QIBA Proffered Protocol to UPICT. CT: Change Measurements in the Volumes of Solid Tumors

Running title: QIBA v-CT Protocol for Solid Tumors V2.0

2011.07.28

QIBA Protocol editor's note: Notes from the editors of the QIBA Profile and the QIBA Protocol are in deep red font. Reviewers' comments are in the margin. Notes and comments will be removed prior to broadcast in pdf format for public comment. Comments from the public will follow a form and format prescribed by QIBA for all work products.

QIBA Protocol editor's note: This is a draft. No portion of the text has been approved by QIBA for release to the public. The purpose of distributing this draft is to obtain input from the QIBA Technical Committee and the Extended Pharma Imaging Group.

QIBA Protocol editor's note: Some UPICT instructions are retained verbatim *in blue italics* for the purposes of discussion about this draft. They will be removed prior to broadcast.

QIBA Protocol editor's note: The Quantitative Imaging Biomarker Alliance (QIBA, pronound KEE'- bah) of the Radiological Society of North America (RSNA) will "proffer" this image acquisition, processing, and analysis protocol to UPICT (the NIH working group for Uniform Protocols for Imaging In Clinical Trials). The format has been prescribed by UPICT, and is essentially non-negotiable.

X. Title of Imaging Protocol

QIBA Proffered Protocol to UPICT. CT: Change Measurements in the Volumes of Solid Tumors

***Instructions to Clinical Trialists** who are adapting this imaging protocol for inclusion in their Clinical Trial Protocol are shown in italics. All italic text should generally be removed as part of preparing the final protocol text.*

0. Executive Summary

This document describes procedures for quantifying longitudinal changes in the volumes of solid tumors with x-ray computed tomography (CT). Compliance with these procedures will meet the claims for precision of measurement described in the corresponding Profile[1] developed by the CT Technical Committee of the Quantitative Imaging Biomarker Alliance (QIBA) of the Radiological Society of North America (RSNA). The QIBA Profile claims that the 95% confidence intervals surrounding the coefficients of variation for repeated measurements of change in tumor volumes can be consistently less than 30% in measurable lesions. Lesions can be classified as measurable providing that the following conditions are met:

- the longest diameter is 10mm or greater
- the tumor possesses sufficient conspicuity to allow its boundaries to be adequately demarcated from surrounding tissue
- the tumor morphology is not unduly complex
- the tumor composition is sufficiently homogeneous, or the various tissue types within a mass can be segmented from each other

[1] http://qibawiki.rsna.org/index.php?title=Quantitative-CT (last accessed 31 May 2011)

1. Context of the Imaging Protocol within the Clinical Trial

1.1. Utilities and Endpoints of the Imaging Protocol

These image acquisition, processing, and analysis procedures are intended for use in patients with cancer who are followed with serial CT scans to assess their responses to treatment. Changes in volume that exceed 30% are highly likely to represent true biological evolution in the health status of a patient. Claims about the precision of measurement hold for patients with solid tumors of sufficient size and conspicuity as described in the corresponding QIBA Profile. In summary, confidence in the claims increases directly with tumor contrast compared to surrounding tissues. When all other factors are equal, precision improves with increasing tumor volume. However, precision decreases with geometric complexity and as tumors invade multiple tissue compartments. Caution is required when masses contain multiple tissue types, such as necrotic debris, fibrotic elements, and fluid-filled spaces.

This protocol is otherwise agnostic about the settings in which the measurements are made and the way the measurements will be used to make decisions. Typical applications include assessing responses to treatment in individual patients starting new therapeutic regimens, and distinguishing between arms of clinical trials.

1.2. Timing of Imaging within the Clinical Trial Calendar

In order to quantify treatment-induced change, the pre-treatment CT scan shall take place prior to any new intervention to treat the disease. This scan is referred to as the "baseline" scan. It should be acquired as closely as possible, but not before, the initiation of treatment, and in no case more than a certain number of days before treatment as specified in the clinical protocol.

In clinical trials, there is an expectation that all patients will have follow up scans acquired at regular, calendar-based intervals specified by the clinical protocol. Otherwise, the QIBA Profile and this derivative imaging protocol does not presume a specific timing.

1.3. Management of Pre-enrollment Imaging

To quantify changes in volume with the precision claimed in the corresponding QIBA Profile, the pre-treatment image acquisition and processing must meet or exceed the minimum specifications described in this document. Images that meet these criteria can serve as "baseline" scans on which change measurements are based. Scans that do not meet minimum specifications must be re-acquired, or the claims will not be valid.

1.4. Management of On-Protocol Imaging Performed Off-Schedule

This protocol does not presume a universal, or even a specific, imaging schedule. It is intended to measure tumor volume change between two arbitrary time points, including scans that are acquired outside of the protocol-specified time-window (OOW scans).

Management of the clinical trial calendar, deviations from the protocol specified time window, and potential impacts of deviations or non-uniformity of interval timing on derived outcomes such are Time-To-Progression (TTP) or Progression-Free-Survival (PFS) are left to clinical trial protocol owners.

1.5. Management of On-Protocol Imaging Performed Off-Specification

Deviation from the specifications and procedures described in this protocol will likely degrade the quality of measurements. QIBA Profile claims about the precision of measurement only apply when minimum specifications are met.

Management of off-specification imaging, including decisions about whether to accept "suboptimal but readable" scans or to require repeat scans are left to the clinical trial protocol owners.

1.6. Management of Unscheduled, Off-Protocol Imaging

This QIBA proffered imaging protocol is limited to measurements based on CT scans. Alternative imaging technologies may be used as indicators of disease progression only. For example, in a subject with lung cancer who is being followed with CT scans of the body, if an unscheduled, off-protocol MRI scan of the head is acquired in the middle of a cycle to evaluate a new complaint of headache, then it may be read either as confirming progression or being negative for progression depending on whether or not new brain metastases are discovered. In contrast, a high resolution CT scan of the chest acquired to evaluate sudden shortness of breath may be used to assess target lesions in the field of view regardless of whether pulmonary embolism is detected provided that image quality conforms with specifications.

1.7. Subject Selection Criteria Related to Imaging

These procedures are applicable to patients with solid tumors that can be measured with CT. Otherwise, patient selection criteria are left to the authors of the clinical trials that use them.

1.7.1. Relative Contraindications and Mitigations

This protocol involves ionizing radiation. Section 13.1 describes radiation risk and safety considerations, e.g., for young children or pregnant women. Local standards for good clinical practice (cGCP) and the ALARA Principle (As Low As Reasonably Achievable radiation exposure) should be followed.

This protocol involves the use of intravenous contrast. Section 13.2 describes risk and safety considerations, e.g., for subjects with chronic renal failure. Local standards for good clinical practice (cGCP) should be followed. Procedures for the use of contrast in Section 5 assume there are no known contra-indications in a particular subject.

1.7.2. Absolute Contraindications and Alternatives

There are few, if any, absolute contra-indications to the image acquisition and processing procedures described in this protocol. Local standards for good clinical practice (cGCP) should be followed.

This protocol does not intend to constrain the use of alternative imaging technologies when clinically indicated. However, the measurement of tumor volume with non-CT based imaging technologies is outside the scope of this protocol.

2. Site Selection, Qualification and Training

2.1. Personnel Qualifications

This protocol does not presume specific personnel or qualifications beyond those normally required for the performance and interpretation of CT exams with contrast. Local rules and regulations for the certification of personnel providing patient care should be followed. Responsibilities for the qualification and maintenance of certification of imaging professionals who participate in clinical trials is left to each clinical trial sponsor.

2.2. Imaging Equipment

This protocol requires a CT scanner with the following characteristics:

- multiple rows of detectors
- see Section 7 for required acquisition capabilities
- conforms to the Medical Device Directive Quality System and the Essential Requirements of the Medical Device Directive
- designed and tested for safety in accordance with IEC 601-1, as well as for ElectroMagnetic Compatibility (EMC) in accordance with the European Union's EMC Directive, 89/336/EEC
- labelled for these requirements, as well as ISO 9001 and Class II Laser Product, at appropriate locations on the product and in its literature
- CSA compliant

Measurement Software: See Section 9 for general capabilities requirements.

Participating sites may be required to qualify for, and consistently perform, at a specific level of compliance. (See the discussion of compliance in Appendix C.)

2.3. Infrastructure

No particular infrastructure or physical environment is specified. It is assumed that imaging procedures will be performed in locations that are in compliance with local regulations for operating medical imaging facilities.

2.4. Quality Control

2.4.1. Procedures

See 12.1.1 for procedures the site must implement and document.

2.4.2. Baseline Metrics Submitted Prior to Subject Accrual

See 12.1.2 for metric submission requirements.

2.4.3. Metrics Submitted Periodically During the Trial

See 12.1.3 for metric submission requirements.

Additional task-specific Quality Control is described in sections below.

2.5. Protocol-specific Training

No UPICT protocol-specific training is specified beyond familiarity with the relevant sections of this document and the QIBA Profile from which it is derived.

3. Subject Scheduling

3.1. Timing Relative to Index Intervention Activity

Timing is left to the discretion of attending physicians in clinical care settings and the owners of clinical trials. Otherwise, calendar based schedules are preferred to cycle based schedules for several reasons:

- Scan schedules can be established at the beginning of the trial, so patients can count on them, and plan their life activities around them.
- They give patients a positive message, namely that their health care providers expect to be working with them for a long time.
- They tend to reduce patient anxiety associated with waiting for scan results before making treatment plans.
- They reduce the work of clinical research coordinators, who can decrease the number of times they engage the radiology scheduling service on behalf of a subject. In fact, they reduce the hassle factor for both site oncology research coordinators and site radiology scheduling services because the farther out they set the schedule, the more degrees of freedom they find on the radiology

appointment books. If cancellations become necessary, they are easier to achieve than "just in time" additions to the schedule.

- Scientific confounders associated with unequal toxicities, and hence unbalanced time intervals between arms, tend to be reduced.
- Definitive timing allows for direct comparisons between arms based on objective response rates after fixed time intervals, e.g., the magnitude of tumor response at 6 weeks or 12 weeks in each arm.
- Fixed calendar schedules are implemented anyway when patients come off trial for non-progression. It is often best to get this schedule established before the disappointment of coming off trial.

3.2. Timing Relative to confounding Activities *(to minimize "impact")*

This protocol does not presume any timing relative to other activities. Obviously, locoregional treatments, such as radiation therapy or cryotherapy that occur during a course of chemotherapy will confound assessments of drug-induced changes in tumor volume; however, these maneuvers should not impact the measurements of tumor volume.

3.3. Scheduling Ancillary Testing

This protocol does not depend on any ancillary testing.

4. Subject Preparation

4.1. Prior to Arrival

No preparation is specified beyond the local standard of care for CT with contrast.

4.2. Upon Arrival

4.2.1. Confirmation of subject compliance with instructions

No preparation is specified beyond the local standard of care for CT with contrast.

4.2.2. Ancillary Testing

No ancillary testing is specified beyond the local standard of care for CT with contrast.

4.2.3. Preparation for Exam

No exam preparation is specified beyond the local standard of care for CT with contrast.

5. Imaging-related Substance Preparation and Administration

5.1. Substance Description and Purpose

The use of contrast is not an absolute requirement for this protocol. However, the use of intravenous and oral contrast materials are often medically indicated for the diagnosis and staging of solid tumors in many clinical settings. Contrast influences the appearance, or conspicuity, of neoplastic masses, and can have an impact on the quantification of solid tumor volumes. Therefore,

- If intravenous contrast was administered during the baseline scan, equivalent contrast shall be used at all subsequent time points. If intravenous contrast was not used at baseline, it shall not be used during follow-up scans.
- If oral contrast was used at baseline, equivalent contrast shall be used at all subsequent time points. If oral contrast was not used at baseline, it shall not be used during follow-up scans.

The professional who acquires the scans shall record the use and type of contrast in the image header.

5.2. Dose Calculation and/or Schedule

Site-specific sliding scales that have been approved by local medical staffs and regulatory authorities shall be used for patients with relative contraindications to contrast, such as impaired renal function (e.g., sliding scale contrast dose reduction based on creatinine clearance).

For a given subject, the same contrast dose should be used for each scan. If a different brand or type of contrast is used, the dose may be adjusted to ensure comparability as indicated and by peer-reviewed literature and/or the contrast manufacturers' package inserts.

5.3. Timing, Subject Activity Level, and Factors Relevant to Initiation of Image Data Acquisition

For a given subject, image acquisition should start at the same time after contrast administration for each scan.

Scan delay after contrast administration is dependent upon both the dose and rate of administration, as well as the type of scanner being used. Contrast administration should be tailored to optimize lesion conspicuity. Generally, since there are multiple concentrations of contrast as well as administration rates and scanning speeds, it is difficult to mandate specific values. Generally, institutional guidelines should be followed so as to optimize reproducibility of the scan technique.

The professional who acquires the scan shall record the actual contrast media dose and administration schedule in the header.

5.4. Administration Route

Intravenous contrast: The claims hold when the administration of IV contrast meets specifications for uniformity at each time-point. Confidence improves with injection into a large antecubital vein known to be patent from observation of intravenous saline drip, but is not an absolute requirement.

Oral contrast: The claims hold when the same contrast agent is given per os at a constant timing interval prior to image acquisition.

5.5. Rate, Delay and Related Parameters / Apparatus

The claims hold when the administration of IV contrast meets specifications for uniformity at each time-point. The technologist shall ensure that the time-interval between the administration of intravenous contrast (or the detection of bolus arrival) and the start of the image acquisition is the same as for prior scans. Confidence improves with the use of a power injector.

If a different brand or type of intravenous contrast is used, the rate may be adjusted to ensure comparability as documented by peer-reviewed literature and/or the contrast manufacturers' package inserts.

5.6. Required Visualization / Monitoring, if any

The potential for adverse reactions to contrast should be monitored according to the local standard of care. The prevention and management of contrast reactions is outside the scope of this quantitative imaging protocol.

5.7. Quality Control

See 12.2.

6. Individual Subject Imaging-Related Quality Control

See 12.3.

7. Imaging Procedure

7.1. Required Characteristics of Resulting Imaging Data

This section describes characteristics of the acquired images that are important for the quantification of tumor volume. Characteristics not covered here are left to the discretion of the clinical protocol authors and professionals at participating sites.

Additional details about the method for acquiring these images are provided in section 7.2.

7.1.1. Data Content

Imaging data for measurement of tumor volume must be performed on qualified equipment. The QIBA Profile describes compliant devices.

All serially acquired CT scans for an individual participant shall be performed on the same platform. In the rare instance of equipment malfunction, follow-up scans of an individual patient can be performed on the same type of platform. All efforts shall be made to have the follow-up scans performed with identical parameters. This shall be inclusive of as many of the scanning parameters as possible, including the same field of view (FOV).

The imaging professional who acquires the images shall set the scan plane to be the same as for prior scans.

A set of scout images shall be initially obtained. For imaging of the chest, contiguous thin section slices from the thoracic inlet to the adrenal glands shall be obtained during a single breath hold. Pitch shall be chosen so as to allow completion of the scan in a single breath hold. The scanner shall be capable of acquiring the imaging data at an axial rate of at least 4cm per second. In some cases two or more breaths may be necessary. In those cases, it is important that the target lesion be fully included within one of the sequences. For imaging of the abdomen and pelvis, the scan should extend from the apex of the dome of the liver to the pubic symphysis. The axial scan rate requirement can be relaxed for abdominopelvic imaging.

The imaging professional who acquires the images shall record the actual Anatomic Coverage, Field of View, Scan Duration, and Scan Plane in the header.

Field of View affects pixel size due to the fixed image matrix size used by most CT scanners. The same settings for field of view should be used during each time-point measurement.

7.1.2. Data Structure

The following parameters describe how the data should be acquired:

Parameter	Specification
Scan Duration for Thorax	The Acquisition Device shall be capable of performing the required scans at an axial rate of at least 4cm per second.
Anatomic Coverage	The Technologist shall perform the scan such that the acquired anatomy is the same as for prior scans.
Scan Plane (Image Orientation)	The Technologist shall set the scan plane to be the same as for prior scans.
Total Collimation Width	The Acquisition Device shall be set up so as to achieve a total collimation width >=20mm.
IEC Pitch	The Acquisition Device shall be set up so as to achieve IEC pitch less than 1.5.
Tube Potential	The Acquisition Device shall be set up so as to achieve same kVp for all scans
Single Collimation Width	The Acquisition Device shall be set up so as to achieve single collimation width <= 1.5mm.

The imaging professional who acquires the images shall ensure that the following parameters are recorded in the image header: Anatomic Coverage, Field of View, Scan Duration, Scan Plane, Total Collimation Width, Single Collimation Width, Scan Pitch, Tube Potential, and Slice Width.

Informative Text: Comments on Data Sampling Specifications:

mAs (milliamperes of current) is not specified here. Instead, the setting is determined for each CT scanner manufacturer's model and represented in Model Specific Parameters of Appendix G. This approach allows each manufacturer to may make recommendations on how to best establish operating points for their equipment that meets all requirements simultaneously.

Collimation Width (defined as the total nominal beam width) is often not directly visible in the scanner interface. Wider collimation widths can increase coverage and shorten acquisition, but can introduce cone beam artifacts which may degrade image quality.

Slice intervals (a.k.a. "reconstruction intervals" that result in discontiguous data are unacceptable as they may "truncate" the spatial extent of the tumor, degrade the identification of tumor boundaries, confound the precision of measurement for total tumor volumes, etc.

Slice Width directly affects voxel size along the subject z-axis. Smaller voxels are preferable to reduce partial volume effects and (likely) provide higher precision due to higher spatial resolution.

Pixel Size directly affects voxel size along the subject x-axis and y-axis. Smaller voxels are preferable to reduce partial volume effects and (likely) provide higher measurement precision.

Isotropic Voxels are expected to improve the reproducibility of tumor volume measurements, since the impact of tumor orientation (which is difficult to control) is reduced by more isotropic voxels.

Scan Plane may differ for some subjects due to the need to position for physical deformities or external hardware, but should be constant for each scan of a given subject.

Faster **Rotation Speed** reduces the breath hold requirements and reduces the likelihood of motion artifacts.

7.1.3. Data Quality

The parameters that describe imaging device characteristics which influence the quality of the images are detailed in the QIBA Profile. Image quality must be uniform at each time-point in order to meet the QIBA Profile claims for precision of measurement when quantifying changes in tumor volumes.

7.2. Imaging Data Acquisition

7.2.1. Subject Positioning

Parameter	Specifications
Subject Positioning	The technologist shall position the subject in the way that the subject was positioned during the prior scans. If the previous positioning is unknown, the technologist shall position the subject Supine/Arms Up/Feet first if possible.
Table Height	The technologist shall adjust the table height to place the mid-axillary line at isocenter.

The imaging professional who acquires the images shall record actual patient positioning and table height in the header:

Informative Text: Comments on Subject Positioning

For a given subject, they may be placed in a different position if medically unavoidable due to a change in clinical status, but otherwise the same positioning should be used for each scan. If possible, that should be Supine/Arms Up/Feet First.

If the previous positioning is unknown, the subject should be positioned Supine/Arms Up/Feet First if possible. This has the advantage of promoting consistency, and reducing cases where intravenous lines, which could introduce artifacts, go through gantry.

Consistent positioning is required to avoid unnecessary variance in attenuation, changes in gravity induced shape, or changes in anatomical shape due to posture, contortion, etc. Careful attention should be paid to details such as the position of their upper extremities, the anterior-to-posterior curvature of their spines as determined by pillows under their backs or knees, the lateral straightness of their spines, and, if prone, the direction the head is turned.

Factors that adversely influence patient positioning or limit their ability to cooperate (breath hold, remaining motionless, etc.) should be recorded in the corresponding DICOM tags and case report forms, e.g., agitation in patients with decreased levels of consciousness, patients with chronic pain syndromes, etc.

7.2.2. Instructions to Subject During Acquisition

Movement

The technologist shall instruct the patient to remain motionless during the procedure to prevent blurring of the pictures.

Breath Hold

The technologist shall ensure that image acquisition occurs at, or at least near, the height of full inspiration.

The technologist shall ensure that the breath hold state is the same as for prior scans.

Factors that adversely influence patient positioning or limit their ability to cooperate (e.g., breath hold, remaining motionless, agitation in patients with decreased levels of consciousness, patients with chronic pain syndromes, etc.) shall be recorded.

Informative Text: Comments on Instructions to Subjects

Breath holding reduces motion that might degrade the image. Full inspiration inflates the lungs, which separates structures and makes lesions more conspicuous.

Although performing the acquisition in several segments (each of which has an appropriate breath hold state) is possible, performing the acquisition in a single breath hold is likely to be more easily repeatable and does not depend on the technologist knowing where the lesions are located.

7.2.3. Timing/Triggers

Parameters	Specifications
Timing / Triggers	The technologist shall ensure that the time-interval between the administration of intravenous contrast (or the detection of bolus arrival) and the start of the image acquisition is the same as for prior scans.

The actual Timing and Triggers shall be recorded.

Informative Text: Comments on Timing and Triggers

For each subject, the time-interval between the administration of intravenous contrast and the start of the image acquisition should be determined in advance, and then maintained as precisely as possible during all subsequent examinations.

For lung masses, image acquisition should be timed to coincide with visualization of the thoracic arteries. For sub-diaphragmatic acquisitions, timing should coincide with opacification of the portal-venous blood vessels.

7.2.4. Model-Specific Parameters

Appendix G.1 lists acquisition parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 7.1.

7.2.5. Archival Requirements for Primary Source Imaging Data

See 11.3.

7.3. Imaging Data Reconstruction

The following parameters describe general characteristics of the reconstruction:

Parameter	Specifications
Reconstruction Field of View	Entire lateral extent of the patient, but no greater than required to image the entire body
Slice Thickness	=<2.5mm
Reconstruction Interval	=<2.5mm
Reconstruction Overlap	> 0 (i.e. no gap, but may have some overlap)
Reconstruction Kernel Characteristics	equivalent for all time points

Actual Spatial Resolution, Noise, Pixel Spacing, Reconstruction Interval, Reconstruction Overlap, Reconstruction Kernel Characteristics, as well as the model-specific Reconstruction Software parameters utilized to achieve compliance with these metrics shall be recorded.

Informative Text: Comments on Data Reconstruction

Spatial Resolution quantifies the ability to resolve spatial details. Lower spatial resolution can make it difficult to accurately determine the borders of tumors, and as a consequence, decreases the precision of volume measurements. Increased spatial resolution typically comes with an increase in noise. Therefore, the choice of factors that affect spatial resolution typically represent a balance between the need to accurately represent fine spatial details of objects (such as the boundaries of tumors) and the noise within the image. Spatial resolution is mostly determined by the scanner geometry (which is not usually under user control) and the reconstruction kernel (which is somewhat under user control as the user usually gets to choose from a limited set of choices of reconstruction kernels provided at the scanner). It is stated in terms of "the number of line-pairs per cm that can be resolved in a scan of resolution phantom (such as the synthetic model provided by the American College of Radiology and other professional organizations)." –OR– "the full width at half of the line spread function".

Reconstruction Field of View affects reconstructed pixel size because the fixed image matrix size of most CT scanners is 512 X 512. If it is necessary to expand the field of view to encompass more anatomy, the resulting larger pixels may be less than is necessary to achieve the claim. A targeted reconstruction with a smaller field of view may be necessary, but a reconstruction with that field of view would need to be performed for every time point. Pixel Size directly affects voxel size along the subject x-axis and y-axis. Smaller voxels are preferable to reduce partial volume effects and provide higher measurement precision. Pixel size in each dimension is not the same as resolution in each dimension; inherent resolution is different than how the data is reconstructed and is strongly affected by the reconstruction kernel. It is important not to throw away resolution to match the worse to the better.

Reconstruction Interval (a.k.a. Slice spacing) that results in discontiguous data is unacceptable as they may "truncate" the spatial extent of the tumor, degrade the identification of tumor boundaries, confound the precision of measurement for total tumor volumes, etc. Decisions about overlap (having an interval that is less than the nominal reconstructed slice thickness) need to consider the technical requirements of the clinical trial, including effects on measurement, throughput, image analysis time, and storage requirements. Reconstructing datasets with overlap will increase the number of images and may slow down throughput, increase reading time and increase storage requirements. For multidetector row CT (MDCT) scanners, creating overlapping image data sets has NO effect on radiation exposure; this is true because multiple reconstructions having different

kernel, slice thickness and intervals can be reconstructed from the same acquisition (raw projection data) and therefore no additional radiation exposure is needed. <Note that the slice thickness is "nominal" since the thickness and is not technically the same at the middle and the edges>

Reconstruction Kernel Characteristics need to be defined to optimize the analysis for each lesion while still meeting the requirements for noise and spatial resolution. A softer kernel can reduce noise at the expense of spatial resolution. An enhancing kernel can improve resolving power at the expense of increased noise.

7.3.1. Device Model-Specific Parameters

Appendix G.2 lists reconstruction parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 7.1.

7.3.2. Archival Requirements for Reconstructed Imaging Data

See 11.4.

7.3.3. Quality Control

See 12.4.

8. Image Post-processing

No post-processing shall be performed on the reconstructed images sent for image analysis. Such processing, if performed, has the potential to disrupt the consistency of the results.

As described in 7.3 above, scans should be delivered as single stacks of images of uniform slice thickness. When images of anatomical regions are reconstructed at different slice thicknesses, they should not then spliced together as a single whole body scan. Quantification of tumor volume can be confounded unless the images are delivered as separate stacks.

9. Image Analysis

The specific aim of image analysis is to measure the volume of neoplastic tumors at each time-point, and then compute the change in volume. The volume of each measurable lesion shall be quantified as described in this section.

Fluid, blood, necrotic debris, and the like should not be included in the measurement of tumor volume. Procedures for segmenting tissue types within a mass are not described by this UPICT protocol, but should be implemented when technically feasible.

9.1. Input Data to Be Used

Images that are reconstructed in compliance with Section 7 of this protocol may be used directly, since no other post-processing is specified.

No other data is required for the quantification of tumor volume. Dates of image acquisition must be known to compute rates of tumor growth. The date that a new treatment regimen began must be known to calculate time-intervals to progressive disease events as defined by the clinical protocol.

9.2. Methods to Be Used

Each lesion shall be characterized by determining the boundary of the lesion on all of the slices it is visible. Demarcating the edge of a tumor from the surrounding tissue is referred to as segmentation. Segmentation may be performed automatically by a software algorithm, manually by a human observer using a marking tool, or semi-automatically by an algorithm working with human guidance/intervention.

General specifications for image analysis tools can be found in the corresponding Profile document. See Reference 1. For each method of segmentation and measurement used, precision shall be characterized with one of the methods described in section 9.6.

Methods for adjudicating discordant results are not described in this UPICT protocol. Various systems of adjudication are to be selected by attending physicians and clinical trial sponsors.

9.3. Required Characteristics of Resulting Data

Tumor volume is defined as the sum of all the voxel volumes containing neoplastic tissue within the boundaries of a discrete tumor mass on all the tomographic slices on which it is visible. The units of measure shall be mm3 or mL.

The **Sum of Target Lesion Volumes** (SOV) is a value computed by adding up the volumes of all the target lesion at a given time-point.

The **Baseline** SOV corresponds to the measurements on the pre-treatment scan acquired most closely to, but before the start of treatment.

The **Nadir** SOV is the lowest value for the sum of the volumes of all target lesions since the start of a new treatment. The nadir is the reference value for computing changes in SOV when determining whether progression has occurred.

The following lesions may not be included in the SOV

Non-Measurable Lesions:

Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter (the greatest distance between any two in-plane pixels) is less than 10 mm or two times the axial slice thickness. Or, neoplastic masses whose volume at baseline is less than 625 mm^3. The precision of measurement of small lesions is low, and small absolute errors can lead to relatively large errors in terms of % change.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition. A tumor that appears to be measurable on some consecutive slices but whose edges become overly obscure on others should be classified as non-measurable.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill defined abdominal masses, etc.

Non-Target Lesions (NTL):

These are lesions which are followed qualitatively (classified at each visit as absent, present, or showing unequivocal progression). All non-measurable lesions (see above) are automatically non-target lesions. Additionally, if the number of measurable lesions is extremely large, it may be impractical to follow all of them quantitatively. Those that are not selected for quantitative assessment are designated non-target lesions, and followed qualitatively.

9.4. Platform-specific Instructions

Appendix G.4 lists parameter values and/or instructions for specific models/versions that can be expected to produce data meeting the requirements of Section 9.3.

9.5. Archival and Distribution Requirements

See 11.6.

9.6. Quality Control

For all measurements, the coefficients of variation should be characterized, and the 95% confidence interval surrounding them should be calculated. Specific quality

assurance procedures for estimating variance are not specified in this UPICT protocol. See 12.6 for more details.

10. Image Interpretation

While Analysis is primarily about computation; Interpretation is primarily about judgment. Interpretation may be performed at both the lesional / target level and in the aggregate at the subject level (e.g., in an oncology study each index lesion may be measured in longest diameter during the analysis phase, but in this phase a judgment may be made as to whether there is a new "non-index" lesion; the aggregation of the measured lesions with comparison to previous studies coupled with the judgment as to the presence or absence of a new lesion will result in the RECIST classification at the subject level).

10.1. Input Data to Be Used

Describe required input data and any necessary validation or adjustments which should be performed on it. May also specify data which should not be used until after the clinical trial interpretation is recorded.

(e.g. particular image series or views; before and after processing versions of images to evaluate/validate the effects of processing; analysis results)

The input data for the assessment of measurable lesions include scalar values for each tumor volume, the sum of all measured volumes (SOV) at each time-point, and their corresponding changes with respect to the baseline or nadir.

10.2. Methods to Be Used

Describe how the interpretation should be performed. (For example, definition of key anatomical points or pathology boundaries; scoring scales and criteria such as BIRADS, interpretation schema such as RECIST, related annotations)

QIBA Protocol editor's note: The corresponding QIBA Profile describes a system of metrology. Compliance leads to confidence that time-point changes in a measurable neoplastic mass of >30% are highly likely to represent a true evolution in tumor biology, not measurement noise. Recommendations about patient management decisions that might follow from the measurement of change are outside the scope of the QIBA Profile. There are no response assessment criteria presented in this section for making judgments about multiple tumors within a given patient. QIBA has not yet examined the evidence that leads to recommendations about how to manage patients based on changes in individual tumors or ensembles of metastases within patients.

The qualitative assessment of non-target lesions is not addressed by the QIBA Profile.

10.3. Required Characteristics of Resulting Data

The results of image analysis should produce confidence that changes >30% are biological, and not simply an artifact of measurement variability.

10.4. Platform-specific Instructions

Appendix G.5 provides instructions for specific models/versions that can be expected to produce data meeting the requirements of Section 10.3.

10.5. Reader Training

Compliance with the QIBA Profile is essential for the claims to be valid. All actors who participate in image acquisition, processing, and analysis must be familiar with the relevant passages of the QIBA Profile that govern their behavior. Otherwise, the issues surrounding reader training, however critical, are nonetheless outside the scope of this imaging protocol.

10.6. Archival Requirements

See 11.7.

10.7. Quality Control

See 12.7.

11. Archival and Distribution of Data

Describe the required data formats, transmission methods, acceptable media, retention periods, …

(e.g. Is the site required to keep local copies in addition to transmitting to the trial repository? Must all intermediate data be archived, or just final results? At what point may various data be discarded?)

11.1. Central Management of Imaging Data

Communication plans, data transmittal plans, and archiving requirements are left to the owners of the clinical trial protocol or the local standards of care for the treatment of individual patients.

Note: The submission of films for digitization is rarely compliant with the QIBA Profile. When digitized films are submitted, they must contain a ruler or quantification will not be possible.

11.2. De-identification / Anonymization Schema(s) to Be Used

The de-identification software should be certified as fit-for-purpose by regulatory authorities at both the site of origin and site of receipt.

All personal patient information that is not needed for achieving the specific aims of the trial should be removed. Pre-specified data, such as height, weight, and in some cases, sex, race, or age, may be retained if it is essential for achieving the specific aims of the study and as such has been approved for use by regulatory authorities. Anonymization software should also retain DICOM information regarding slice locations, slice thickness, reconstruction interval, pixel size and FOV.

Data should be transferred to a "quarantine area" of a "safe harbor" for cleaning and certification of de-identification by professional research organizations or trained operators using procedures that have been certified by regulatory authorities at the site of receipt. Quality assurance procedures performed by the recipient should verify that the images that will be submitted for analysis have been properly de-identified. Images that were not properly de-identified prior to receipt by the central archiving facility should be obliterated after assuring that copies conform to quality standards for patient privacy.

11.3. Primary Source Imaging Data

This protocol presumes no archiving the pre-reconstruction image data.

11.4. Reconstructed Imaging Data

Reconstructed images shall be archived locally, formatted as either DICOM CT image objects or DICOM Enhanced CT image objects.

Retention period and policy are left to the Clinical Trial Protocol author or local standards of care.

11.5. Post-Processed Data

No post processing is specified; however, if post-processing is performed, the images shall be archived as DICOM objects as described in 11.4.

11.6. Analysis Results

Segmentation results may be recorded as DICOM Segmentation Objects, or STL Model Files.

The data described in 9.3 may be provided in any of the following formats:

- DICOM SR

- DICOM RTSS

• DICOM secondary capture

• XLS, CSV, XML

11.7. Interpretation Results

The QIBA Profile claims that changes in tumor volume of >30% are likely to represent true changes in tumor biology, not measurement error. Otherwise, interpretation of the results is left to the attending physicians taking care of individual patients and/or the owners of the clinical protocol.

12. Quality Control

12.1. QC Associated with the Site

12.1.1. Quality Control Procedures

Describe required procedures and documentation for routine and periodic QC for the site and various pieces of equipment.

The imaging system and workflow must be compliant with the QIBA Profile. Otherwise, details are left to the local institution or the owners of the clinical trial protocol.

12.1.2. Baseline Metrics Submitted Prior to Subject Accrual

List required baseline metrics and submission details.

The imaging system and workflow must be compliant with the QIBA Profile. Procedures for site qualification are left to the owners of the clinical trial protocol.

12.1.3. Metrics Submitted Periodically During the Trial

List required periodic metrics and submission details.

None specified. Details are left to the local institution or the owners of the clinical trial protocol.

12.2. QC Associated with Imaging-related Substance Preparation and Administration

None specified. Details are left to the local institution or the owners of the clinical trial protocol.

12.3. QC Associated with Individual Subject Imaging

Acquisition System Calibration: The QA/QC program shall be designed consistent with the goals of the clinical trial. This program may include (a) elements to verify that sites are performing the specified protocol correctly, and (b) elements to verify that sites' CT scanner(s) is (are) performing within specified calibration values. These may involve additional phantom testing that address a limited set of issues primarily relating dose and image quality (such as water calibration and uniformity). This phantom testing may be done in additional to the QA program defined by the device manufacturer as it evaluates performance that is specific to the goals of the clinical trial.

12.3.1. Phantom Imaging and/or Calibration

None specified. Details are left to the local institution or the owners of the clinical trial protocol.

12.3.2. Quality Control of the Subject Image and Image Data

Acknowledged as mission critical, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

12.4. QC Associated with Image Reconstruction

Acknowledged as mission critical, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

12.5. QC Associated with Image Processing

Acknowledged as mission critical, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

12.6. QC Associated with Image Analysis

Acknowledged as mission critical, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

12.7. QC Associated with Interpretation

Acknowledged as mission critical, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

13. Imaging-associated Risks and Risk Management

13.1. Radiation Dose and Safety Considerations

It is recognized that X-ray CT uses ionizing radiation. Exposure to radiation poses some risks to the patients. Acceptable levels of risk should be based on the relative

benefits of acquiring the images, and factor in parameters such as age and disease status (e.g., known disease or screening populations).

13.2. Imaging Agent Dose and Safety Considerations

Acknowledged, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

13.3. Imaging Hardware-specific Safety Considerations

Acknowledged, but not specified by the QIBA Profile. Details are left to the local institution or the owners of the clinical trial protocol.

13.4. Management and Reporting of Adverse Events Associated with Imaging Agent and Enhancer Administration

None specified by the QIBA Profile. Compliance with local regulations and the standard of care is assumed. Compliance with regulatory requirements for reporting adverse events during a clinical trial as specified by a sponsor is assumed.

13.5. Management and Reporting of Adverse Events Associated with Image Data Acquisition

None specified by the QIBA Profile. Compliance with local regulations and the standard of care is assumed. Compliance with regulatory requirements for reporting adverse events during a clinical trial as specified by a sponsor is assumed.

Appendix A: Acknowledgements and Attributions

This imaging protocol is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Volumetric Computed Tomography (v-CT) Technical Committee.

The v-CT technical committee is composed of scientists representing the imaging device manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, academia, government research organizations, professional societies, and regulatory agencies, among others. All work is classified as pre-competitive. A more detailed description of the v-CT group and its work can be found at the following web link: http://qibawiki.rsna.org/index.php?title=Volumetric_CT

Contributors to this imaging protocol from the Volumetric CT Technical Committee included the following people (in alphabetical order):

QIBA Protocol editor's note: No one has yet endorsed this protocol.

Contributors to this imaging protocol from the Extended Pharma Imaging Group included the following people (in alphabetical order):

QIBA Protocol editor's note: No one has yet endorsed this protocol. If you or your organization want to sign on, then please inform the editor by e-mailing mozley@merck.com

The v-CT Committee is deeply grateful for the remarkable support and technical assistance provided by the staff of the Radiological Society of North America.

Appendix B: Background Information

The long-term goal of the v-CT technical committee is to qualify the quantification of tumor volumes with x-ray computed tomography (CT) as a biomarker of response to treatment.

The specific aim of this image acquisition and processing protocol is to describe procedures that seem sufficient for quantifying the volumes of neoplastic masses that have relatively simple geometric shapes and are adequately demarcated from surrounding non-neoplastic tissues. This particular image acquisition and processing protocol is limited to masses that have measurable, in-plane, longest diameters of 10 mm or more. The basis for this limit is referenced in the corresponding QIBA Profile. Briefly, the surface area to volume ratio becomes too small in tumors with a longest diameter of less than 10 mm. The QIBA Profile on which this protocol is based claims that following these image acquisition and processing procedures will produce volume measures with a 95% confidence interval of less than 30%.

The protocol describes, in predominantly chronological order, procedures that are required to achieve this level of precision.

The protocol describes procedures that should be universally followed in this setting, regardless of the instrument that is used to acquire the data. It also provides links to tables that list specific settings on various makes-and-models of CT scanners.

This protocol should be considered for use in the care of individual patients in conventional medical settings, as well as in clinical trials of new therapies for solid tumors.

Appendix C: Conventions and Definitions

Acquisition vs. Analysis vs. Interpretation

This document organizes acquisition, reconstruction, post-processing, analysis and interpretation as sequential steps in a workflow that transforms data to information to knowledge.

Acquisition, reconstruction and post-processing address the collection and structuring of new data from the subject. Analysis consists of those computational steps that transform the data into information by extracting important values. Interpretation is primarily considered to be judgment that transforms the information into knowledge.

Judgment and the transformation of knowledge into wisdom are beyond the scope of this document.

Other Definitions

Unless explicitly described above or in the corresponding QIBA Profile, QIBA has not yet examined the evidence required to offer any other definitions.

Appendix D: Documents included in the imaging protocol (e.g., CRFs)

Not specified by the QIBA Profile. These are left to the owners of the clinical trial.

Appendix E: Associated Documents (derived from the imaging protocol or supportive of the imaging protocol)

Not specified by the QIBA Profile. These are left to the owners of the clinical trial.

Appendix F: TBD

Appendix G: Model-specific Instructions and Parameters

For acquisition modalities, reconstruction software and software analysis tools, profile compliance requires meeting the activity specifications above.

This Appendix provides, as an informative tool, some specific acquisition parameters, reconstruction parameters and analysis software parameters that are expected to be compatible with meeting the profile requirements. Just using these parameters without meeting the requirements specified in the profile is not sufficient to achieve compliance. Conversely, it is possible to use different compatible parameters and still achieve compliance.

These settings were determined to be reasonable by the QIBA CT 1C groundwork study team.

Sites using models listed here are encouraged to consider using these parameters for both simplicity and consistency. Sites using models not listed here may be able to devise their own settings that result in data meeting the requirements.

Table Model-specific Parameters for Acquisition Devices

IMPORTANT NOTE: <u>The presence of a product model/version in the table does not imply it has demonstrated compliance with the QIBA Profile.</u> Refer to the QIBA Compliance Statement for the product.

Acquisition Device	Settings Compatible with Compliance	
GE Discovery HD750 sct3	kVp	120
	Number of Data Channels (N)	64
	Width of Each Data Channel (T, in mm)	0.625
	Gantry Rotation Time in seconds	1
	mA	120
	Pitch	0.984
	Scan FoV	Large Body (500mm)
Philips Brilliance iCT IDT mx8000	kVp	120
	Number of Data Channels (N)	16
	Width of Each Data Channel (T, in mm)	0.75
	Gantry Rotation Time in seconds	0.75
	Effective mAs	50
	Pitch	1.0
	Scan FoV	500

Acquisition Device	Settings Compatible with Compliance	
Philips Brilliance 64	kVp	120
	Number of Data Channels (N)	64
	Width of Each Data Channel (T, in mm)	0.625
	Gantry Rotation Time in seconds	0.5
	Effective mAs	70
	Pitch	0.798
	Scan FoV	500
Siemens Sensation 64	kVp	120
	Collimation (on Operator Console)	64 x 0.6 (Z-flying focal spot)
	Gantry Rotation Time in seconds	0.5
	Effective mAs	100
	Pitch	1.0
	Scan FoV	500
Toshiba Aquilion 64	kVp	120
	Number of Data Channels (N)	64
	Width of Each Data Channel (T, in mm)	0.5
	Gantry Rotation Time in seconds	0.5
	mA	25
	Pitch	.828
	Scan FoV	Medium and Large

Table Model-specific Parameters for Reconstruction Software

IMPORTANT NOTE: The presence of a product model/version in the table does not imply it has demonstrated compliance with the QIBA Profile. Refer to the QIBA Compliance Statement for the product.

Reconstruction Software	Settings Compatible with Compliance	
GE Discovery HD750 sct3	Reconstructed Slice Width, mm	1.25
	Reconstruction Interval	1.0mm
	Display FOV, mm	350
	Recon kernel	STD
Philips	Reconstructed Slice Width, mm	1.00

Reconstruction Software	Settings Compatible with Compliance	
Brilliance 16 IDT mx8000	Reconstruction Interval	1.0mm (contiguous)
	Display FOV, mm	350
	Recon kernel	B
Philips Brilliance 64	Reconstructed Slice Width, mm	1.00
	Reconstruction Interval	1.0mm (contiguous)
	Display FOV, mm	350
	Recon kernel	B
Siemens Sensation 64	Reconstructed Slice Width, mm	1.00
	Reconstruction Interval	1.0mm
	Display FOV, mm	350
	Recon kernel	B30
Toshiba Aquilion 64	Reconstructed Slice Width, mm	1.00
	Reconstruction Interval	1.0mm
	Display FOV, mm	350
	Recon kernel	FC11

Table Model-specific Parameters for Image Analysis Software

IMPORTANT NOTE: The presence of a product model/version in the table does not imply it has demonstrated compliance with the QIBA Profile. Refer to the QIBA Compliance Statement for the product.

Image Analysis Software	Settings Compatible with Compliance	
Siemens LunCARE	a	<settings to achieve…>
	b	<settings to achieve…>
	c	<settings to achieve…>
	d	<settings to achieve…>
GE Lung VCAR	e	<settings to achieve…>
	f	<settings to achieve…>
	g	<settings to achieve…>
	h	<settings to achieve…>

Image Analysis Software	Settings Compatible with Compliance	
R2 ImageChecker CT Lung System	i	<settings to achieve…>
	j	<settings to achieve…>
	k	<settings to achieve…>
	l	<settings to achieve…>
Definiens (name specific product)	m	<settings to achieve…>
	n	<settings to achieve…>
	o	<settings to achieve…>
	p	<settings to achieve…>
Median (name specific product)	q	<settings to achieve…>
	r	<settings to achieve…>
	s	<settings to achieve…>
	t	<settings to achieve…>
Intio (name specific product)	u	<settings to achieve…>
	v	<settings to achieve…>
	w	<settings to achieve…>
	x	<settings to achieve…>