spot
2890 image quality per the ACRIN CQIE guidelines. Additional review
2891 of resolution and noise should be performed according to
2892 specific trial guidelines and as stated below. Currently there is
2893 no consensus phantom that should be used. CT and PET co-
2894 registration should meet the manufacturers recommendations
2895 at scanner acceptance and after any major service events that
2896 involve moving scanner gantries.
2897
2898 For individual patients studies, qualitative assessment should be
2899 performed to evaluate co-registration, noise, resolution, and
2900 other aspects of image quality (see 9.6.1). See sections below
2901 for specifics aspects of (resolution and noise).
2902
2903
2904 **Target/Ideal**: Minimum standards for image quality should be
2905 defined based on the requirements of specific trials. Ideally co-
2906 registration should be inspected visually with a weight load to
2907 evaluate bed deflection due to patient weight.
2908
2909 12.1.1.11.   Resolution / SUV Recovery:
2910
2911 **Acceptable**: At a minimum annually, each site shall perform
2912 and document a qualitative resolution QC test by using the
2913 manufacturer's settings and demonstrating resolution of normal
2914 gross anatomic features within clinical images of the brain,
2915 heart, and abdomen (e.g., the images should not appear "too
2916 smooth").
2917
2918 Per SNM criteria and using the CTN PET Oncology Phantom (and
2919 based on the use of the site's standard clinical acquisition and
2920 reconstruction protocols), all lesions 10mm or greater should be
2921 visually detectable for those sites that have access to this
2922 phantom. For sites without access to this phantom an
2923 equivalent quantitative test should be performed.
2924
2925 The ACR criteria for resolution (based on the use of the site's
2926 standard clinical acquisition and reconstruction protocols) are:
2927 The lower portion of the cylinder contains six sets of acrylic rods
2928 arranged in a pie-shaped pattern with the following diameters:
2929 4.8, 6.4, 7.9, 9.5, 11.1, and 12.7 mm. At this target level, the
2930 9.5, 11.1, and 12.7 mm diameter rods must be visible.
2931 By ACR criteria, resolution should be achieved as measured by a
2932 25 mm cylinder is >1.8 and <2.8 3 or by a 16/25 mm cylinder

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ratio: >0.7 Ref ACR PET phantom test guidelines (revised 2/22/10).

For specifications per the EANM guidelines please see EANM paper and EARL: http://earl.eanm.org/cms/website.php. The EANM/EARL provides harmonizing performance criteria for SUVmax and mean recovery as function of sphere size (NEMA NU 2 2007 IQ phantom) and thereby ensures comparable quantitative scanner performance between sites.

For information on the SNMMI/CTN phantom please see the SNMMI/CTN website: http://interactive.snm.org/index.cfm?PageID=10641. Using the CTN PET Oncology Phantom the scanner resolution is accessed by ensuring that all lesions =>10mm are visually detectable and that lesions SUVmax values are within an acceptable range..

Target: Scanner reconstruction protocols are adjusted to provide at least appropriate resolution properties as defined for the specific trial (i.e., recovery coefficient versus sphere or cylinder diameter) for a standard test object (e.g., ACR cylinders or NEMA spheres or other similar phantoms) that contains specific "hot spot" objects (e.g., Boellaard 2008, 2010.).

Ideal: Vendors implement a reconstruction protocol that ensures pre-defined image recovery coefficient characteristics are met. This implementation has two components. The first component is that every site in a particular trial and preferably across all trials would use the same calibration methods / phantom as prescribed in an accepted standard (either the same methods and phantom or the same methods coupled with a defined set of phantoms that have equivalent performance characteristics. The second component is that the vendors would provide or support the users to implement an acquisition / reconstruction protocol that produces the desired results and the vendors provide an automated image assessment tool to verify that the acquisition and reconstruction protocols produce the desired results.

12.1.1.12. Noise:

Acceptable: During routine testing, e.g. done as a regular QA or QC procedure or for qualification purposes, and when the site uses the trial-specific acquisition parameters (e.g., time per bed position, dose, reconstruction etc.), the noise in phantom

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images should be assessed <u>qualitatively</u> to be of consistent and acceptable quality.

Target: During routine testing, e.g. done as a regular QA or QC procedure or for qualification purposes, and when the site uses the trial-specific acquisition parameters (e.g., time per bed position, dose, reconstruction etc.), the noise in phantom images should be <u>measured</u> by reporting the mean, standard deviation (SD), and COV of voxel values within a volume of interest (VOI) as described in section 7.2.

Images are reconstructed with a voxel size of 3-4 mm all three dimensions, but not necessarily isotropic.

Ideal: During routine testing, e.g. done as a regular QA or QC procedure or for qualification purposes, and when the site uses the trial-specific acquisition parameters (e.g., time per bed position, dose, reconstruction etc.), the noise in phantom images should be <u>measured</u> by reporting the mean, standard deviation (SD), and COV of voxel values within a volume of interest (VOI) as described in section 7.2.[2]

11.1.1 Baseline Metrics Submitted Prior to Subject Accrual
See section 12.1.1.

Acceptable: Representative human subjects images consistent with the specifics of the clinical trial should be carefully examined to finalize site qualification. This may be accomplished by one of several strategies. For example, one strategy would be to require submission of patient studies performed prior to the trial and outside of the trial. A second potential strategy may be to require rigorous QC review of the first one or two accrued subjects in the context of the trial. A third potential strategy would be to include initial "human subjects imaging" on subjects not getting the targeted intervention but obtained purely for the purposes of site qualification for the study. A combination of these mechanisms might also be used. Whatever mechanism is used should be compliant with human subjects protection regulations and the sites' IRB requirements.

21.1.1 Metrics Performed and/or Submitted Periodically During the Trial
See section 12.1.1.

Acceptable / Target: The results of the QC procedures performed per Section 12.1.1 and Appendix E should be provided at least annually and should be available for any site audit. Should a new PET/CT system be installed that equipment must be qualified for the trial if it is to be used in the trial. Any PET/CT system that undergoes a major upgrade (i.e., an upgrade that may affect the SUV determination) during the trial must be re-qualified prior to use in the trial.

3027
3028   Ideal: Variances in performance characteristics that remain within the range of normal
3029   but exceed a pre-specified threshold of percentage change should be documented and
3030   data should be aggregated for later analysis.
3031
3032   21.4   QC Associated with Imaging-related Substance Preparation and Administration
3033
3034 Acceptable: FDG must be obtained from a source that is approved by the geographically
3035 appropriate regulatory mechanism (e.g., in the USA an FDA-submitted NDA or ANDA). For
3036 geographic sites that lack such regulatory oversight, equivalency to the USA FDA NDA or ANDA
3037 standards is required.
3038
3039   12.3.   QC Associated with Individual Subject Imaging (performed per subject or
3040   performed daily and therefore available for association with individual subject imaging)
3041
3042   12.3.1. Phantom Imaging and/or Calibration
3043
3044   Acceptable: None
3045
3046   Target: Daily phantom uniformity and calibration testing using Germanium
3047   cylindrical source or equivalent per manufacturers specifications
3048
3049   Ideal: Daily phantom uniformity, resolution, noise, and calibration testing using
3050   a F18 - fillable source* or a Germanium-68 cylindrical source or equivalent per
3051   manufacturers specifications
3052
3053   *If an F-18 fillable phantom is used, there may be more human error associated
3054   with the procedure and hence use of a Germanium-68 cylindrical source is
3055   preferred.
3056
3057   12.3.2. Quality Control of the Subject Image and Image Data
3058
3059   Consolidated Statement – The integrity of DICOM image headers should be
3060   reviewed and confirmed for regulatory compliance (HIPAA), protocol
3061   compliance, and consistency with source data such as CRFs. In some cases,
3062   internal references such as the liver can be used for quality control to confirm
3063   acceptable ranges of SUVs (ACRIN 6678).
3064   Acceptable:
3065   1. QC tests as described in sections 12.1.1 - 12.3.1 pertinent to the QC   of the
3066   subject image data (i.e., visual qualitative inspection, alignment, motion artifact,
3067   noise, etc.)
3068
3069   2. DICOM header integrity and compliance with protocol and institutional /
3070   other policies (e.g., for multi-site trials HIPAA compliance), consistency with CRF
3071   data.
3072

3073   3. Internal QC control should be performed consistent with the performance
3074   standards expressed in Section 9.3.2.2.

3075

3076   4. Syringes and injection tubing are assayed pre- and post-injection and
3077   pertinent information (i.e., time of measurement and amount of residual
3078   activity) is recorded and is consistent with the data used for quantitative
3079   analysis.

3080

3081   Noise:
3082   When the site uses the trial-specific acquisition parameters (e.g., time per bed
3083   position, dose, reconstruction etc.), the noise in patient images should be
3084   assessed <u>qualitatively</u> to be of consistent and acceptable quality. I.e., the images
3085   should not appear too noisy' for trial-specific purposes.

3086

3087   Target (in addition to Acceptable):
3088   Noise:
3089   When the site uses the trial-specific acquisition parameters (e.g., time per bed
3090   position, dose, reconstruction etc.), the noise in patient images should be
3091   <u>measured</u> by reporting the mean, SD, and COV within a VOI using methods as
3092   described in Section 7.2. The VOI should be positioned in the mid or lower
3093   region of the right liver.

3094

3095   Ideal (in addition to Acceptable and Target):
3096   Noise:
3097   When the site uses the trial-specific acquisition parameters (e.g., time per bed
3098   position, dose, reconstruction etc.), the noise in patient images should be
3099   measured as described immediately above. The COV of the voxel values thus
3100   determined should be recorded and should be below 15%.

3101

3102

3103   12.4.   QC Associated with Image Reconstruction

3104

3105 Consolidated and Consensus Statement – Acceptable: CT images should be reviewed for
3106 potential artifacts such as beam hardening, metal objects, and motion. PET images should be
3107 compared to the CT images for proper image registration and potential attenuation correction
3108 artifacts. (ACRIN 6678).

3109

3110 See Section 12.3.2 – Put text here and have reference in 12.3.2.

3111

3112   12.5.   QC Associated with Image Post-processing

3113

3114 Acceptable: QC plan should be based on the type of post-processing that was performed (i.e.,
3115 DICOM Header manipulation including, but not limited to de-identification tasks; post-
3116 processing that affects quantitation; and/or post-processing that affects visualization). The rigor
3117 of the QC process should be commensurate with the type of post-processing that was
3118 performed and the potential for unintended consequences associated with the post-processing
3119 performed. The QC process employed for post-processing tasks should be described in

3120   sufficient detail to allow "downstream" consumers of the trial data to have the necessary
3121   confidence in the imaging data for the purposes intended. The description of the QC process
3122   should be sufficiently detailed to allow non-trial personnel to perform validation checks of the
3123   QC process should they so desire.
3124
3125   12.6.   QC Associated with Image Analysis
3126
3127   Acceptable: The imaging protocol should include a QC program for Image Analysis whether
3128   analysis is performed at a core facility, the acquisition sites, or both. Whatever program is
3129   stated should be followed and documented.
3130
3131   12.7.   QC Associated with Interpretation
3132
3133   Acceptable: The imaging protocol should include a QC program for Image Interpretation
3134   whether interpretation is performed at a core facility, the acquisition sites, or both. Whatever
3135   program is stated should be followed and documented.
3136
3137 13.   Imaging-associated Risks and Risk Management
3138
3139   13.2.   Radiation Dose and Safety Considerations
3140
3141   The radiation dose of the PET/CT study results from radiation exposure from the injection of
3142   FDG and from the CT study (EANM, ACRIN, Hallet). One source (EANM) indicates that CT scans
3143   can be performed as low dose CT to be used for attenuation correction purposes to minimize
3144   radiation dose. Two sources (EANM, Hallet) indicate that radiation dose from the CT scans
3145   should be estimated specific to the system and imaging protocol used (EANM) or by means of
3146   standard estimates. [5] These standard estimates can be utilized within the framework of local
3147   regulatory requirements for risk analysis, [5] which will also depend on patient populations and
3148   life expectancy [5] and particular considerations to reduce radiation exposure should be given for
3149   pediatric applications (EANM). There are several publications reporting radiation doses for FDG.
3150   A paper that summarizes both adult and pediatric doses is Alessio et al, 2009. [47] For a typical
3151   administered dose of 370 MBq the estimated whole body radiation dose is 7 mSv. There is
3152   greater variability in the radiation doses from CT, which is very dependent on the exact protocol
3153   used (e.g., 1. CT for attenuation correction only, 2. CT with improved anatomic localization, or 3.
3154   diagnostic CT). A recent study (Huang, 2009) suggests that the CT doses can range from 7 to 26
3155   mSv. [48] Many hardware and software improvements that have been developed for dose
3156   reduction in diagnostic CT studies are being used in PET/CT such as automated tube current
3157   modulation and iterative reconstruction. For pediatric studies, a common approach is to reduce
3158   kVp and tube current. Alessio et al. suggest that, with care it is feasible to decrease the CT doses
3159   to 3 to 6 mSv. [47] Particular consideration to reduce radiation exposure should be given for
3160   pediatric patients. One common approach in children is to administer approximately 5.3
3161   MBq/Kg of FDG with a minimum dose of 37 MBq and a maximum dose of 370 MBq.
3162
3163
3164   Acceptable / Target: The protocol and the informed consent form should contain language
3165   describing the estimated administered dose range and estimated whole body radiation
3166   exposure (expressed as effective dose in mSv) for the FDG to be administered. In addition both

68

3167   documents should provide comparator (equivalency) radiation examples. The estimates of
3168   radiation dose will be site and protocol-specific and based on factors such as the number and
3169   frequency of studies. Useful comparators are annual background radiation (~ 3 mSV/yr) and the
3170   allowable dose to radiation workers (50 mSv/yr).
3171
3172   Ideal: In addition to the above, each site should document the estimated radiation dose for
3173   each subject (whole body) inclusive of FDG and CT. The protocol should contain the estimated
3174   critical organ dose attributable to FDG based on the proposed administered dose.
3175
3176   13.3.   Imaging Agent Dose and Safety Considerations
3177
3178   There is a potential small risk of allergic reactions, but there have been no reports of such
3179   reactions associated with intravenous administration of FDG.
3180
3181   Approximately 1 person in 1000 may have an allergic reaction from the iodinated contrast
3182   drugs. These reactions are temporary and treatable. Allergic reactions may include: mild itching
3183   or hives (small bumps on the skin), and shortness of breath and swelling of the throat or other
3184   parts of the body. The subject should be instructed to tell the technologist immediately if s/he
3185   experience any of these symptoms so s/he can be treated promptly.
3186
3187   The placement of intravenous catheters has the associated risk of making the patient
3188   temporarily uncomfortable and a small bruise may form. A slight bruise may form where the
3189   needle has been in a vessel. There is a slight risk of infection at the site, but sterile technique
3190   reduces this risk nearly completely. The patient may also experience claustrophobia from the
3191   imaging ring apparatus or discomfort from lying on the scanner table for 60-120 minutes.
3192
3193   Acceptable: The protocol and informed consent form should contain language stating that there
3194   have been no serious reported reactions to FDG. If iodinated contrast is used in the study, the
3195   protocol and informed consent should contain language outlining the risks associated with that
3196   contrast. The risks of intravenous access and the potential of extravasation of FDG and
3197   iodinated contrast should also be included in the protocol and informed consent document.
3198
3199   13.4.   Imaging Hardware-specific Safety Considerations
3200
3201   Acceptable:
3202   Per recommendations from the FDA, before beginning the first CT portion of the PET/CT
3203   scan, the operator should use history, physical examination, and CT scout views to
3204   determine if implanted or externally worn electronic medical devices are present and if
3205   so, their location relative to the programmed scan range.
3206
3207   For CT procedures in which the medical device is in or immediately adjacent to the
3208   programmed scan range, the operator should:
3209   •   Determine the device type;
3210   •   If practical, try to move external devices out of the scan range;
3211   •   Ask patients with neurostimulators to shut off the device temporarily while the scan
3212   is performed;

- Minimize x-ray exposure to the implanted or externally worn electronic medical device by:
  - Using the lowest possible x-ray tube current consistent with obtaining the required image quality; and
  - Making sure that the x-ray beam does not dwell over the device for more than a few seconds;

After CT scanning directly over the implanted or externally worn electronic medical device:
- Have the patient turn the device back on if it had been turned off prior to scanning.
- Have the patient check the device for proper functioning, even if the device was turned off.
- Advise patients to contact their healthcare provider as soon as possible if they suspect their device is not functioning properly after a CT scan.

13.5.   Management and Reporting of Adverse Events Associated with PET radiopharmaceutical or CT contrast agent

Acceptable: Adverse event (AE) tracking and reporting for FDG-PET/CT in the course of a clinical trial should be embedded in the general trial AE tracking and reporting mechanism. It is reasonable to limit the time frame for possible AE attribution to less than twenty-four (24) hours after administration.

13.6.   Management and Reporting of Adverse Events Associated with Image Data Acquisition
Does not apply to this protocol.

3241   ACRONYMS AND ABBREVIATONS
3242
3243   ACRIN: American College of Radiology Imaging Network
3244   AE: Adverse Event
3245   ANDA: Abbreviated New Drug Application
3246   CT: X-ray Computed Tomography
3247   CTDI: CT Dose Index
3248   DICOM: Digital Imaging and Communications in Medicine
3249   DLP: Dose-Length-Product
3250   EORTC: European Organisation for Research and Treatment of Cancer
3251   EU: European Union
3252   FDG: Fluorodeoxyglucose
3253   GHS: Global Harmonization Summit
3254   HIPAA: Health Insurance Portability and Accountability Act
3255   IRB: Institutional Review Board
3256   kVp: Peak Kilovoltage
3257   mAs: milliamp-seconds
3258   MIP: Maximum Intensity Projection
3259   MTV: Metabolic Tumor Volume
3260   NDA: New Drug Application
3261   PET: Positron Emission Tomography
3262   PERCIST: PET Response Criteria in Solid Tumors
3263   PHI: Protected Health Information
3264   RECIST: Response Evaluation Criteria in Solid Tumors
3265   RSNA: Radiological Society of North America
3266   QA: Quality Assurance
3267   QC: Quality Control
3268   QIBA: Quantitative Imaging Biomarker Alliance
3269   ROI: Region-Of-Interest
3270   TLG: Total Lesion Glycolysis
3271   UPICT: Uniform Protocols in Clinical Trials
3272   VOI: Volume-Of-Interest
3273

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