

Quantitative
Imaging
Biomarkers
Alliance



QIBA Profile: CT Tumor Volume Change for Advanced Disease (CTV-AD)

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Stage 3: Technically Confirmed

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1. Executive Summary

75 A QIBA Profile is an implementation guide for generating a biomarker. The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker.

Profile development is an evolutionary, phased process; this Profile is in the Consensus stage. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document's context: http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages.

80 The **Claim** (Section 2) describes the biomarker performance target. The **Profile Requirements** (Section 3) constrain **Activities** contributing to generating the biomarker. **Actors** that participate in those activities have requirements as necessary to achieve the Claim. **Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.

85 This QIBA Profile (CT Tumor Volume Change for Advanced Disease) addresses tumor volume change which is often used as a biomarker of disease progression or response to treatment. It places requirements on actors (Scanners, Technologists, Physicists, Radiologists, Reconstruction Software and Image Analysis Tools) involved in activities (Periodic QA, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis).

90 The requirements are primarily focused on achieving sufficient accuracy and reducing variability of the tumor volume measurements. The Claim (biomarker performance target) is that:

A true change in a tumor volume has occurred with 95% confidence if the measured change is larger than 24%, 29% or 39% when the longest in-plane diameter is initially 50-100mm, 35-49mm or 10-34mm, respectively.

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This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, regulators of such products, purchasers of such products and investigators designing trials with imaging endpoints.

100 For convenience, the QIBA website also provides a "checklist" document which has re-grouped the requirements from Section 3 for each Actor to more easily communicate and confirm conformance of sites, staff and equipment to this Profile.

Note that this Profile document only states requirements to achieve the Claim, not "requirements on standard of care." Further, meeting the goals of this Profile is secondary to properly caring for the patient.

105 QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

2. Clinical Context and Claim(s)

Clinical Context

110 Quantifying the volumes of thoracic tumors and measuring tumor longitudinal changes within subjects (i.e. evaluating growth or regression with image processing of CT scans acquired at different timepoints).

Conformance with this Profile by all relevant staff and equipment supports the following claims (see Disclaimer in Discussion below):

115 **Claim 1: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 24% when the longest in-plane diameter at baseline is within 50-100mm.**

120 **Claim 2: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 29% when the longest in-plane diameter at baseline is within 35-49mm.**

125 **Claim 3: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 39% when the longest in-plane diameter at baseline is within 10-34mm.**

Claim 4: The tumor volume measurement performance, expressed as within-tumor coefficient of variation (wCV), is 0.085, 0.103, and 0.141 respectively for tumors with diameters of 50-100mm, 35-49mm, and 10-34mm. The resulting 95% confidence interval for the true change in volume for several example measured tumors is:

Baseline Volume (Diameter)	Subsequent Volume (Diameter)	Volume Change Confidence Interval Calculation	95% Confidence Interval of True Volume Change
524 cm ³ (100mm)	65 cm ³ (50mm)	-459 cm ³ ± 88 cm ³	[-547 cm ³ , -371 cm ³]
34 cm ³ (40mm)	268 cm ³ (80mm)	234 cm ³ ± 45 cm ³	[189 cm ³ , 279 cm ³]
0.5 cm ³ (10mm)	4.2 cm ³ (20mm)	3.7 cm ³ ± 1.2 cm ³	[2.5 cm ³ , 4.9 cm ³]

130 computed as $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV_1)^2 + (Y_2 \times wCV_2)^2}$, where Y_1 and Y_2 are the volume measurements at baseline and the subsequent timepoint, and wCV_1 and wCV_2 are the wCV estimates corresponding to these measurements.

135 Note: The computed confidence interval in the first example includes a volume reduction of 547 cm³ for a tumor with an initial measured volume of 524 cm³ because it accounts for variability in the initial measurement (i.e. the tumor may have been larger).

These claims hold when:

- the tumor is measurable at both timepoints (i.e., tumor margins are sufficiently conspicuous and geometrically simple enough to be recognized on all images in both scans; the tumor is unattached to other structures of equal density)

- **the tumor longest in-plane diameter is between 10 mm (volume 0.5 cm³) and 100 mm (volume 524 cm³) at both timepoints**

Discussion

Disclaimer: While this Profile is written to be applicable to thoracic tumors, the quantitative performance values were derived from analysis of tumor volumetry consisting solely of lung data. The claims assert that this performance holds for tumors throughout the thorax based on the expert opinion of key contributors to this Profile who anticipate that performance for segmentation and volumetry of tumors in the liver, lymph nodes and elsewhere will meet or exceed performance in the lung.

Confidence Thresholds:

The 95% confidence thresholds ($\pm 24\%$, $\pm 29\%$, $\pm 39\%$) in Claims 1, 2 and 3 can be thought of as “error bars” or “noise” around the measurement of volume change. If change is measured within this range, it cannot be ascertained that there has really been a change. However, if a tumor changes size beyond these limits, it can be ascertained with 95% statistical confidence that there has been a true change in the size of the tumor, and the perceived change is not just measurement variability. Note that this does not address the biological significance of the change, just the likelihood that the measured change is real.

Clinical interpretation (progression/response):

The existence of a true change is described in Claims 1, 2 and 3 in terms of the minimum measured change required to be 95% confident a change has occurred. So, to be 95% confident there has been a true increase or decrease in tumor volume, the measured change should be at least 24% for a tumor that had a longest in-plane diameter of between 50mm and 100mm at baseline (and at least 29% or 39% for the next two size categories respectively).

Clinical interpretation (magnitude of change):

The magnitude of the true change is described in Claim 4 in terms of the 95% Confidence Interval of the measured volume change value. (See Confidence Interval of Result in section 3.2.2 below). If volume was measured as 34 cm³ at baseline and 268 cm³ at follow-up (corresponding to a diameter change from 40mm to 80mm), then the 95% CI for the true change would be an increase in volume of 234 cm³ \pm 45. A confidence interval that contains zero indicates one should not conclude a true change has occurred.

Whether a change in tumor volume constitutes *clinically meaningful* disease progression or response is a distinct decision that requires a clinician’s judgment. There are currently no validated response criteria based on volume. The most commonly used response criteria in solid tumors, RECIST 1.1, uses unidimensional measurements. For comparison, RECIST 1.1 specifies that progression has occurred when there has been a 20% increase in tumor diameter from baseline, which corresponds to a 73% increase in volume for a spherical tumor, and favorable treatment response has occurred when there has been a 30% decrease in diameter, which corresponds to a 66% decrease in volume.

The lower bound of 10mm on the tumor longest in-plane diameter is set to limit the variability introduced when approaching the resolution of the dataset, e.g. partial volume. The upper bound of 100mm is set to limit the variability introduced by more complex tumor morphology and organ involvement, and also to keep performance assessment procedures manageable.

While the claims have been informed by an extensive review of the literature and expert consensus, they have not yet been fully substantiated by studies that strictly conform to the specifications given here. The expectation is that during field test, data on the actual field performance will be collected and appropriate revisions will be made to the Claims and/or the details of the Profile. At that point, this caveat may be removed or re-stated.

The performance values in Claims 1, 2, 3 and 4 reflect the likely impact of variations permitted by this Profile. The Profile requires that for a given tumor the same conformant radiologist actor and image analysis tool actor must make the measurement at both timepoints. If a different radiologist and/or image analysis tool was used at the baseline, this means the current radiologist and image analysis tool must repeat the baseline measurement for the result to be conformant with this Profile. The Profile permits the other actors (scanner, technologist, physicist, etc.) to differ at the two timepoints, i.e. it is not required that the same scanner be used for both exams of a patient. If one or more of the actors that are permitted to differ are the same, such as the same scanner for both exams, the implementation is still conformant with this Profile and it is expected that the measurement performance will be improved. To give a sense of the possible improvement, the following table presents expected precision for alternate scenarios; however, except for the bolded column, these precision values are not Claims of this Profile. If the radiologist or image analysis tool are different (or any other requirement of the Profile is not met), the measurement might still be clinically useful, but the measurement is no longer conformant with the Profile and the measurement Claims should not be presumed.

Table 2-1: Minimum Detectable Change in Tumor Volume (Informative)

Tumor Diameter	Different Scanner				Same Scanner			
	Different Radiologist		Same Radiologist		Different Radiologist		Same Radiologist	
	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool
>50mm	43%	24%	43%	24%	37%	10%	37%	8%
35-49mm	67%	33%	65%	29%	62%	22%	60%	14%
10-34mm	139%	120%	80%	39%	136%	117%	75%	28%

Notes:

1. Scanner actors being different means the scanner used at the two timepoints were different models (from the same or different vendors). Two scanners with different serial numbers but of the same model are considered to be the same Scanner actor.
2. Precision is expressed here as the repeatability or reproducibility coefficient, depending on the column.
3. A measured change in tumor volume that exceeds the relevant precision value in the table indicates 95% confidence in the presence of a true change.
4. Minimum detectable differences can be calculated from the following formula: $1.96 \times \sqrt{2 \times wCV^2}$, where wCV is estimated from the square root of the sum of the variances from the applicable sources of uncertainty (which makes the assumption that the variance components are additive, an assumption that has not yet been tested).
5. The estimates of the sources of variation were derived from several groundwork studies, some of which were performed on phantoms and some of which were performed on human subjects.

3. Profile Requirements

The Profile is documented in terms of “Actors” performing “Activities”. Equipment, software, staff or sites may claim conformance to this Profile as one or more of the “Actors” in the following table.

Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced Section.

Table 3-1: Actors and Required Activities

Actor	Activity	Section
Site	Site Conformance	3.1
Scanner	Product Validation	3.2
Reconstruction Software	Product Validation	3.2
Image Analysis Tool	Product Validation	3.2
Radiologist	Staff Qualification	3.3
	Protocol Design	3.5
	Subject Handling	3.6
	Image QA	3.9
	Image Analysis	3.10
Physicist	Periodic QA	3.4
	Protocol Design	3.5
Technologist	Subject Handling	3.6
	Image Data Acquisition	3.7
	Image Data Reconstruction	3.8

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. QIBA Conformance Statements for Scanners, Reconstruction Software and Image Analysis Tools shall describe configuration settings or “Model-specific Parameters” (e.g. protocols) used to achieve conformance.

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a “shall” in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable and the

230 radiologist or supervising physician is expected to do so when required by the best interest of the patient or
 235 research subject. How study sponsors and others decide to handle deviations for their own purposes is
 entirely up to them.

For the Scanner, Reconstruction Software and Image Analysis Tool actors, while it will typically be the
 235 manufacturer who claims the actor is conformant, it is certainly possible for a site to run the necessary
 tests/checks to confirm conformance and make a corresponding claim. This might happen in the case of an
 older model device which the manufacturer is no longer promoting, but which a site needs a conformance
 claim to participate in a clinical trial.

The Physicist actor represents the person at the site responsible for managing the equipment performance
 related specifications. At some sites this will be a staff physicist, and at other sites it may be a person who
 240 manages a contractor or a service provided by a vendor.

The sequencing of the Activities specified in this Profile are shown in Figure 1:

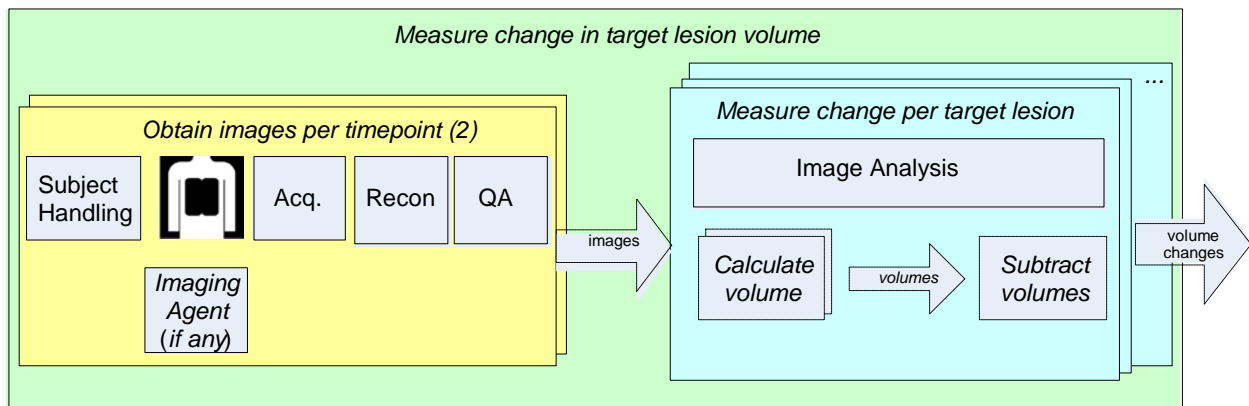


Figure 1: CT Tumor Volumetry – Activity Sequence

The method for measuring change in tumor volume may be described as a pipeline. Subjects are prepared
 245 for scanning, raw image data is acquired, and images are reconstructed and evaluated. Such images are
 obtained at two (or more) time points. Image analysis assesses the degree of change between two time
 points for each evaluable target tumor by calculating absolute volume at each time point and subtracting.
 When expressed as a percentage, volume change is the difference in volume between the two time points
 250 divided by the volume at time point 1. Although this introduces some asymmetry (volume measurements
 of 50cm³ and 100cm³ represent either a 100% increase or a 50% decrease depending on which was
 measured first), it is more familiar to clinicians than using the average of the two timepoints as the
 denominator.

Criteria for clinical interpretation of volume change in relation to patient management are beyond the
 255 scope of this document. Detection and classification of tumors as target is also beyond the scope of this
 document.

The Profile does not intend to discourage innovation, although it strives to ensure that methods permitted
 by the Profile requirements will result in performance that meets the Profile Claim. The above pipeline
 provides a reference model. Algorithms which achieve the same result as the reference model but use

different methods may be permitted, for example by directly measuring the change between two image sets rather than measuring the absolute volumes separately. Developers of such algorithms are encouraged to work with the appropriate QIBA committee to conduct any groundwork and assessment procedure revisions needed to demonstrate the requisite performance.

The requirements included herein are intended to establish a baseline level of capabilities. Providing higher performance or advanced capabilities is both allowed and encouraged. The Profile does not intend to limit how equipment suppliers meet these requirements.

This Profile is “lesion-oriented”. The Profile requires that images of a given tumor be acquired and processed the same way each time. It does not require that images of tumor A be acquired and processed the same way as images of tumor B; for example, tumors in different anatomic regions may be imaged or processed differently, or some tumors might be examined at one contrast phase and other tumors at another phase.

Since much of this Profile emphasizes performing subsequent scans consistent with the baseline scan of the subject, the parameter values chosen for the baseline scan are particularly significant and should be considered carefully.

In some scenarios, the “baseline” might be defined as a reference point that is not necessarily the first scan of the patient.

3.1. Site Conformance

This activity involves establishing the overall conformance of an imaging site to this Profile. It includes criteria to confirm the conformance of each of the participating Actors at the site.

3.1.1 DISCUSSION

A site conforms to the Profile if each relevant actor conforms to each requirement assigned in the Activities of the Profile. Activities represent steps in the chain of preparing for and generating biomarker values (e.g. product validation, system calibration, patient preparation, image acquisition, image analysis, etc.).

Since a site may assess conformance actor by actor, a checklist document is available (Appendix C) which extracts, for convenient reference, all the requirements in this Profile and regroups the requirements by Actor.

Sites may be able to obtain a QIBA Conformance Statement for some actors (e.g. Scanners) attesting to their conformance to this Profile, rather than the site having to confirm conformance themselves.

3.1.2 SPECIFICATION

Parameter	Actor	Specification
Scanners	Site	Shall confirm all participating scanners conform to this Profile.
Reconstruction Software	Site	Shall confirm all participating reconstruction software conforms to this Profile.

Parameter	Actor	Specification
Image Analysis Tools	Site	Shall confirm all participating image analysis tools conform to this Profile.
Radiologists	Site	Shall confirm all participating radiologists conform to this Profile.
Physicists	Site	Shall confirm all participating physicists conform to this Profile.
Technologists	Site	Shall confirm all participating technologists conform to this Profile.

290 **3.2. Product Validation**

This activity involves evaluating the product Actors (Scanner, Reconstruction Software, and Image Analysis Tool) prior to their use in the Profile (e.g. at the factory). It includes validations and performance assessments that are necessary to reliably meet the Profile Claim.

3.2.1 DISCUSSION

295 Performance measurements of specific protocols are not addressed here. Those are included in section 3.5.2.

Volume Calculation values from a segmentation may or may not correspond to the total of all the segmented voxels. The algorithm may consider partial volumes, do surface smoothing, tumor or organ modeling, or interpolation of user sculpting of the volume. The algorithm may also pre-process the images prior to segmentation. Note that volume calculation could potentially be derived from non-segmentation-based approaches, such as model-based estimators.

Segmentation may be performed automatically by a software algorithm, manually by a human observer, or semi-automatically by an algorithm with human guidance/intervention, for example to identify a starting seed point, stroke, or region, or to edit boundaries.

305 If a human observer participates in the segmentation, either by determining while looking at the images the proper settings for an automated process, or by manually editing boundaries, the settings for conversion of density into display levels (window and level) should either be fixed during the segmentation process or documented so that observers can apply consistent display settings at future scans (or a different observer for the same scan, if multiple readers will read each scan, as for a clinical trial).

310 **Tumor Volume Computation** is assessed to confirm that the software is computing the volume correctly and confirm there is a reasonable lack of bias at individual timepoints.

Tumor Volume Change Repeatability is assessed to confirm that the software produces sufficiently consistent results over a set of test data. Recall that *repeatability* considers multiple measurements taken under the same conditions (same equipment, parameters, reader, algorithm, etc.) but different subjects, while *reproducibility* considers multiple measurements taken where one or more conditions have changed. So while the Profile Claims address reproducibility, this particular requirement is limited to repeatability. The target repeatability values were chosen based on the work referenced here:

- Athelougou M, Kim HJ, Dima A, et al., Algorithm Variability in the Estimation of Lung Nodule Volume From Phantom CT Scans: Results of the QIBA 3A Public Challenge. Acad Radiol 2016.
- Buckler AJ, Danagouljian J, Johnson K, et al., Inter-Method Performance Study of Tumor Volumetry Assessment on

Computed Tomography Test-Retest Data. Acad Radiol 2015; 22:1–16.

- Fenimore C, Lu ZQ, McNitt-Gray MF, et al., Clinician sizing of synthetic nodules to evaluate CT interscanner effects. RSNA 2012.
- McNitt-Gray MF, Kim GH, Zhao B, et al., Determining the Variability of Lesion Size Measurements from CT Patient Datasets Acquired Under "No Change" Conditions. Transl Oncol 2015 Feb; 8(1):55-64.
- Petrick NP, PhD, Kim HJ, Clunie DA, et al., Comparison of 1D, 2D, and 3D Nodule Sizing Methods by Radiologists for Spherical and Complex Nodules on Thoracic CT Phantom Images. Acad Radiol 2014; 21:30–40.

Methods that calculate volume change directly without calculating volumes at individual time points are acceptable so long as the results are conformant with the specifications set out by this Profile.

The Image Analysis Tool should be prepared to process the data from the two time points at the same time and support matching up the appearance of each tumor in both data sets in order to derive volume change values. Although it is conceivable that data from the two time points could be processed separately and the results of prior processing could be imported and matched, such interoperability mechanisms are not defined or mandated here and cannot be depended on to be present or used.

Reading Paradigms (such as the “sequential locked” paradigm described here) can reduce variability from inconsistent judgments (such as where to separate an attached tumor) but also have the potential to introduce subconscious biases. The current edition of the Profile does not prohibit the Image Analysis Tool from displaying the actual volume value from the previous timepoint since that might unnecessarily disqualify existing products. If it is determined to be the source of problems, it might be prohibited in future editions. Also, note that while the Image Analysis Tool is required to be capable of displaying the image from the previous timepoint, the radiologist is not required to look at it for every case. It is up to their judgment when to use that capability.

Storing segmentations and measurement results at different time points for access to an Image Analysis Tool is certainly a time- and cost-saving practice. For this to happen reliably, the data must be stored and conveyed in compatible format. Although DICOM Segmentation objects are appropriate to store tumor segmentations, and DICOM SR objects are appropriate to store measurement results, these standards are not yet deployed widely enough to justify making their support mandatory in this Profile. Similarly, conveying the segmentations and measurements from baseline (and other time points prior to the current exam) is not done consistently enough to mandate that it happen and to require their import into the Image Analysis Tool. Managing and forwarding the data files may exceed the practical capabilities of the participating sites.

Medical Devices such as the Image Analysis Tool are typically made up of multiple components (the hardware, the operating system, the application software, and various function libraries within those). Changes in any of the components can affect the behavior of the device. In this specification, the “device version” should reflect the total set of components and any changes to components should result in a change in the recorded device version. This device version may thus be different than the product release version that appears in manufacturer documentation.

For analysis methods that involve an operator (e.g. to draw or edit boundaries, set seed points or adjust parameters), the operator is effectively a component of the system, with an impact on the reproducibility of the measurements, and it is important to record the operator’s identify as well. Fully automated analysis software removes that source of variation; although even then, since a human is generally responsible for

the final results, they retain the power to approve or reject measurements so their identity should be recorded.

The Tumor Volume Change performance specification below includes the operator performance and is intended to be evaluated based on a typical operator (i.e. with standard training and experience). This should be kept in mind by manufacturers measuring the performance of their tools and sites validating the performance of their installation. Although the performance of some methods may depend on the judgment and skill of the operator, it is beyond this Profile to specify the qualifications or experience of the operator.

Confidence Interval of Result provides a range of plausible values for the change in tumor volume. The 95% confidence interval (CI) can be interpreted as follows: If the change in a tumor's volume over two timepoints is measured repeatedly and the 95% CI constructed for each measurement, then 95% of those CI ranges would contain the true volume of the tumor.

A reference implementation of a calculator that uses the specified equation is available at the following location: <http://www.accumetra.com/NoduleCalculator.html>

While it has been suggested that the provision of a calculator inside the Analysis Tool that takes a wCV value configured by the operator and displays the calculated 95% CI on the screen alongside each volume change measurement would be more convenient for the radiologist than requiring them to transcribe measurement values into a web tool, it is currently unclear whether providing such a calculator constitutes a product claim requiring detailed evidence for the FDA. For this reason the Confidence Interval of Result parameter has been made a suggestion and is not a requirement for conformance to the Profile.

Recording various details can be helpful when auditing the performance of the biomarker and the site using it. For example, it is helpful for the system to record the software version, set-up and configuration parameters used, or to be capable of recording the tumor segmentation boundary as a DICOM Segmentation. Model-based measurement tools should be capable of recording the model and parameters. Currently Analysis Tools are not required to systematically record the volume values and confidence intervals since it is assumed the radiologist will dictate any relevant values into the report.

It is up to products that do not use contours to propose a method for verification by the radiologist.

3.2.2 SPECIFICATION

Parameter	Actor	Requirement
Acquisition Protocol	Scanner	Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.
	Scanner	Shall prepare a protocol conformant with section 3.5.2 "Protocol Design Specification".
	Scanner	Shall validate that the protocol achieves an f50 value that is between 0.3 mm ⁻¹ and 0.5 mm ⁻¹ for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
	Scanner	Shall validate that the protocol achieves a standard deviation < 60HU.

Parameter	Actor	Requirement
		See 4.2. Assessment Procedure: Voxel Noise
Reconstruction Protocol	Reconstruction Software	Shall be capable of performing reconstructions and producing images with parameters set as specified in 3.5.2 "Protocol Design Specification".
Image Header	Reconstruction Software	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column in 3.5.2 "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance.
Multiple Tumors	Image Analysis Tool	Shall allow multiple tumors to be measured. Shall either correlate each measured tumor across time points or support the radiologist to unambiguously correlate them.
Reading Paradigm	Image Analysis Tool	Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint. Shall be able to re-process the first time point (e.g. if it was processed by a different Image Analysis Tool or Radiologist).
Tumor Volume Computation	Image Analysis Tool	Shall be validated to compute volume within 5% of the true volume. See 4.3 Assessment Procedure: Tumor Volume Computation.
Tumor Volume Repeatability	Image Analysis Tool	Shall be validated to achieve tumor volume repeatability with: <ul style="list-style-type: none"> • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Repeatability.
Tumor Volume Bias & Linearity	Image Analysis Tool	Shall be validated to achieve: <ul style="list-style-type: none"> • an overall tumor volume %Bias of less than the Allowable Overall %Bias • a tumor volume %Bias for each shape subgroup (spherical, ovoid, lobulated) of less than the Allowable Shape Subgroup %Bias • slope ($\hat{\beta}_1$) between 0.98 and 1.02 • quadratic-term ($\hat{\beta}_2$) between -0.05 and 0.05 The Allowable Overall %Bias and the Allowable Shape Subgroup %Bias are taken from Table 3.2.2-1 based on the overall repeatability coefficient achieved by the Image Analysis Tool using the assessment procedure in section 4.4. See 4.5 Assessment Procedure: Tumor Volume Bias and Linearity.
Confidence Interval of	Image Analysis Tool	Is encouraged to calculate and make available to the operator the 95% confidence interval for tumor volume change based on the equation:

Parameter	Actor	Requirement								
Result		$(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV_1)^2 + (Y_2 \times wCV_2)^2}$ <p>Where Y_1 and Y_2 is the volume measurement at timepoint 1 and 2, wCV_1 and wCV_2 is the within-nodule coefficient of variation for Y_1 and Y_2 as taken from the following table, D_1 and D_2 is the longest in-plane diameter of the volume at timepoint 1 and 2:</p> <table border="1"> <thead> <tr> <th>D_1, D_2</th> <th>10-34mm</th> <th>35-49mm</th> <th>50-100mm</th> </tr> </thead> <tbody> <tr> <td>$wCV_1,$ wCV_2</td> <td>0.141</td> <td>0.103</td> <td>0.085</td> </tr> </tbody> </table>	D_1, D_2	10-34mm	35-49mm	50-100mm	$wCV_1,$ wCV_2	0.141	0.103	0.085
D_1, D_2	10-34mm	35-49mm	50-100mm							
$wCV_1,$ wCV_2	0.141	0.103	0.085							

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**Table 3.2.2-1:
Allowable Tumor Volume %Bias based on Overall Repeatability Coefficient**

Overall Repeatability Coefficient \widehat{RC}	Allowable Overall %Bias (RMSE Target: 7.1%)	Allowable Shape Subgroup %Bias (RMSE Target: 7.8%)
0.05	6.60%	7.32%
0.06	6.37%	7.11%
0.07	6.09%	6.86%
0.08	5.75%	6.56%
0.09	5.35%	6.20%
0.10	4.88%	5.79%
0.11	4.30%	5.31%
0.12	3.59%	4.75%
0.13	2.63%	4.06%
0.14	0.84%	3.17%
0.15	0.00%	1.84%
0.155	0.00%	0.00%
0.16	n/a (failed repeatability)	n/a (failed repeatability)

3.3. Staff Qualification

395

This activity involves evaluating the human Actors (Radiologist, Physicist, and Technologist) prior to their participation in the Profile. It includes training, qualification or performance assessments that are necessary to reliably meet the Profile Claim.

3.3.1 DISCUSSION

400

These requirements, as with any QIBA Profile requirements, are focused on achieving the Profile performance target. Evaluating the medical or professional qualifications of participating actors is beyond the scope of this Profile.

Note: If the Radiologist has an Image Analyst prepare the measurement contours but the Radiologist still reviews and edits them, then the requirement is to validate the measurement performance of the Radiologist. If the Radiologist completely delegates performing the measurements to an Image Analyst, then requirement is to validate the measurement performance of the Image Analyst.

3.3.2 SPECIFICATION

Parameter	Actor	Specification
Tumor Volume Change Repeatability	Radiologist	<p>Shall, if operator interaction is required by the Image Analysis Tool to perform measurements, be validated to achieve tumor volume change repeatability with:</p> <ul style="list-style-type: none"> • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 <p>See 4.4. Assessment Procedure: Tumor Volume Repeatability.</p>

3.4. Periodic QA

This activity involves periodic quality assurance of the scanners that is not directly associated with a specific subject. Periodic QA includes calibrations, phantom imaging, performance assessments or validations that are necessary to reliably meet the Profile Claim.

3.4.1 DISCUSSION

This activity is focused on ensuring that the scanner is aligned/calibrated/functioning normally. Performance measurements of specific protocols are not addressed here. Those are included in section 3.5.

3.4.2 SPECIFICATION

Parameter	Actor	Requirement
QC	Physicist	<p>Shall perform relevant quality control procedures as recommended by the manufacturer.</p> <p>Shall record the date/time of QC procedures for auditing.</p>

3.5. Protocol Design

This activity involves designing acquisition and reconstruction protocols for use in the Profile. It includes constraints on protocol acquisition and reconstruction parameters that are necessary to reliably meet the Profile Claim.

3.5.1 DISCUSSION

The Profile considers Protocol Design to take place at the imaging site, however, sites may choose to make use of protocols developed elsewhere.

425 The approach of the specifications here is to focus as much as possible on the characteristics of the
resulting dataset, rather than one particular technique for achieving those characteristics. This is intended
to allow as much flexibility as possible for product innovation and reasonable adjustments for patient size
(such as increasing acquisition mAs and reconstruction DFOV for larger patients), while reaching the
performance targets. Again, the technique parameter sets in the QIBA Conformance Statements for
430 Scanners and Reconstruction Software may be helpful for those looking for more guidance.

The purpose of the minimum **scan duration** requirement is to permit acquisition of an anatomic region in a
single breath-hold, thereby preventing respiratory motion artifacts or anatomic gaps between breath-
holds. This requirement is applicable to scanning of the chest and upper abdomen, and is not required for
imaging of the head, neck, pelvis, spine, or extremities.

435 **IEC Pitch** is chosen to allow completion of the scan in a single breath hold.

Total Collimation Width (defined as the total nominal beam width, $N \times T$, where N is the number of detector
rows and T is the nominal tomographic section thickness, for example $64 \times 1.25 \text{mm}$) 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. Imaging protocols will seek to
440 strike a balance to preserve image quality while providing sufficient coverage to keep acquisition times
short.

Nominal Tomographic Section Thickness (T), the term preferred by the IEC, is sometimes also called the
Single Collimation Width. It affects the spatial resolution along the subject z-axis. It also affects image
noise.

445 Smaller voxels are preferable to reduce partial volume effects and provide higher accuracy due to higher
spatial resolution. The resolution/voxel size that reaches the analysis software is affected by both
acquisition parameters and reconstruction parameters. On the other hand thinner sections may result in
increased image noise.

450 X-ray CT uses ionizing radiation. Exposure to radiation can pose risks; however as the radiation dose is
reduced, image quality can be degraded. It is expected that health care professionals will balance the need
for good image quality with the risks of radiation exposure on a case-by-case basis. It is not within the
scope of this document to describe how these trade-offs should be resolved.

The acquisition parameter constraints here have been selected with scans of the chest, abdomen and pelvis
in mind.

455 Image reconstruction is modeled as a separate Activity in the QIBA Profile. Although it is closely related to
image acquisition, and is usually performed on the Scanner, reconstruction may be performed, or re-
performed, separate from the acquisition. Many reconstruction parameters will be influenced or
constrained by related acquisition parameters. This specification is the result of discussions to allow a
degree of separation in their consideration without suggesting they are totally independent.

460 Many reconstruction parameters can have direct or indirect effects on identifying, segmenting and
measuring tumors. To reduce this potential source of variance, all efforts should be made to have as many
of the parameters as possible consistent with the baseline. Reconstruction and acquisition parameters may

also interact with tumor characteristics such as size, shape, and density affecting the resulting volume estimate.

465 **Spatial Resolution** quantifies the ability to resolve spatial details and scales the impact of partial volume effects. Lower spatial resolution can make it difficult to accurately determine the borders of tumors, and as a consequence, decreases the accuracy and precision of volume measurements. Increased spatial resolution typically comes with an increase in noise which may degrade segmentation. If the spatial resolution is significantly different between the two timepoints, these impacts will change which can affect
470 repeatability. So both balance and consistency is desirable. Maximum spatial resolution is mostly determined by the scanner geometry (which is not usually under user control) and the reconstruction algorithm/kernel (over which the user has some choice).

Resolution is assessed (See section 4.1) in terms of the f50 value of the modulation transfer function (MTF) measured in a scan of a resolution phantom (such as module 1 of the CT Accreditation Program (CTAP)
475 phantom from the American College of Radiology). An implication of using the ACR phantom is that the resolution is assessed at only one distance from the isocenter. Although spatial resolution may vary with distance from the isocenter and tumors can be expected at various distances from the isocenter, it is considered fair to assume that resolution does not degrade drastically relative to the acceptable range of the resolution specification here. Since this Profile addresses tumors both in the lung and elsewhere in the
480 torso, the f50 is evaluated for both air and soft tissue edges.

Voxel Noise Metrics quantify the magnitude of the random variation in reconstructed CT numbers. Increased levels of noise can make it difficult to identify the boundary of tumors by humans and automated algorithms. If algorithms become uniformly more "noise tolerant", the maximum threshold may be raised. Decreased image noise is not always beneficial, if achieved through undesirable image manipulation (e.g.
485 extreme amounts of image smoothing that can affect resolution), or scanning technique (e.g. increases in radiation dose or decreases in resolution). The Profile does not currently define a minimum threshold, although it could be introduced as a means of forcing a balance between the goal of noise reduction, and other priorities.

The preferred metric for voxel noise is the standard deviation of reconstructed CT numbers over a uniform
490 region in a phantom. The use of standard deviation has limitations since it can vary with different reconstruction kernels, which will also impact the spatial resolution. While the Noise-Power Spectrum would be a more comprehensive metric, it is not practical to calculate (and interpret) at this time.

Voxel noise (pixel standard deviation in a region of interest) can be reduced by reconstructing images with greater thickness for a given mAs. It is not expected that the Voxel Noise be measured for each subject
495 scan, but rather the Scanner and Reconstruction Software be qualified for the expected acquisition and reconstruction parameters.

Note that specific constraints are not placed on most of the acquisition and reconstruction parameters in a protocol. It is presumed that significant changes to those parameters would result in non-conformant changes in Noise and Resolution. Changes that do not affect the Noise and Resolution are considered
500 insignificant.

Note also that most modern CT scanners are equipped with Automatic Exposure Control that adjusts the scanner radiation output to achieve pre-determined target noise levels in the images as a function of patient size. The qualification of CT scanner noise needs to account for this provision in that the noise is quantified in a standard size phantom object (such as the CT Accreditation Program phantom from the American College of Radiology) and further as a function of size if there is any concern that the noise performance may be outside compliance for larger sizes.

Reconstructed Image Thickness is the nominal width of the reconstructed image along the z-axis (reconstructed image thickness) since the thickness is not technically the same at the middle and at the edges.

Reconstructed Image Interval is the distance between two consecutive reconstructed images. An interval that results in noncontiguous data is unacceptable as it 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. Some studies have shown a benefit in accuracy and precision of overlapping reconstruction with the magnitude of the benefit increasing for smaller nodules.

Reconstructing datasets with **overlap** will increase the number of images and may slow down throughput, increase reading time and increase storage requirements. For multi-detector 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.

Reconstruction Characteristics influence the texture and the appearance of tumors in the reconstructed images, which may influence measurements. Characteristics here refer to the type of a reconstruction algorithm (filtered back projection (FBP) or iterative algorithms) and different reconstruction kernels utilized by the algorithm (if applicable, since model-based iterative reconstruction algorithms do not utilize kernels). 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. Kernel characteristics also interact with acquisition parameters and reconstruction algorithm types; a sharper kernel in a low-dose scan might make a greater difference with an FBP Algorithm than with an Iterative Algorithm. The characteristics of different tissues (e.g. lung) may call for the use of different kernels, and implementers are encouraged to use kernels suitable for the anatomic region and tissue imaged. The use of multiple kernels in a single study is not prohibited by the specification below, but any given tumor must be measured on images reconstructed using consistent kernels at each time point.

The **stability of HU** between time points and its effect on volume measurements is not fully understood as of the writing of this version of the Profile.

3.5.2 SPECIFICATION

Note: The Radiologist is responsible for the protocol parameters, although they may choose to use a protocol provided by the vendor of the scanner. The Radiologist is also responsible for ensuring that the protocol has been validated, although the Physicist actor is responsible for performing the validation. The

role of the Physicist actor may be played by an in-house medical physicist, a physics consultant or other staff (such as vendor service or specialists) qualified to perform the validations described. Protocol design should be done collaboratively between the physicist and the radiologist with the ultimate responsibility to the radiologist. Some parameters are system dependent and may require special attention from a physicist.

545

Parameter	Actor	Specification	DICOM Tag
Acquisition Protocol	Radiologist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this Profile.	
Total Collimation Width	Radiologist	Shall set to Greater than or equal to 16mm.	Total Collimation Width (0018,9307)
IEC Pitch	Radiologist	Shall set to Less than 1.5.	Spiral Pitch Factor (0018,9311)
Nominal Tomographic Section Thickness (T)	Radiologist	Shall set to Less than or equal to 1.5mm.	Single Collimation Width (0018,9306)
Scan Duration for Thorax	Radiologist	Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)
Reconstruction Protocol	Radiologist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this Profile.	
Reconstructed Image Thickness	Radiologist	Shall set to between 0.5mm and 2.5mm (inclusive).	Slice Thickness (0018,0050)
Reconstructed Image Interval	Radiologist	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap).	Spacing Between Slices (0018,0088)
In-plane Spatial Resolution	Physicist	Shall validate that the protocol achieves an f50 value between 0.3 mm^{-1} and 0.5 mm^{-1} for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution	
Voxel Noise	Physicist	Shall validate that the protocol achieves a standard deviation $< 60\text{HU}$. See 4.2. Assessment Procedure: Voxel Noise	

3.6. Subject Handling

This activity involves handling each imaging subject at each time point. It includes subject handling details that are necessary to reliably meet the Profile Claim.

3.6.1 DISCUSSION

550 This Profile will refer primarily to “subjects”, keeping in mind that the requirements and recommendations apply to patients in general, and subjects are often patients too.

Timing Relative to Index Intervention Activity

555 When the Profile is being used in the context of a clinical trial, refer to relevant clinical trial protocol for further guidance or requirements on timing relative to index intervention activity.

Timing Relative to Confounding Activities

This document does not presume any timing relative to other activities. Fasting prior to contemporaneous FDG PET scans or the administration of oral contrast for abdominal CT is not expected to have any adverse impact on this Profile.

Contrast Preparation and Administration

560 Contrast characteristics influence the appearance, conspicuity, and quantification of tumor volumes. Most studies upon which this Profile was based were conducted without contrast. But non-contrast CT might not permit an accurate characterization of some malignant visceral/nodal/soft-tissue tumors and assessment of their tumor boundaries.

565 The **use of contrast** material (intravenous or oral) may not be medically indicated in defined clinical settings or may be contra-indicated for some subjects. It is up to Radiologists and supervising physicians to determine if the contrast protocol is appropriate for the subject. They may omit intravenous contrast or vary administration parameters when required by the best interest of patients or research subjects, in
570 which case tumors may still be measured but the measurements will not be subject to the Profile claims.

It is important that the **Contrast Protocol** achieves a consistent phase and degree of enhancement. Bolus tracking is a good tool if available, but is not required. When using bolus tracking, be consistent between scans with where the ROI used for triggering is placed and the threshold used to trigger the scan. When
575 bolus tracking is not available, be consistent between the scans with the contrast volume, rate, scan timing after injection, and use (or lack) of a saline flush. The use of oral contrast material should be consistent for all abdominal imaging timepoints (although the tolerances for oral timing are larger than for intravenous).

580 Note: non-contrast at both timepoints is considered to be consistent enhancement at the two timepoints.

If oral contrast is used, it is recommended to record the total volume and type of contrast used. If intravenous contrast is used, it is recommended to record the type of contrast, actual total volume administered, concentration, injection rate, delay and whether a saline flush was used. Ideally this should be recorded in the image header by the Scanner. This may be by automatic interface with contrast administration devices in combination with text entry fields filled in by the Technologist. Alternatively, the
585 technologist may enter this information manually on a form that is scanned and included with the image data as a DICOM Secondary Capture image.

Subject Positioning

590 Positioning the subject Supine/Arms Up/Feet First has the advantage of promoting consistency (if it's
always the same, then it's always consistent with baseline), and reducing cases where intravenous lines go
through the gantry, which could introduce artifacts. Consistent positioning avoids unnecessary changes in
attenuation, changes in gravity induced shape and fluid distribution, or changes in anatomical shape due to
posture, contortion, etc. Significant details of subject positioning include the position of their arms, the
595 anterior-to-posterior curvature of their spines as determined by pillows under their backs or knees, the
lateral straightness of their spines. Prone positioning is not recommended. The sternum should be
positioned over the midline of the table. The Table Height and Centering should be adjusted so that the
mid-axillary line is at the widest part of the gantry.

600 Positioning the chest (excluding the breasts) in the center of the gantry improves the consistency of relative
attenuation values in different regions of the lung, and should reduce scan-to-scan variation from the effect
of dose modulation algorithms. The subject should be made comfortable, to reduce the potential for
motion artifacts and to facilitate compliance with breath holding instructions.

605 When the patient is supine, the use of positioning wedges under the knees and head is recommended so
that the lumbar lordosis is straightened and the scapulae are both in contact with the table. However, the
exact size, shape, etc. of the pillows is not expected to significantly impact the Profile Claim. It is expected
that clinical trial documentation or local clinical practice will specify their preferred patient positioning. An
approach that promotes scan-to-scan consistency is essential.

610 When imaging head and neck tumors, it is not unusual to use gantry tilt, or positioning aids to adjust the
slice orientation in the head and neck. Again, it is important to achieve reasonable consistency over
timepoints for a given patient.

615 The Subject Handling specification does not place requirements on patient positioning directly, but rather
has the radiologist disqualify measurements from the Profile when the positioning at the two time points is
different. Consistent positioning will help ensure the majority of studies are conformant and thus achieve
the Profile performance target.

620 Recording Subject Positioning and Table Heights in the image header is helpful for auditing and repeating
baseline characteristics. Bismuth breast shields (used by some to reduce radiation exposure in diagnostic
CT settings) increase image noise. The effect of breast shields on image quality may vary depending on the
type of shields and their positioning. The American Association of Physicists in Medicine currently does not
endorse the use of breast shields, recommending the use of other dose reduction methods, such as dose
625 modulation techniques, instead (<https://www.aapm.org/publicgeneral/BismuthShielding.pdf>). Thus, the
use of breast shields is not recommended for this Profile. If used, position breast shields so they do not
degrade the reconstructed images.

630 Artifact sources, in particular metal and other high density materials, can degrade the reconstructed
volume data such that it is difficult to determine the true boundary of a tumor. Due to the various scan
geometries, artifacts can be induced some distance from the artifact source. The simplest way to ensure
no degradation of the volume data is to remove the artifact sources completely from the patient during the
scan, if feasible. Although artifacts from residual oral contrast in the esophagus could affect the
measurement of small tumors near the esophagus, this is not addressed here.

635 Consistent centering of the patient avoids unnecessary variation in the behavior of dose modulation algorithms during scan.

Instructions to Subject During Acquisition

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

640 Since some motion may occur due to diaphragmatic relaxation in the first few seconds following full inspiration, a proper breath hold will include instructions like "Lie still, breathe in fully, hold your breath, and relax", allowing 5 seconds after achieving full inspiration before initiating the acquisition.

645 Efforts should be made to obtain consistent, reproducible, maximal inspiratory lung volume on all scans. The use of live breathing instructions given at a pace easily tolerated by the patient is strongly recommended. However, depending on local practice preference and expertise, the use of prerecorded breathing instructions may provide acceptable results. Compliance with breathing instructions should be monitored by carefully observing the movement of the chest wall and abdomen to insure that the
650 breathing cycle stays in phase with the verbal instructions. The scan should not be initiated until maximal inspiratory volume is reached and all movement has ceased.

To promote patient compliance, performing a practice round of the breathing instructions prior to moving the patient into the scanner also is strongly recommended. This will make the subject familiar with the
655 procedure, make the technologist familiar with the subject’s breathing rate, and allow the technologist to address any subject difficulties in following the instructions.

Sample breathing instructions:

- 1. "Take in a deep breath" (watch anterior chest rise)
- 660 2. "Breathe all the way out" (watch anterior chest fall)
- 3. "Now take a deep breath in.....in.....in.....in all the way as far as you can"
- 4. When chest and abdomen stop rising, say "Now hold your breath".
- 5. Initiate the scan when the chest and abdomen stop moving, allowing for the moment it takes for the diaphragm to relax after the glottis is closed.
- 665 6. When scan is completed, say "You can breathe normally"

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 repeatable and does not depend on the Technologist knowing where the tumors are located.

670 **Timing/Triggers**

The amount and distribution of contrast during acquisition can affect tumor appearance and conspicuity.

3.6.2 SPECIFICATION

Parameter	Actor	Specification
Contrast Protocol	Radiologist	Shall prescribe a contrast protocol (which may be No Contrast) that achieves enhancement consistent with baseline.
Use of	Radiologist	Shall determine whether the selected contrast protocol, if any, will achieve

Parameter	Actor	Specification
intravenous contrast		sufficient tumor conspicuity.
	Technologist	Shall use the prescribed intravenous contrast parameters.
Use of oral contrast	Radiologist	Shall determine whether the selected contrast protocol, if any, will achieve sufficient tumor conspicuity.
	Technologist	Shall use the prescribed oral contrast parameters.
Artifact Sources	Technologist	Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads and other metal equipment) such that they will not degrade the reconstructed CT volumes.
Table Height & Centering	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter. Shall position the patient such that the “sagittal laser line” lies along the sternum (e.g. from the suprasternal notch to the xiphoid process).
Breath hold	Technologist	Shall instruct the subject in proper breath-hold and start image acquisition shortly after full inspiration, taking into account the lag time between full inspiration and diaphragmatic relaxation.

3.7. Image Data Acquisition

675 This activity involves acquisition of image data for a subject at either time point. It includes details necessary to reliably meet the Profile Claim. This activity applies to every patient. The Protocol Design activity (Section 3.5) touches on some similar parameters, but addresses details that are not done for each patient, such as designing standard protocols and validating their performance with phantoms.

3.7.1 DISCUSSION

680 CT scans for tumor volumetric analysis can be performed on any equipment that complies with the specifications set out in this Profile. However, we strongly encourage performing all CT scans for an individual subject on the same scanner manufacturer, model and version which we expect will further reduce variation.

685 Many scan parameters can have direct or indirect effects on identifying, segmenting and measuring tumors. To reduce this potential source of variance, all efforts should be made to have as many of the scan parameters as possible consistent with the baseline.

690 **Acquisition Protocols** are often selected by the technologist at scan time based on the procedure requested in the modality worklist. For the measurements to be conformant, this Profile requires that the protocol used has been validated (e.g. by a physicist) to meet certain requirements and performance metrics (see Section 3.5.2). The site will need to find some way to communicate to the technologist which protocols have been validated. This may be something in the protocol names, or a paper list for the technologist to consult, or a special pick-list on the modality console. Or a site might validate ALL protocols for a given procedure so that any protocol the technologist selects will have been validated.

Image Header recordings of parameter values facilitates confirming conformance.

695 The **Localizer** provides an opportunity for the technologist to observe and mitigate artifact sources.

For subjects needing two or more **breath-holds** to fully cover an anatomic region, different tumors may be acquired on different breath-holds. It is still necessary that each tumor be fully included in images acquired within a single breath-hold to avoid discontinuities or gaps that would affect the measurement.

700 **Scan Plane** (transaxial is preferred) may differ between subjects due to the need to position for physical deformities or external hardware. For an individual subject, a consistent scan plane will reduce unnecessary differences in the appearance of the tumor. A vertical scan plane (no tilt) is expected for all imaging except some head and neck exams.

3.7.2 SPECIFICATION

Parameter	Actor	Specification	DICOM Tag
Acquisition Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose. (See 3.5.2 "Protocol Design Specification")	
Localizer	Technologist	Shall confirm on the localizer (scout) image the absence of artifact sources that could affect the planned volume acquisitions or alter the attenuation of lung nodules.	
Scan Duration for Thorax	Technologist	Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)

3.8. Image Data Reconstruction

705 This activity involves the reconstruction of image data for a subject at either time point. It includes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim. This activity applies to every patient. The Protocol Design activity (Section 3.5) touches on some similar parameters, but addresses details that are not done for each patient, such as designing standard protocols and validating their performance with phantoms.

710 3.8.1 DISCUSSION

Note that the requirement to "select a protocol that has been prepared and validated for this purpose" is not asking the technologist to scan phantoms before every patient, or to validate the protocol themselves. Sites are required in section 3.5.2 to have validated the protocols that the technologist will be using and conformance with the Profile depends on the technologist selecting those protocols.

715 **Reconstruction Protocol** affects the image pixel characteristics. As long as the protocol has been validated to achieve the required image characteristics then they are considered interchangeable. Requirements here imply a need to record and communicate the protocol selected and any significant modifications and make that information available to the radiologist for the QA Activity. The Profile does not dictate any specific method for this. Manual methods are acceptable.

720 **Reconstruction Field of View** is typically selected at the time of each scan and affects reconstructed pixel size because the fixed image matrix size of most reconstruction algorithms is 512x512. If it is necessary to expand the field of view to encompass more anatomy, the resulting larger pixels may be insufficient 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
 725 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 spatial resolution in each dimension. The spatial resolution of the reconstructed image depends on a number of additional factors including a strong dependence on the reconstruction kernel, however since the kernel is configured in the protocol, it's effect on the spatial
 730 resolution will have been evaluated by the f50 requirement in the Protocol Design activity (See 3.5.2).

3.8.2 SPECIFICATION

Parameter	Actor	Specification	DICOM Tag
Reconstruction Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose (See 3.5.2 "Protocol Design Specification").	
Reconstructed Image Thickness	Technologist	Shall set to between 0.5mm and 2.5mm (inclusive) if not set in the protocol.	
Reconstructed Image Interval	Technologist	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap) and consistent with baseline.	
Reconstruction Field of View	Technologist	Shall ensure the Field of View spans at least the full extent of the thoracic and abdominal cavity, but not substantially greater than that.	Reconstruction Field of View (0018,9317)

3.9. Image QA

This activity involves evaluating the reconstructed images prior to image analysis. It includes image criteria that are necessary to reliably meet the Profile Claim. This activity applies to every patient. Prior activities,
 735 such as Subject Handling (Section 3.6), include requirements that attempt to avoid issues mentioned here, but it is still necessary to confirm during this QA step whether or not those prior activities were successful.

3.9.1 DISCUSSION

This Image QA activity represents the portion of QA performed between image generation and analysis where characteristics of the content of the image are checked for conformance with the Profile. The Image
 740 QA details listed here are the ones QIBA has chosen to highlight in relation to achieving the Profile claim. It is expected that sites will perform many other QA procedures as part of good imaging practices.

The Radiologist is identified here as ultimately responsible for this activity; however sites may find it beneficial for technologists to review these details at the time of imaging and identify cases which might
 745 require repeating acquisition and/or reconstruction to address issues with patient motion or artifacts.

Similarly, some or all of these checks may be performed by the radiologist at reporting time to detect

whether the technologist was unsuccessful in avoiding them at acquisition time and as a result some or all of the tumor measurements may then be identified as not falling within the performance target of the Profile.

Patient positioning variation refers to differences in patient orientation (prone, supine, decubitus, etc.) and the use of positioning wedges. If the patient is supine at one time point and prone at another, then the direction of gravity changes and some tumors may deform differently in a cavity, be compressed differently by other structures, or be affected by deformations of the organ in which they are sited.

Scan Plane variation refers to differences in gantry tilt or differences in head/neck positioning. Since several factors that affect volumetry are not isotropic, changing the orientation of the tumor relative to the scan plane from one time point to another can increase variability.

Patient motion artifacts can manifest in a variety of ways, such as a perceptible tram tracking appearance of the bronchioles or blurring of the lung architectural contours with lung windows.

Dense object artifacts (both internal and external to the patient) can variably degrade the ability to assess tumor boundaries as discussed in section 3.6, resulting in poor change measures and repeatability.

Clinical conditions can also degrade the ability to assess tumor boundaries, or influence the structure of the tumor itself. For example, atelectasis, pleural effusion, pneumonia and/or pneumothorax can result in architectural changes to the lung surrounding a nodule. Necrosis may complicate decisions on the tumor extent.

Other than subject-specific factors, the following tumor characteristics can affect image quality.

Tumor Size can affect the accuracy of measurements. Both theoretical considerations and the groundwork projects done by QIBA indicate that for tumors that are small, errors in measurement represent a greater percentage of the measured size. For tumors that are smaller than the limits defined in this Profile, please see the Profile produced by the QIBA Small Nodule group for more information on imaging recommendations and performance claims. For tumors that are extremely large, the limitations on measurement are based less on imaging physics and more on anatomy. Such tumors are likely to cross anatomical boundaries and abut structures that make consistent segmentation difficult.

Tumor Margin Conspicuity refers to the clarity with which the boundary of the tumor can be discerned from the surroundings. Conspicuity can directly impact the ability to segment the tumor to properly determine its volume. Conspicuity problems can derive from poor contrast enhancement, from the inherent texture, homogeneity or structure of the tumor, or from attachment of the tumor to other structures.

Contrast Enhancement is required to be consistent between the two timepoints. A non-contrast scan at both timepoints satisfies that requirement.

Tumor Measurability is a general evaluation that is essentially left to the judgement of the radiologist, and it is their responsibility to oversee segmentation and disqualify tumors with poor measurability or inconsistent segmentation between the two timepoints. If the tumor has varying margin conspicuity on

795 different slices, or is conspicuous but has complex geometry, or the segmentation software is visibly failing, or the background didn't respond to contrast the same way in the two timepoints, the radiologist should disqualify the tumor. Conversely, if the tumor is attached to another structure but the radiologist is confident they can get consistent segmentation over the two timepoints, they may allow a tumor that would be otherwise disqualified.

800 **Tumor Shape** is not explicitly identified as a specification parameter. No specific tumor shapes are considered a priori unsuitable for measurement. Although groundwork has shown that consistent measurements are more readily achieved with simple shapes than with complex shapes (such as spiculated tumors), the descriptors for tumor size, tumor margin conspicuity and tumor measurability are felt to be sufficient. Moreover, complex shapes are even more difficult to assess accurately using simple linear
805 measurements, increasing the relative added value of volumetry.

Keep in mind that this Profile is "lesion-oriented". If one tumor in a study is excluded from the Profile Claim because the tumor does not conform with the specifications in this section, that does not affect other tumors in the same study which do conform with these specifications at both timepoints. Further, if a
810 future study results in the excluded tumor being conformant at two timepoints, then the claim holds across those two timepoints.

While the radiologist is responsible for confirming case conformance with the Image QA specifications in Section 3.9.2, it is left to individual sites to determine the best approach in their work environment for
815 capturing this audit data. Possible approaches include the use of a QIBA worksheet that captures this information, or asking the radiologist to dictate each parameter into the clinical report (e.g. the scan is free of motion or dense object artifacts, contrast enhancement is consistent with baseline, the tumor margins are sufficiently conspicuous").

3.9.2 SPECIFICATION

820 The Radiologist shall ensure that the following specifications have been evaluated for each tumor being measured.

Parameter	Actor	Specification
Patient Motion Artifacts	Radiologist	Shall confirm the images containing the tumor are free from artifact due to patient motion.
Dense Object Artifacts	Radiologist	Shall confirm the images containing the tumor are free from artifact due to dense objects, materials or anatomic positioning.
Clinical Conditions	Radiologist	Shall confirm that there are no clinical conditions affecting the measurability of the tumor.
Tumor Size	Radiologist	Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm ³ and 524 cm ³ .)
Tumor Margin Conspicuity	Radiologist	Shall confirm the tumor margins are sufficiently conspicuous and unattached to other structures of equal density to distinguish the volume of the tumor.

Parameter	Actor	Specification
Contrast Enhancement	Radiologist	Shall confirm that the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
Patient Positioning Consistency	Radiologist	Shall confirm that any tumor deformation due to patient positioning is consistent with baseline (e.g. tumors may deform differently if the patient is supine in one scan and prone in another).
Breath Hold Consistency	Radiologist	Shall confirm that the breath hold state and degree of inspiration is consistent with baseline.
Scan Plane Consistency	Radiologist	Shall confirm that the anatomical slice orientation (due to gantry tilt or patient head/neck repositioning) is consistent with baseline.
Reconstructed Image Thickness	Radiologist	Shall confirm that the reconstructed image thickness is between 0.5mm and 2.5mm, and consistent with baseline (e.g. within 0.5mm).
Field of View	Radiologist	Shall confirm that the image field of view (FOV) resulting from acquisition and reconstruction settings appears consistent with baseline.
Tumor Measurability	Radiologist	Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the radiologist is confident and prepared to edit the contour to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.

3.10. Image Analysis

This activity involves measuring the volume change for subjects over one or more timepoints. It includes criteria and procedures related to producing quantitative measurements from the images that are necessary to reliably meet the Profile Claim.

3.10.1 DISCUSSION

This Profile characterizes each designated tumor by its volume change relative to prior image sets.

This is typically done by determining the boundary of the tumor (referred to as segmentation), computing the volume of the segmented tumor and calculating the difference of the tumor volume in the current scan and in the baseline scan.

The Profile requires that the same Image Analysis Tool and the same Radiologist measure both timepoints of a given tumor. This requirement is due to the variability introduced when a different Image Analysis Tool and/or Radiologist is used between the two timepoints. See Table 2-1 and the related Discussion for more details.

The Analysis Tool is recommended (See section 3.2.2) to present to the Radiologist for each volume change the Confidence Interval of Result which indicates a range of plausible values for the change in tumor volume. The 95% confidence interval (CI) can be interpreted as follows: If the change in a tumor's volume

over two timepoints is measured repeatedly and the 95% CI constructed for each measurement, then 95% of those CI ranges would contain the true volume of the tumor.

Determination of which tumors should be measured is out of scope for this Profile. Such determination may be specified within a protocol or specified by formal response criteria standards, or may be determined by clinical requirements. Tumors to be measured may be designated by the oncologist or clinical investigator, by a radiologist at a clinical site, by a reader at a central reading facility, or they may be designated automatically by a software analysis tool.

3.10.2 SPECIFICATION

Parameter	Actor	Specification
Reading Paradigm	Radiologist	Shall re-process the first timepoint if it was processed by a different Image Analysis Tool or Radiologist.
Result Verification	Radiologist	Shall review & approve margin contours produced by the tool.

4. Assessment Procedures

To conform to this Profile, participating staff and equipment (“Actors”) shall support each activity assigned to them in Table 3-1.

To support an activity, the actor shall conform to the checklist of requirements (indicated by “shall language”) listed in the Specification table of that activity in Section 3.

Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement references an Assessment Procedure subsection here in Section 4.

4.1. Assessment Procedure: In-plane Spatial Resolution

This procedure can be used by a manufacturer or an imaging site to assess the In-plane Spatial Resolution of reconstructed images. Resolution is assessed in terms of the f50 value (in mm⁻¹) of the modulation transfer function (MTF). Loosely speaking, the MTF represents the blur of an infinitely small feature of interest, f50 represents the spatial frequency at which the contrast of the feature has decreased by 50%, and the inverse of the f50 value represents the size of a feature that would be degraded 50%. Thus, for an f50 value of 0.4 mm⁻¹, features that are 2.5mm (or smaller) would have their contrast degraded by 50% (or more).

The assessor shall first warm up the scanner’s x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.

The assessor shall scan a spatial resolution phantom, such as the ACR CT Accreditation Program (CTAP) Phantom’s module 1 or the AAPM TG233 phantom, which has a series of HU-value cylindrical inserts including one with soft-tissue equivalence. The acquisition protocol and reconstruction parameters shall

conform to this Profile (See Section 3.5.2, 3.7.2 and 3.8.2). The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2, i.e., the noise level during resolution assessment should correspond to that measured during noise assessment.

- 875 The phantom shall be positioned with the center of the phantom at isocenter and properly aligned along the z-axis. For further details, refer to Section C, Step 3 of the CT Accreditation Testing Instructions: <http://www.acraccreditation.org/~media/ACRAccreditation/Documents/CT/CT-Accreditation-Testing-Instructions.pdf>
- 880 When the scan is performed, the assessor shall generate an MTF curve, measured as an average of the MTF in the x-y plane along the edge of a target soft-tissue equivalent insert using AAPM TG233 or equivalent methodology as implemented in manufacturer analysis software, AAPM TG233 software or equivalent. The assessor shall then determine and record the f50 value, defined as the spatial frequency (in mm^{-1} units) corresponding to 0.5 MTF on the MTF curve.
- 885 The assessor shall also generate the MTF curve and determine the f50 value using the edge of the "air insert" (i.e. an empty cutout in the phantom). If the phantom does not have a cutout that provides an internal air edge to assess, it is permitted to use the outer edge of the phantom.
- 890 The procedure described above is provided as a reference method. This reference method and the method used by the particular scanner manufacturer for FDA submission of MTF values are accepted methods for this assessment procedure. Note that for iterative reconstruction, the manufacturer may have specific test methodologies appropriate for the given algorithm.
- 895 Sites may submit to QIBA a proposed alternative method and evidence that the results produced by the proposed method are equivalent to this reference method or to the manufacturer method. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.
- 900 This assessment procedure is applicable to conventional filtered back-projection and to iterative reconstruction.

Note that in addition to the x-y plane MTF, the AAPM TG233 phantom and software also provides an axial resolution measurement (MTF in the z-direction).

905 **4.2. Assessment Procedure: Voxel Noise**

This procedure can be used by a manufacturer or an imaging site to assess the voxel noise of reconstructed images. Voxel noise is assessed in terms of the standard deviation of pixel values when imaging a material with uniform density.

- 910 The assessor shall first warm up the scanner's x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations. The assessor shall then scan a phantom of uniform density, such as the ACR CT Accreditation Program (CTAP) Phantom's module 3, which includes a 20 cm diameter cylinder of water equivalent material. The phantom shall be placed at the isocenter of the scanner. The acquisition protocol and reconstruction parameters shall be conformant with

915 this Profile (See Section 3.5.2, 3.7.2 and 3.8.2). The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2.

When the scan is performed, the assessor shall select a single representative slice, likely close to the center, from the uniformity portion of the phantom.

920 A region of interest (ROI) of at least 400 mm² shall be placed near the center of the slice. The assessor shall record the values reported for the ROI mean and standard deviation.

925 The assessor is encouraged to record and retain the images and associated measurement details but it is not required beyond the two values listed above. Such details can be helpful when the voxel noise is close to the acceptable limit.

930 Note that noise is assessed here in a standard sized object. In cases of protocols adaptive to the patient size (such as those using Automatic Exposure Control), the qualification of CT scanner noise should include noise as a function of size (using phantom such as that provisioned in AAPM TG233) if there is any concern that the noise performance may be outside compliance for different sizes.

935 The procedure described above is provided as a reference method. Sites may submit to QIBA a proposed alternative method (such as using the water phantom portion of a manufacturer's QA phantom) and evidence that the results produced by the proposed method are equivalent to this reference method or manufacturer methodology. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.

940 This assessment procedure is intended to be a simple phantom measurement that can be used to set a reasonable limit on the noise which is considered sufficient to avoid degrading segmentation performance. The procedure may be used for both conventional filtered backprojection and iterative reconstruction methods. It is noted that when characterizing reconstruction methods, voxel noise is a limited representation of image noise when noise texture is varied.

4.3. Assessment Procedure: Tumor Volume Computation Accuracy

945 This procedure can be used by a manufacturer or an imaging site to assess whether an Image Analysis Tool computes the volume of a single tumor accurately. Accuracy is assessed in terms of the percentage error when segmenting and calculating the volume of a tumor with known truth.

950 The assessor shall download the test files by going to the Quantitative Imaging Data Warehouse (QIDW <http://qidw.rsna.org/>), selecting QIDW Data Inventory, selecting CT Volumetry Profile Conformance Testing, and downloading the LungMan DRO zip file.

Note: The assessor will not be permitted to access the QIDW Data Inventory until they have registered for a (free) user account and logged in.

955 The test files include 11 DICOM sequential images representing a digital reference object (a "virtual phantom") with z-axis resolution of 1.5mm. A spherical "tumor" and a box-shaped "tumor", both with -10 HU radio-density, are placed within a flat -1000 HU region of the phantom to make the segmentation

intentionally easy since the test is not intended to stress the segmentation tool but to instead evaluate any bias in the volume computation after the tumor is segmented.

960 The assessor shall use the Image Analysis Tool to segment both the spherical tumor and the box-shaped tumor present in the test images and calculate the volume of each tumor.

The assessor shall record the percentage difference between the reported volume and the true value.

965 The downloaded zip file contains an Excel spreadsheet named "QIBA Volumetry CT - 4.3 Assessment Procedure Tumor Volume Computation" with the coordinates of the centroid of each tumor, the true value for its volume, and statistical analysis tooling to record the results and assess the performance.

4.4. Assessment Procedure: Tumor Volume Repeatability

970 This procedure can be used by a manufacturer or an imaging site to assess the repeatability with which the volume of a single tumor is measured. Repeatability is assessed in terms of the repeatability coefficient when segmenting and calculating the volume of a tumor with known truth at two time points. The procedure assesses an Image Analysis Tool and a Radiologist operating the tool as a paired system.

The assessment procedure has the following steps:

- Obtain a designated test image set (see section 4.4.1).
- Determine the volume for designated tumors at two time points (see section 4.4.2).
- Calculate statistical metrics of performance (see section 4.4.3).

975 Note that tumor detection is not evaluated by this procedure since the locations of the target lesions are provided.

980 4.4.1 OBTAIN TEST IMAGE SET

The test image set consists of multiple target tumors in the lung in multiple subjects, which is representative of the stated scope of the Profile.

985 The assessor shall download the test files by going to the Quantitative Imaging Data Warehouse (QIDW <http://qidw.rsna.org/>), selecting QIDW Data Inventory, selecting CT Volumetry Profile Conformance Testing, selecting RIDER Lung CT Data, and downloading the RIDER Lung CT Data zip file (roughly 4GB).

Note: The assessor will not be permitted to access the QIDW Data Inventory until they have registered for a (free) user account and logged in.

990 The test files represent 31 cases, with two time points per case, each with one target tumor to segment. Each timepoint of each case is represented by a set of DICOM files. The scans have multiple nodules of varying sizes. The target tumor is identified in terms of its x/y/z coordinates. The list of target tumors and coordinates are provided in a .csv file associated with each study in the download package. The RIDER Lung CT Data download package also contains an Excel spreadsheet named "QIBA CTVol TumorVolumeChange Assessment4.4-Repeatability" that summarizes all the tumor locations and will also help the assessor perform the record keeping and calculations later in this assessment procedure. Note that for some of the cases the two timepoints are in different series in the same study and for some of the cases the two timepoints are in different studies.

1000 Future editions of the Profile may address a larger number of body parts (e.g., metastases in the mediastinum, liver, adrenal glands, neck, retroperitoneum, pelvis, etc.) by including such tumors in the test data, and may test boundary condition performance by including test data that is marginally conformant (e.g. maximum permitted slice thickness, maximum permitted noise, etc.) to confirm conformant performance is still achieved.

1005 The target tumors have been selected to be measurable (as defined in the Profile) and have a range of volumes, shapes and types to be representative of the scope of this Profile.

1010 The test image set has been acquired according to the requirements of this Profile (e.g. patient handling, acquisition protocol, reconstruction).

If the algorithm has been developed using the specified test files, that shall be reported by the assessor. It is undesirable to test using training data, but until more datasets are available it may be unavoidable.

4.4.2 DETERMINE VOLUME

1015 Import the DICOM files into the analysis software. The assessor shall segment each target tumor at each timepoint as described in the Image Analysis Activity (See section 3.10). The assessor is permitted to edit the tumor segmentation or seed point if that is part of the normal operation of the tool. If segmentation edits are performed (e.g. to ensure the volumetric assessment incorporates the whole nodule and excludes any adjacent tissues), results shall be reported both with and without editing.

1020 When evaluating an Image Analysis Tool, a single reader shall be used for this entire assessment procedure. When evaluating a Radiologist, a single tool shall be used for this entire assessment procedure.

1025 Note: Eleven of the 31 cases in the test files do not meet the Image QA criteria specified by the Profile (See 3.9.2). These cases are marked as "excluded" on the Results page of the QIBA spreadsheet and are not included in the calculation of performance metrics. Assessors may skip measuring those cases.

1030 The assessor shall calculate the volume (Y) of each target tumor at time point 1 (denoted Y_{i1}) and at time point 2 (Y_{i2}) where i denotes the i -th target tumor.

The assessor shall calculate the resulting % volume change (d) for each target tumor as $d_i = \ln(Y_{i2}) - \ln(Y_{i1})$.

1035 The downloaded QIBA spreadsheet may be used to record the volume measurements and will perform these calculations and the statistical metrics that follow. Recording the amount of time spent on each case and any comments or concerns is not required for the assessment but is appreciated as feedback to the QIBA Biomarker Committee.

4.4.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The assessor shall calculate the within-subject Coefficient of Variation (wCV), where $N=20$ and

$$wCV = \sqrt{\sum_{i=1}^N d_i^2 / N}$$

The assessor shall estimate the Repeatability Coefficient (RC) as

$$\widehat{RC} = 2.77 \times wCV$$

The assessor shall divide the target tumors into a small subgroup (containing the 14 target tumors with the smallest measured volumes; tagged in the spreadsheet) and a large subgroup (containing the 6 tumors with the largest measured volumes; tagged in the spreadsheet). The assessor shall repeat the above calculations on both subgroups to estimate a small subgroup repeatability coefficient and a large subgroup repeatability coefficient.

The assessor is recommended to also compute Bland-Altman plots of the volume estimates as part of the assessment record.

4.5. Assessment Procedure: Tumor Volume Bias and Linearity

This procedure can be used by a manufacturer or an imaging site to assess the bias and linearity with which the volume of a single tumor is measured. Bias is assessed in terms of the percentage population bias when segmenting and calculating the volume of a number of tumors with known truth. Linearity is assessed in terms of the slope of an ordinary least squares (OLS) regression fit to the volume data.

4.5.1 OBTAIN TEST IMAGE SET

The test image set consists of scans from two different scanners of an anthropomorphic ("Lungman") phantom with multiple synthetic target tumors of different shapes and sizes in the lung.

The assessor shall download the test files by going to the Quantitative Imaging Data Warehouse (QIDW <http://qidw.rsna.org/>), selecting QIDW Data Inventory, selecting CT Volumetry Profile Conformance Testing, and downloading the QIBA Lung Collection zip file (roughly 1GB).

Note: The assessor will not be permitted to access the QIDW Data Inventory until they have registered for a (free) user account and logged in.

The test image set consists of scans of the FDA Lungman N1 phantom using two different scanners from different vendors. Several phantom configurations, using a set of 7 synthetic tumors, each with a different combination of size, shape and diameter (see Table 4.5.1-1), were scanned. The scan of a configuration is repeated 3 times, each resulting in a set of DICOM files. The list of target tumors and centroid coordinates for each scan are provided in an Excel spreadsheet named "QIBA Volumetry CT - 4.5 Tumor volume bias and linearity" in the QIBA Lung Collection download package. The spreadsheet also helps the assessor perform the record keeping and calculations later in this assessment procedure.

Note that the images contain additional tumors that are not identified in the .csv files. Do NOT include measurements of the additional tumors in the results or calculations described in sections 4.5.2 & 4.5.3.

Table 4.5.1-1: Phantom Target Tumor Characteristics

Shape	Nominal Diameter	Nominal Density
Spherical	10 mm	+100 HU
	20 mm	
	40 mm	
Ovoid	10 mm	+100 HU
	20 mm	
Lobulated	10 mm	+100 HU
	20 mm	

1080

The target tumors have been placed to be measurable (as defined in the Profile) and have a range of volumes and shapes to be representative of the scope of the Profile.

1085

The test image set has been acquired according to the requirements of this Profile (e.g. patient handling, acquisition protocol, reconstruction). See Table 4.5.1-2.

Table 4.5.1-2: Test Image Set Acquisition and Reconstruction Parameters

Scanner	Key Parameters
Philips 16 (Mx8000 IDT)	KVp: 120 Pitch: 1.2 Collimation: 16x1.5 Exposure: 100 mAs Slice Thickness: 2 mm Increment: 1 mm Filter: Medium Repeat Scans: 3
Siemens 64	KVp: 120 Pitch: 1.2 Collimation: 64x0.6 Exposure: 100 mAs Slice Thickness: 1.5 mm Increment: 1.5 mm Filter: Medium Repeat Scans: 3

4.5.2 DETERMINE VOLUME

1090

For each scan, the assessor shall import the DICOM files into their analysis software and segment the tumors identified in the spreadsheet as described in the Image Analysis Activity (See 3.10). In total, the assessor will do 39 target tumor segmentations (3 scans each for 7 tumors on 1 scanner and 6 tumors on the other scanner)

1095

The assessor is permitted to edit the tumor segmentation or seed point if that is part of the normal operation of the tool. If segmentation edits are performed (e.g. to ensure the volumetric assessment incorporates the whole nodule and excludes any adjacent tissues), results shall be reported both with and without editing.

1100 When evaluating an Image Analysis Tool, a single reader shall be used for this entire assessment procedure. When evaluating a Radiologist, a single tool shall be used for this entire assessment procedure.

The assessor shall calculate the volume (Y) of each target tumor (denoted Y_i) where i denotes the i -th target tumor.

1105

The downloaded QIBA spreadsheet may be used to record the volume measurements and will perform these calculations. Recording the amount of time spent on each case and any comments or concerns is not required for the assessment but is appreciated as feedback to the QIBA Biomarker Committee.

4.5.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

1110

The natural log of the true volumes (X_i) of each target tumor are known and are provided in the dataset.

The assessor shall calculate the individual percentage bias (b_i) of the measurement of each target tumor as $b_i = \ln Y_i - \ln X_i$

1115

The assessor shall estimate the population bias over the N target tumors as

$$\hat{D} = \sum_{i=1}^N b_i / N$$

The assessor shall convert to a percentage bias estimate as

$$\% \widehat{bias} = (\exp(\hat{D}) - 1) \times 100.$$

1120

The assessor shall estimate 95% confidence intervals for the population bias as

$$CI_{\hat{D}} = \hat{D} \pm t_{[\alpha=0.025, df=N-1]} \times SE(\hat{D})$$

and

$$CI_{\% \widehat{bias}} = (\exp(CI_{\hat{D}}) - 1) \times 100$$

1125

The Overall $\% \widehat{bias}$ metric used to compare to the bias specifications is

$$Overall \% \widehat{bias} = \max(|CI_{\% \widehat{bias}}|)$$

1130

The assessor shall fit a quadratic model to the volume data $\log Y_i$ on $[\ln X_i, (\ln X_i)^2]$ and shall estimate the quadratic term ($\hat{\beta}_2$).

The assessor shall fit an ordinary least squares (OLS) regression of the $\ln Y_i$ on $\ln X_i$ and shall estimate the slope ($\hat{\beta}_1$).

1135

The assessor shall divide the target tumors into three subgroups (containing the spherical, ovoid and lobulated target tumors respectively). The assessor shall repeat the percentage population bias calculation on each subgroup to estimate a spherical subgroup percentage bias, an ovoid subgroup percentage bias and a lobulated subgroup percentage bias.

1140

The assessor is recommended to also plot the volume estimate ($\ln Y_i$ versus $\ln X_i$) and the OLS regression curve of the volume estimates as part of the assessment record.

4.6. Assessment Procedure: Imaging Site Performance

Note: In this Consensus Stage of the Profile, there is no overall performance requirement on the Site. The future Claim Confirmed Stage of the QIBA Profile development process will include measuring the overall site performance and confirming the performance stated in the Profile Claim is achieved. The procedure in this section is an outline of the process that is expected to be used at that time and will include more details in the future.

1145 This procedure can be used by an imaging site to evaluate the combined performance of all the Actors and Activities at the site.

The assessment procedure has the following steps:

- Validate image acquisition (see section 4.6.1).
- Generate a test image set (see section 4.6.2).
- Assess Tumor Volume Change Variability (see section 4.4.2, 4.4.3 above).

1150 The procedure presumes that the Actors being used by the site meet the requirements described in Section 3 of this document; however it is not a pre-requisite that those Actors have published QIBA Conformance Statements (although that would be both useful and encouraging).

4.6.1 ACQUISITION VALIDATION

1155 Review patient handling procedures for conformance with Section 3.6

Establish acquisition protocols and reconstruction settings on the Scanner conformant with Section 3.5. If a QIBA Conformance Statement is available from the Scanner manufacturer, it may provide parameters useful for this step.

1160 Acquire images of a 20cm water phantom, reconstruct and confirm performance requirements in Section 3.5.2 are met.

4.6.2 TEST IMAGE SET

Locally acquire a test image set using the protocols established and tested in Section 3.5.

1165 The test image set should conform to the characteristics described in Section 3.9.

Discussion:

It is highly likely that due to practical constraints the test image set prepared at an individual site would be much less comprehensive than the test image sets prepared by QIBA. Consider what a more limited but still useful test image set would look like.

Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Volumetric Computed Tomography (CTVol) Biomarker Committee. The committee is composed of representatives from academia, professional societies, scanner manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, government research organizations and regulatory agencies, among others. All work is classified as pre-competitive.

A more detailed description of the committee and its work can be found at the following web link:
<http://qibawiki.rsna.org/index.php?title=Committees>.

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1189 Appendix B: Conventions and Definitions

1190 Acquisition vs. Analysis vs. Interpretation: This document organizes acquisition, reconstruction, post-
1191 processing, analysis and interpretation as steps in a pipeline that transforms data to information to
1192 knowledge. Acquisition, reconstruction and post-processing are considered to address the collection and
1193 structuring of new data from the subject. Analysis is primarily considered to be computational steps that
1194 transform the data into information, extracting important values. Interpretation is primarily considered to
1195 be judgment that transforms the information into knowledge. (The transformation of knowledge into
1196 wisdom is beyond the scope of this document.)

1197 Image Analysis, Image Review, and/or Read: Procedures and processes that culminate in the generation of
1198 imaging outcome measures, such tumor response criteria. Reviews can be performed for eligibility, safety
1199 or efficacy. The review paradigm may be context specific and dependent on the specific aims of a trial, the
1200 imaging technologies in play, and the stage of drug development, among other parameters.

1201 Image Header: that part of the image file (or dataset containing the image) other than the pixel data itself.

1202 Imaging Phantoms: devices used for periodic testing and standardization of image acquisition. This testing
1203 must be site specific and equipment specific and conducted prior to the beginning of a trial (baseline),
1204 periodically during the trial and at the end of the trial.

1205 Time Point: a discrete period during the course of a clinical trial when groups of imaging exams or clinical
1206 exams are scheduled.

1207 Tumor Definition Variability: the clarity of the tumor boundary in the images. It originates from the
1208 biological characteristics of the tumor, technical characteristics of the imaging process, and perhaps on the
1209 perception, expertise and education of the operator.

1210 Technical Variability - originates only from the ability to drawing unequivocal objects. In other words, the
1211 perception of tumor definition is supposed absolutely clear and similar for any given operator when
1212 attempting to assess "Technical" variability.

1213 Repeatability – considers multiple measurements taken under the same conditions (same equipment,
1214 parameters, reader, algorithm, etc) but different subjects.

1215 Reproducibility – considers multiple measurements taken where one or more conditions have changed.

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1219 **Appendix C: Conformance Checklists**



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1222 **QIBA Checklist:**

1223 **CT Tumor Volume Change for Advanced Disease**
1224 **(CTV-AD)**
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1226 **INSTRUCTIONS**

1227 This Checklist is organized by "Actor" for convenience. If a QIBA Conformance Statement is already
1228 available for an actor (e.g. your analysis software), you may choose to provide a copy of that statement
1229 rather than confirming each of the requirements in that Actors checklist yourself.

1230 Within an Actor Checklist the requirements are grouped by the corresponding Activity in the QIBA Profile
1231 document. If you are unsure about the meaning or intent of a requirement, additional details may be
1232 available in the Discussion section of the corresponding Activity in the Profile.

1233 Conforms (Y/N) indicates whether you have performed the requirement and confirmed conformance.
1234 When responding **N**, please explain why.

1235 Since several of the requirements mandate the use of specific assessment procedures, those are also
1236 included at the end to minimize the need of referring to the Profile document.

1237 Feedback on all aspects of the Profile and associated processes is welcomed.
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1239	Site checklist	Page 2
1240	Physicist checklist	Page 2
1241	Image Analysis Tool checklist	Page 3
1242	Scanner checklist	Page 4
1243	Radiologist checklist	Page 5
1244	Technologist checklist	Page 7

SITE CHECKLIST

Site Checked:

Parameter	Conforms (Y/N)	Requirement
Site Conformance (section 3.1)		
Scanners		Shall confirm all participating scanners conform to this Profile.
Reconstruction Software		Shall confirm all participating reconstruction software conforms to this Profile.
Image Analysis Tools		Shall confirm all participating image analysis tools conform to this Profile.
Radiologists		Shall confirm all participating radiologists conform to this Profile.
Physicists		Shall confirm all participating physicists conform to this Profile.
Technologists		Shall confirm all participating technologists conform to this Profile.

PHYSICIST CHECKLIST

Note: The role of the Physicist actor may be played by an in-house medical physicist, a physics consultant or other staff (such as vendor service or specialists) qualified to perform the validations described.

Physicist(s) Checked:

Parameter	Conforms (Y/N)	Requirement
Periodic QA (section 3.4)		
QC		Shall perform relevant quality control procedures as recommended by the manufacturer.
QC		Shall record the date/time of QC procedures for auditing.
Protocol Design (section 3.5)		
In-plane Spatial Resolution		Shall validate that the protocol achieves an f50 value between 0.3 mm ⁻¹ and 0.5 mm ⁻¹ for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
Voxel Noise		Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise

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IMAGE ANALYSIS TOOL CHECKLIST

Image Analysis Tool(s) Checked - Make/Model/Version :

Parameter	Conforms (Y/N)	Requirement								
Product Validation (section 3.2)										
Multiple Tumors		Shall allow multiple tumors to be measured.								
Multiple Tumors		Shall either correlate each measured tumor across time points or support the radiologist to unambiguously correlate them.								
Reading Paradigm		Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint.								
Reading Paradigm		Shall be able to re-process the first time point (e.g. if it was processed by a different Image Analysis Tool or Radiologist).								
Tumor Volume Computation		Shall be validated to compute volume within 5% of the true volume. See 4.3 Assessment Procedure: Tumor Volume Computation.								
Tumor Volume Repeatability		Shall be validated to achieve tumor volume repeatability with: <ul style="list-style-type: none"> • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Repeatability.								
Tumor Volume Bias & Linearity		Shall be validated to achieve: <ul style="list-style-type: none"> • an overall tumor volume %bias of less than the Allowable Overall %Bias • a tumor volume %bias for each shape subgroup (spherical, ovoid, lobulated) of less than the Allowable Shape Subgroup %Bias • slope ($\hat{\beta}_1$) between 0.98 and 1.02 • quadratic-term ($\hat{\beta}_2$) between -0.05 and 0.05 The Allowable Overall %Bias and the Allowable Shape Subgroup %Bias are taken from Table 3.2.2-1 based on the overall repeatability coefficient achieved by the Image Analysis Tool using the assessment procedure in section 4.4. See 4.5 Assessment Procedure: Tumor Volume Bias & Linearity.								
Confidence Interval of Result		Is encouraged to calculate and make available to the operator the 95% confidence interval for tumor volume change based on the equation: $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV_1)^2 + (Y_2 \times wCV_2)^2}$ Where Y_1 and Y_2 is the volume measured at timepoint 1 and 2, wCV_1 and wCV_2 is the within-nodule coefficient of variation for Y_1 and Y_2 as taken from the following table, D_1 and D_2 is the longest in-plane diameter of the volume at timepoint 1 and 2: <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>D_1, D_2</th> <th>10-34mm</th> <th>35-49mm</th> <th>50-100mm</th> </tr> </thead> <tbody> <tr> <td>$wCV_1,$ wCV_2</td> <td>0.141</td> <td>0.103</td> <td>0.085</td> </tr> </tbody> </table>	D_1, D_2	10-34mm	35-49mm	50-100mm	$wCV_1,$ wCV_2	0.141	0.103	0.085
D_1, D_2	10-34mm	35-49mm	50-100mm							
$wCV_1,$ wCV_2	0.141	0.103	0.085							

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**Table 3.2.2-1:
Allowable Tumor Volume %Bias based on Overall Repeatability Coefficient**

Overall Repeatability Coefficient \widehat{RC}	Allowable Overall %Bias (RMSE Target: 7.1%)	Allowable Shape Subgroup %Bias (RMSE Target: 7.8%)
0.05	6.60%	7.32%
0.06	6.37%	7.11%
0.07	6.09%	6.86%
0.08	5.75%	6.56%
0.09	5.35%	6.20%
0.10	4.88%	5.79%
0.11	4.30%	5.31%
0.12	3.59%	4.75%
0.13	2.63%	4.06%
0.14	0.84%	3.17%
0.15	0.00%	1.84%
0.155	0.00%	0.00%
0.16	n/a (failed repeatability)	n/a (failed repeatability)

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SCANNER AND RECONSTRUCTION SOFTWARE CHECKLIST

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Scanner(s) Checked - Make/Model/Version :

Parameter	Conforms (Y/N)	Requirement
Product Validation (section 3.2)		
Acquisition Protocol		Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.
		Shall prepare a protocol conformant with section 3.5.2 "Protocol Design Specification".
		Shall validate that the protocol achieves an f50 value that is between 0.3 mm ⁻¹ and 0.5 mm ⁻¹ for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
		Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise
Reconstruction Protocol		Shall be capable of performing reconstructions and producing images with parameters set as specified in 3.5.2 "Protocol Design Specification".

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RADIOLOGIST CHECKLIST

Note: The Radiologist is responsible for the protocol parameters, although they may choose to use a protocol provided by the vendor of the scanner. The Radiologist is also responsible for ensuring that the protocol has been validated, although the Physicist actor is responsible for performing the validation. Protocol design should be done collaboratively between the physicist and the radiologist with the ultimate responsibility to the radiologist. Some parameters are system dependent and may require special attention from a physicist.

Radiologist(s) Checked:

Parameter	Conforms (Y/N)	Specification	
Staff Qualification (section 3.3)			
Tumor Volume Computation Repeatability		Shall, if operator interaction is required by the Image Analysis Tool to perform measurements, be validated to achieve tumor volume change repeatability with: <ul style="list-style-type: none"> • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Change Repeatability.	
Protocol Design (section 3.5)			
Acquisition Protocol		Shall prepare a protocol to meet the specifications in this table.	
Acquisition Protocol		Shall ensure technologists have been trained on the requirements of this Profile.	
Total Collimation Width		Shall set to Greater than or equal to 16mm.	Total Collimation Width (0018,9307)
IEC Pitch		Shall set to Less than 1.5.	Spiral Pitch Factor (0018,9311)
Nominal Tomographic Section Thickness (T)		Shall set to Less than or equal to 1.5mm.	Single Collimation Width (0018,9306)
Scan Duration for Thorax		Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)
Reconstruction Protocol		Shall prepare a protocol to meet the specifications in this table.	
Reconstruction Protocol		Shall ensure technologists have been trained on the requirements of this Profile.	
Reconstructed Image Thickness		Shall set to between 0.5mm and 2.5mm (inclusive).	Slice Thickness (0018,0050)
Reconstructed Image Interval		Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap).	Spacing Between Slices (0018,0088)
Subject Handling (section 3.6)			
Contrast Protocol		Shall prescribe a contrast protocol (which may be No Contrast) that achieves	

Parameter	Conforms (Y/N)	Specification
		enhancement consistent with baseline.
Use of intravenous contrast		Shall determine whether the selected contrast protocol, if any, will achieve sufficient tumor conspicuity.
Use of oral contrast		Shall determine whether the selected contrast protocol, if any, will achieve sufficient tumor conspicuity.
Image QA (section 3.9)		
Patient Motion Artifacts		Shall confirm the images containing the tumor are free from artifact due to patient motion.
Dense Object Artifacts		Shall confirm the images containing the tumor are free from artifact due to dense objects, materials or anatomic positioning.
Clinical Conditions		Shall confirm that there are no clinical conditions affecting the measurability of the tumor.
Tumor Size		Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm ³ and 524 cm ³ .)
Tumor Margin Conspicuity		Shall confirm the tumor margins are sufficiently conspicuous and unattached to other structures of equal density to distinguish the volume of the tumor.
Contrast Enhancement		Shall confirm that the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
Patient Positioning Consistency		Shall confirm that any tumor deformation due to patient positioning is consistent with baseline (e.g. tumors may deform differently if the patient is supine in one scan and prone in another).
Breath Hold Consistency		Shall confirm that the breath hold state and degree of inspiration is consistent with baseline.
Scan Plane Consistency		Shall confirm that the anatomical slice orientation (due to gantry tilt or patient head/neck repositioning) is consistent with baseline.
Reconstructed Image Thickness		Shall confirm that the reconstructed image thickness is between 0.5mm and 2.5mm, and consistent with baseline (e.g. within 0.5mm).
Field of View		Shall confirm that the image field of view (FOV) resulting from acquisition and reconstruction settings appears consistent with baseline.
Tumor Measurability		Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the radiologist is confident and prepared to edit the contour to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.
Image Analysis (section 3.10)		
Reading Paradigm		Shall re-process the first time point if it was processed by a different Image Analysis Tool or Radiologist.
Result Verification		Shall review & approve margin contours produced by the tool.

TECHNOLOGIST CHECKLIST

Technologist(s) Checked:

Parameter	Conforms (Y/N)	Specification	
Subject Handling (section 3.6)			
Use of intravenous contrast		Shall use the prescribed intravenous contrast parameters.	
Use of oral contrast		Shall use the prescribed oral contrast parameters.	
Artifact Sources		Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads and other metal equipment) such that they will not degrade the reconstructed CT volumes.	
Table Height & Centering		Shall adjust the table height for the mid-axillary plane to pass through the isocenter.	
Table Height & Centering		Shall position the patient such that the "sagittal laser line" lies along the sternum (e.g. from the suprasternal notch to the xiphoid process).	
Breath hold		Shall instruct the subject in proper breath-hold and start image acquisition shortly after full inspiration, taking into account the lag time between full inspiration and diaphragmatic relaxation.	
Image Data Acquisition (section 3.7)			
Acquisition Protocol		Shall select a protocol that has been previously prepared and validated for this purpose (See 3.5.2 "Protocol Design Specification").	
Localizer		Shall confirm on the localizer (scout) image the absence of artifact sources that could affect the planned volume acquisitions or alter the attenuation of lung nodules.	
Scan Duration for Thorax		Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)
Image Data Reconstruction (section 3.8)			
Reconstruction Protocol		Shall select a protocol that has been previously prepared and validated for this purpose (See section 3.5.2 "Protocol Design Specification").	
Reconstructed Image Thickness		Shall set to between 0.5mm and 2.5mm (inclusive) if not set in the protocol.	
Reconstructed Image Interval		Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap) and consistent with baseline.	
Reconstruction Field of View		Shall ensure the Field of View spans at least the full extent of the thoracic and abdominal cavity, but not substantially greater than that.	Reconstruction Field of View (0018,9317)