

QIBA Profile:

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

Edition: 2022?

When referencing this document, please use the following format:

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Stage: Technically Confirmed

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# 1. Executive Summary

A QIBA Profile is an implementation guide to generate a biomarker with an effective level of performance, mostly by reducing variability and bias in the measurement.

The expected performance is expressed as **Claims** (Section 1.2). To achieve those claims, **Actors** (Scanners, Technologists, Physicists, Radiologists, Reconstruction Software, and Image Analysis Tools) must meet the Checklist **Requirements** (Section 3) covering Periodic QA, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, and Image Analysis.

This Profile is at the Technically Confirmed stage ([qibawiki.rsna.org/index.php/QIBA\_Profile\_Stages](http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages)) so,

* The requirements have been performed and found to be practical by multiple sites
* The claim is a hypothesis based on committee assessment of literature and QIBA groundwork

QIBA Profiles for other CT, MRI, PET, and Ultrasound biomarkers can be found at [qibawiki.rsna.org](https://wiki.ihe.net/index.php/Profiles).

## 1.1 Clinical Context

CT Tumor Volume Change is used as a biomarker of disease risk, characterization, progression, and response to treatment.

This involves measuring thoracic tumor volumes and assessing longitudinal changes within subjects, based on image processing of CT scans acquired at different timepoints. See Appendix B for a discussion of usage of this biomarker in practice.

## 1.2 Claims

Conformance with this Profile by all relevant staff and equipment supports the following claims:

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

**Repeatability Claim: Tumor volume measurement within-tumor coefficient of variation (wCV), is 0.085, 0.103, and 0.141 respectively for tumors with diameters of 50-100mm, 35-49mm, or 10-34mm.**

The resulting 95% confidence interval (CI) for a true change in volume for several example tumors is:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Change Example (Diameter)** | **Baseline Volume** | **Subsequent Volume** | **Volume Change Confidence Interval Calculation** | **95% CI of  True Volume Change** |
| 100mm -> 50mm | **524 cm3** (100mm) | **65 cm3** (50mm) | **-459 cm3 ±** **88 cm3** | **[ -547 cm3, -371 cm3 ]** |
| 40mm -> 80mm | **34 cm3**  (40mm) | **268 cm3**  (80mm) | **234 cm3 ±** **45 cm3** | **[ 189 cm3, 279 cm3 ]** |
| 10mm -> 20mm | **0.5 cm3** (10mm) | **4.2 cm3** (20mm) | **3.7 cm3 ±** **1.2 cm3** | **[ 2.5 cm3, 4.9 cm3 ]** |

computed as , where and are the volume measurements at baseline and the subsequent timepoint, and and are the wCV estimates corresponding to these measurements.

Note: The 95% CI in the first example includes a volume reduction of 547 cm3 for a tumor initially measured as 524 cm3 because it accounts for variability in the initial measurement (i.e. the tumor may have been larger).

### 1.2.1 Current Performance

<TODO Work up straw man based on latest input>

<Crystalize the value proposition><Consider pulling a few numbers from referencing Table 2-1>

But, based on committee groundwork and review of the literature, the performance of typical sites that are not conforming to this profile might be expected to be… on the order of 140% *< Quantify what our groundwork says about existing (pre-Profile) performance to answer the question “What do I gain from implementing the profile?”><Might not cover all the applications/organs/etc but even part makes the case><MUST stay brief><****TODO*** *sketch up an example of what this looks like – e.g. when you don’t follow these protocols – here’s your number and here’s the citation. DO NOT spend text summarizing the paper that is cited>*

<Historically no previously validated approach to validating accuracy/precision for biomarker performance.><Particular importance for longitudinal change – Note without using this profile your performance is unknown/unguaranteed>

Also highlight the benefit of having a KNOWN statistical performance rather than fuzzy unknown. Statistical relevance.

## 1.3 Disclaimers

**Standard of Care**: The requirements are defined to achieve the Claim and do not supersede proper patient management considerations.

**Confirmation of Claims**: The claims are informed by groundwork studies, extensive literature review and expert consensus; they have not yet been fully substantiated by studies that strictly conform to the requirements given here. The QIBA Claim Confirmation and Clinical Confirmation Stages will collect data on the actual field performance 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. (<http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages>)

**Scope of Claims**: 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.

**Innovation**: Profile requirements are intended to establish a baseline level of performance. Exceeding the requirements and providing higher performance or advanced capabilities is allowed and encouraged. The Profile does not limit the methods institutions and equipment suppliers use to meet the requirements.

# 2. Conformance

**To conform to this Profile, participating staff and equipment (“Actors”) shall meet each checklist requirement assigned to them in Section 3.**

* Some requirements reference a specific **assessment procedure** in section 4 that shall be used to assess conformance to that requirement. For the rest, any reasonable assessment procedure is acceptable.
* Actors must ensure requirements assigned to them are met; however, for the purpose of conforming to the profile, they may delegate a task rather than physically doing it themselves.
* Actor names represent roles in the profile, not formal job titles or certifications. E.g., The Physicist actor is assigned site equipment performance requirements. The role may be filled by any appropriate person: a staff physicist, a managed contractor, or a service provided by a vendor.
* If a QIBA Conformance Statement is available for an actor (e.g., your scanner), a copy of that statement may be used in lieu of confirming each requirement in that Actors checklist yourself.

**To make a formal claim of conformance, the organization responsible for an Actor shall publish a QIBA Conformance Statement.**

* QIBA Conformance Statements:
  + shall follow the current template: (<http://qibawiki.rsna.org/index.php/QIBA_Conformance_Statement_Template>)
  + shall include an Appendix with details the requirement or the assessment procedure indicated the assessor should record (e.g., acquisition parameters)
  + shall describe or provide access to the test data used for conformance testing

While Conformance Statements for equipment (e.g., Scanners, Reconstruction SW, Analysis Tools) would typically be published manufacturers, sites might also run the necessary tests to confirm and document equipment conformance if, for example, the equipment was an older model no longer promoted by the manufacturer, but for which the site needed conformance to participate in a clinical trial.

*Points to clarify (probably on the webpages rather than in detail in each profile document)*

* *what does Conformance mean for Tech Confirmed and Claim Confirmed Profiles*
  + *Claim Confirmation is something QIBA does to prove that someone following the requirements will result in meeting the claim*
  + *Site Conformance is something a site does to prove it’s following the requirements*
  + *Does conformance require a test-retest study?*
* *how does* ***one*** *actor completing its checklist relate to Site Conformance to a Profile*
* *how do presets for specific models appear.*
* *FAQ?*
  + *What if I only complete one actor checklist?*
  + *Do I have to use the presets shown in the Appendix?*
  + *Which parts of the profile do you have to read to conform*

*EARL Pilot – did you read the profile? (which parts)*

*Recruit some users to read through and comment*

Target FDG as our third pilot/example?

# 3. Profile Requirement Checklists

The following Actor Checklists are the basis for conforming to this Profile (See Section 2).

Conforms (Y/N) indicates whether conformance to the requirement has been confirmed by the assessor. When responding **N**, please explain why.

Feedback on all aspects of the Profile and associated processes is welcomed. Contact: qiba@rsna.org

## 3.1 Site Checklist

Site Name: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Requirement** |
| --- | --- | --- |
| **Site Conformance (see Section A.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. |

## 3.2 Scanner and Reconstruction Software Checklist

Make/Model/Version: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Requirement** |
| --- | --- | --- |
| **Product Validation (see Section A.2)** | | |
| Acquisition & Reconstruction Protocol |  | Shall prepare a conformant protocol (see "Protocol Design" on Radiologist Checklist). |
|  | 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 |

## 3.3 Image Analysis Tool Checklist

Make/Model/Version: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Requirement** |
| --- | --- | --- |
| **Product Validation (see Section A.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:   * 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:   * 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 ( between 0.98 and 1.02 * quadratic-term ( between -0.05 and 0.05   The Allowable Overall %Bias and the Allowable Shape Subgroup %Bias are taken from Table 3.3.2-1 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:  Where  *Y1* and *Y2* is the volume measured at timepoint 1 and 2,  *wCV1* and *wCV2* is the within-nodule coefficient of variation for *Y1* and *Y2* as taken from the following table,  *D1* and *D2* is the longest in-plane diameter of the volume at timepoint 1 and 2:     |  |  |  |  | | --- | --- | --- | --- | | ***D1*, *D2*** | **10-34mm** | **35-49mm** | **50-100mm** | | ***wCV1*, *wCV2*** | 0.141 | 0.103 | 0.085 | |

**Table 3.3.2-1:   
Allowable Tumor Volume %Bias based on Overall Repeatability Coefficient**

|  |  |  |
| --- | --- | --- |
| **Overall Repeatability Coefficient** | **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) |

## 3.4 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 Name: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Requirement** |
| --- | --- | --- |
| **Protocol Design (see Section A.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 |

## 3.6 Technologist Checklist

Technologist Name: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Specification** | |
| --- | --- | --- | --- |
| **Subject Handling (see Section A.6)** | | | |
| 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 |  | Shall adjust the table height for the mid-axillary plane to pass through the isocenter. | |
| Table 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, accounting for lag time between full inspiration and diaphragmatic relaxation. | |
| **Image Data Acquisition (see Section A.7)** | | | |
| Acquisition Protocol |  | Shall select a protocol that has been previously prepared and validated for this purpose. |  |
| Localizer |  | Shall confirm on the localizer image the absence of artifact sources that could affect the volume acquisitions or the attenuation of lung nodules. |  |
| Scan Duration for Thorax |  | Shall set parameter values to cover an axial field of view of 35cm in 10 seconds or less. | Table Speed  (0018,9309) |
| **Image Data Reconstruction (see Section A.8)** | | | |
| Reconstruction Protocol |  | Shall select a protocol that has been previously prepared and validated for this purpose. |  |
| 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) |

## 3.5 Radiologist Checklist

**Note:** The Radiologist is responsible for the protocol parameters. They may choose to use a protocol provided by the scanner vendor. Working collaboratively with a physicist is recommended as some parameters are system dependent and may require special attention.

Radiologist Name: Assessment Date: .

| **Parameter** | **Conforms (Y/N)** | **Specification** | |
| --- | --- | --- | --- |
| **Staff Qualification (see Section A.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:   * 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 (see Section A.5)** | | | |
| Acquisition & Reconstruction Protocol |  | Shall prepare a protocol to meet the specifications in this table. |  |
| 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 set parameter values to cover an axial field of view of 35cm in 10 seconds or less. | Table Speed  (0018,9309) |
| 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 (see Section A.6)** | | | |
| Contrast Protocol |  | Shall prescribe a contrast protocol (which may be No Contrast) expected to achieve enhancement consistent with baseline. | |
| **Image QA (see Section A.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) each tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor, this roughly corresponds to a volume between 0.5 cm3 and 524 cm3.) | |
| 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 the phase of enhancement, if any, and degree of enhancement are consistent with baseline. | |
| Patient Positioning Consistency |  | Shall confirm any tumor deformation due to patient positioning is consistent with baseline (e.g. a tumor may deform differently if the patient is supine in one scan and prone in another). | |
| Breath Hold Consistency |  | Shall confirm breath hold state and degree of inspiration is consistent with baseline. | |
| Scan Plane Consistency |  | Shall confirm the anatomical slice orientation (due to gantry tilt or patient head/neck repositioning) is 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 (see Section A.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 the margin contours produced by the tool. | |

# 4. Assessment Procedures

Although most requirements in Section 3 can be assessed for conformance by direct observation and checked off, some requirements (e.g., performance metrics) cannot, in which case the requirement references an Assessment Procedure 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 (for both conventional filtered back-projection and iterative). 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 would have their contrast degraded by 50% (and smaller features would be degraded more).

The assessor shall:

1. Warm up the scanner’s x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.
2. Select and record acquisition and reconstruction parameters that conform to the Profile (See Protocol Design in the Radiologist Checklist 3.5). Use the same parameters for 4.1 & 4.2, i.e., the noise level during resolution assessment should be that measured during noise assessment.
3. Scan a spatial resolution phantom that has a series of HU-value cylindrical inserts including one with soft-tissue equivalence. E.g., the ACR CT Accreditation Program (CTAP) Phantom module 1 or the AAPM TG233 phantom.
4. Position the phantom with the center of the phantom at isocenter and properly aligned along the z-axis. For 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>
5. 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.

Note: The AAPM TG233 software provides axial resolution (MTF in the z-direction) in addition to the x-y plane MTF.

1. Determine and record the f50 value, defined as the spatial frequency (in mm-1 units) corresponding to 0.5 MTF on the MTF curve.
2. Generate another MTF curve and determine and record 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.

The above procedure is provided as a reference method. This reference method, and the method used by the scanner manufacturer for FDA submission of MTF values, are accepted methods for this assessment procedure. The manufacturer may have specific test methods for non-linear reconstruction algorithms.

Proposed alternative methods may be submitted to QIBA with evidence that the results produced are equivalent to this reference method or to the manufacturer method. Upon review by QIBA, the proposed method may be approved as an accepted assessment procedure in this Profile.

## 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 (for both conventional filtered back-projection and iterative). Voxel noise is assessed in terms of the standard deviation of pixel values when imaging a material with uniform density.

This simple assessment is intended to set a reasonable noise limit that is sufficient to avoid degrading segmentation performance. When characterizing reconstruction methods, voxel noise is a limited representation of image noise when noise texture is varied.

The assessor shall:

1. Warm up the scanner’s x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.
2. Select and record acquisition and reconstruction parameters that conform to the Profile (See Protocol Design in the Radiologist Checklist 3.5). Use the same parameters as used for section 4.1.
3. Place at the isocenter of the scanner a phantom of uniform density that includes a 20 cm diameter cylinder of water equivalent material. E.g. ACR CT Accreditation Program (CTAP) Phantom module 3
4. Scan the phantom and select a single representative slice, likely close to the center, from the uniformity portion of the phantom.
5. Place a region of interest (ROI) of at least 400 mm2 near the center of the slice and record the values reported for the ROI mean and standard deviation.

The assessor is encouraged, but not required, to record and retain the images and associated measurement details. Such details support assessment when the voxel noise is close to the acceptable limit.

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 a phantom such as that provisioned in AAPM TG233) if there is any concern that the noise performance may be outside compliance for different sizes.

The above procedure is provided as a reference method. This reference method and the method used by the scanner manufacturer for FDA submissions are accepted methods for this assessment procedure.

Proposed alternative methods (such as using the water phantom portion of a manufacturer’s QA phantom) may be submitted to QIBA with evidence that the results produced are equivalent to this reference method or to the manufacturer method. Upon review by QIBA, the proposed method may be approved as an accepted assessment procedure in this Profile.

## 4.3. Assessment Procedure: Tumor Volume Computation Accuracy

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.

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, exist in 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.

The assessor shall:

1. Download the test files from the Quantitative Imaging Data Warehouse (QIDW)
   1. Go to <http://qidw.rsna.org/>, Select QIDW Data Inventory,

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.

* 1. Select CT Volumetry Profile Conformance Testing
  2. Download the LungMan DRO zip file

1. Use the Image Analysis Tool to segment both the spherical tumor and the box-shaped tumor present in the test images
2. Calculate the volume of each tumor
3. Record the percentage difference between the reported volume and the true value.

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 tools to support recording the results and assessing the performance.

## 4.4. Assessment Procedure: Tumor Volume Repeatability

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).

Note: tumor detection is not evaluated by this procedure; the locations of the target lesions are provided.

### 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.

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.

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.

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.

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.

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

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.

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.

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.

The assessor shall calculate the volume (Y) of each target tumor at time point 1 (denoted Y*i*1) and at time point 2 (Y*i*2) where *I* denotes the *i*-th target tumor.

The assessor shall calculate the resulting % volume change (d) for each target tumor as

.

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

The assessor shall estimate the Repeatability Coefficient (RC) as

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  20 mm  40 mm | +100 HU |
| Ovoid | 10 mm  20 mm | +100 HU |
| Lobulated | 10 mm  20 mm | +100 HU |

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.

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

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)

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.

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.

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

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

The assessor shall calculate the individual percentage bias (*bi*) of the measurement of each target tumor as

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

The assessor shall convert to a percentage bias estimate as

=

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

and

The Overall metric used to compare to the bias specifications is

The assessor shall fit a quadratic model to the volume data on and shall estimate the quadratic term ().

The assessor shall fit an ordinary least squares (OLS) regression of the on and shall estimate the slope ).

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.

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

## 4.6. Assessment Procedure: Imaging Site Performance

Note: In the Consensus Stage, 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 be updated in the future.

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

The procedure presumes the Actors conform to the Profile but 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

The assessor shall:

* 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.
* 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.

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.

### 4.6.3 Assess Tumor Volume Change Variability

See Section 4.4.2, 4.4.3 above.

# Appendices

# Appendix A: Activity Requirements

This Appendix organizes the Profile requirements into the sequence of activities involved in generating the biomarker. The requirements here are the same as those in the requirement checklists in Section 3. The activity focus

## A.2. Product Validation

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

3.2.1 Discussion

**Volume Calculation** values from a segmentation may or may not correspond to the total of all 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.

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).

**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:

* Athelogou 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, Danagoulian 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 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.  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 header values for 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:   * 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:   * 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 ( between 0.98 and 1.02 * quadratic-term ( 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 Result | 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:  Where  *Y1* and *Y2* is the volume measurement at timepoint 1 and 2,  *wCV1* and *wCV2* is the within-nodule coefficient of variation for *Y1*   and *Y2* as taken from the following table,  *D1* and *D2* is the longest in-plane diameter of the volume at   timepoint 1 and 2:     |  |  |  |  | | --- | --- | --- | --- | | ***D1*, *D2*** | **10-34mm** | **35-49mm** | **50-100mm** | | ***wCV1*, *wCV2*** | 0.141 | 0.103 | 0.085 | |

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

|  |  |  |
| --- | --- | --- |
| **Overall Repeatability Coefficient** | **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) |

## A.3. Staff Qualification

This activity evaluates human Actors (Radiologist, Physicist, and Technologist) prior to their participation in the Profile. Staff Qualification includes training, qualification or performance assessments necessary to reliably meet the Profile Claim.

| **Parameter** | **Actor** | **Specification** |
| --- | --- | --- |
| Tumor Volume  Change Repeatability | Radiologist | Shall, if operator interaction is required by the Image Analysis Tool to perform measurements, be validated to achieve tumor volume change repeatability with:   * 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. |

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.

## A.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 necessary to reliably meet the Profile Claim.

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.

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

## A.5. Protocol Design

This activity involves designing and validating image acquisition protocols. This is typically done once and used for many procedures, not repeated for each imaging subject. Protocol design includes constraints on acquisition and reconstruction parameters 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.

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 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.

**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, NxT, where N is the number of detector rows and T is the nominal tomographic section thickness, for example 64x1.25mm) 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 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.

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.

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.

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.

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.

**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 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) 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 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. 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 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 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 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.

| **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 < 60HU.  See 4.2. Assessment Procedure: Voxel Noise |  |

## A.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

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**

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**

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.

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 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 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).

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 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**

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 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.

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.

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.

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.

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.

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 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.

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.

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.

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.

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 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 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)
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.
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.

**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 intravenous contrast | Radiologist | Shall determine whether the selected contrast protocol, if any, will achieve 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. |

## A.7. Image Data Acquisition

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

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.

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.

**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.

The **Localizer** provides on 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.

**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) |

## A.8. Image Data Reconstruction

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.

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.

**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.

**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 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 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) |

## A.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, 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 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 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 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.

**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 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 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 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

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 cm3 and 524 cm3.) |
| 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. |
| 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. |

## A.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. |

# Appendix B: Biomarker Usage?

TODO – characterize the purpose/content of this section

**Discussion**

**Confidence Thresholds:**  
The 95% confidence thresholds (**±**24%, **±**29%, **±**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 ± 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.

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. Different Scanner means different models (from the same or different vendors) were used at the two timepoints. Two scanners with different serial numbers but of the same model are considered to be the Same Scanner.

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 x sqrt(2 x wCV2), where wCV is estimated from the square root of the sum of the variances from the applicable sources of uncertainty (assuming 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 on phantoms and some on human subjects.

# Appendix C: 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 considered 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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# Appendix D: Conventions and Definitions

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

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

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

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

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

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

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

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

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

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

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.

# Bibliography / References

<Insert references>

# Open Issues

<TODO Subsections/describe keeping open and closed issues here for the committee and when they can/should be removed for publication>

## Open Issues

## Closed Issues

# Template Refinement Topics

How do we keep it short while allowing the early exploration process to keep everything on the table. Maybe a clean-break step? Make the case .

People have sweated over text and are loathe to see it go. (But it needs to be short)