



QIBA Profile: Atherosclerosis Biomarkers Assessment - 2018

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Stage: Initial authoring

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60 **1. Executive Summary**

Currently, clinical application of (C)CTA and atherosclerosis imaging is widely available as a technique used as a first line investigation of coronary vascular disease and in carotid as a second line for assessment of the plaque structure in order to choose the therapeutic approach (best medical treatment or revascularization). Evaluation of atherosclerotic arterial plaque characteristics is currently based-on qualitative markers. However, the reproducibility of such findings is poor even among experts [1]. While certain imaging biomarkers such as carotid stenosis and coronary calcium scores are well accepted in clinical practice, there are opportunities to add further biomarkers currently only applied in the research arena.

Quantitative imaging markers have been shown to have additive value above traditional qualitative imaging metrics and clinical risk scores regarding patient outcomes [2]. However, many definitions and cut-offs are present in the current literature, therefore standardization of quantitative evaluation of CTA datasets is needed before becoming a valuable tool in daily clinical practice. In order to establish these biomarkers in clinical practice, techniques to standardize quantitative imaging across different manufacturers with cross-calibration is required. Moreover, post processing of atherosclerotic disease segmentation needs to be optimized and standardized.

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker. Profile development is an evolutionary, phased process; this Profile is in the initial authoring stage. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document’s context: http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages.

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

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

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

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2. Clinical Context and Claim(s)

Clinical Context

Atherosclerosis is a major health concern for our aging population. The most significant underlying disease cause of mortality and morbidity in individuals older than 55 years and becoming the leading cause of death worldwide. Given the devastating impact of this widespread disease on individuals and population reflected in spiraling healthcare costs, biomarkers for better risk assessment and diagnosis at early stages, and monitoring of atherosclerosis will have a significant impact on public health. Noninvasive imaging biomarkers that would provide this information will have an impact to transform health care delivery and management. There is a critical gap in the biomarker qualification process, which needs to be addressed in order to move these quantitative imaging biomarkers forward.

The presence of atherosclerosis and the amount and type of arterial plaque have strong predictive value for acute events and for future cardiovascular events. Moreover, plaque composition may change dramatically over a few years and cardiovascular risk factors play a major role in these changes – changes that can be tracked with imaging. Further, recent evidences show that atherosclerosis is not only a progressive disease but it is possible to obtain also the plaque reversion. Intensive medical (lipid-lowering and anti-inflammatory) therapies may drive plaque reversion and conversion to a stable phenotype by strengthening the need to objectively quantify the amount and composition of the atherosclerotic plaque in order to monitor the plaque's response to the therapies. Multiple platforms and approaches exist in plaque assessment. They included both qualitative and quantitative methods. Many of these methods have been associated with outcomes.

CT angiography (CTA) offers the potential to non-invasively detect, quantify and characterize atherosclerotic plaque. Accurate identification and quantification of plaque components using CTA is challenging because of the technical limitations of CTA and requires optimization of image quality, however, CTA may provide valuable information for characterization of plaques. Plaque composition is associated with the likelihood for rupture and downstream ischemic events, but is known to be highly variable presently. Standardized protocols and analysis of plaque characteristics can increase early identification of patients at increased risk for adverse events.

Plaque imaging has been widely used to show association with ACS in acute chest pain setting. Data on prognostic value for 2-4 year follow up are also available (e.g., PROMISE, CONFIRM). Atherosclerosis compositional imaging biomarkers allow earlier diagnosis, better prediction and more sensitive monitoring of vessel wall disease. In particular, compositional atherosclerotic biomarkers (lipid core, calcification, vessel wall area) represent quantitative measures that could reduce the size and duration as well as increase the objectivity of clinical, multi-center trials. The key advantage of these measures is earlier detection before atherosclerotic plaque progression and end organ symptom presentation.

While clearly the scanning protocols and approaches differ widely across different anatomies, e.g., chest vs. neck scanning, differences in the analysis of images post reconstruction have sometimes resulted in unnecessary fragmentation in analysis product offerings and inability to leverage histopathologic validation (of course differences in the hardware scanning protocols are appropriate; here we refer to the analysis of reconstructed data). The prevalence of carotid artery disease and CAD are closely related [3]. Furthermore, carotid atherosclerosis has been shown to be an independent predictor for MACE, even in patients without pre-existing CAD [4]. Such findings suggest a common underlying pathogenesis shared in both conditions, which is further supported by the Multi-Ethnic Study of Atherosclerosis (MESA) [5]. Atherosclerosis develops progressively through continuous evolution of arterial wall lesions centered on the accumulation

of cholesterol-rich lipids and the accompanying inflammatory response, which changes are closely similar in the coronary arteries, the carotid arteries, and even the aorta [6]. Certain plaque characteristics such as large atheromatous core with lipid-rich content, thin fibrous cap, outward remodeling, infiltration of the plaque with macrophages and lymphocytes and thinning of the media are predisposing to vulnerability and rupture; and are similar in both carotid and coronary artery disease [7].

Plaque composition is similar in coronary and carotid arteries, irrespective of its age, and this will largely determine relative stability [8], suggesting similar presentation at CCTA as at CTA. Minor differences in the extent of the various plaque features may include a thicker fibrous cap and a higher prevalence of intraplaque hemorrhage and calcified nodules in the carotid arteries, however, without difference in the nature of plaque components [7]. In addition, the carotid and coronary arteries have many similarities in the physiology of vascular tone regulation that has effect on plaque evolution [9]. Myocardial blood perfusion is regulated by the vasodilation of epicardial coronary arteries in response to a variety of stimuli such as NO, causing dynamic changes in coronary arterial tone that can lead to multifold changes in coronary blood flow. In a similar fashion, carotid arteries are more than simple conduits supporting the brain circulation; they demonstrate vasoreactive properties in response to stimuli, including shear stress changes [10]. Endothelial shear stress contributes to endothelial health and a favorable vascular wall transcriptomic profile [11]. Clinical studies have demonstrated that areas of low endothelial shear stress in the coronary tree are associated with atherosclerosis development and high-risk plaque features [12]. Similarly, in the carotid arteries lower wall shear stress is associated with plaque development and localization [13].

It is important to acknowledge that technical challenges are different across beds (e.g. use of gating, vessel size, amount and nature of motion) – but these effects are mitigated by scan protocol, which result in approximate in-plane voxel sizes in the 0.5-0.75mm range, and the through-plane resolution of coronary (the smaller vessels) is actually better than, rather than inferior to, that of carotids (with the voxels being isotropic in coronary and not so in the neck and larger vessels extremities).

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

Claim 1: A true change in a lesion characteristic has occurred with 95% confidence if the measured measurand change is larger than 24% when the longest in-plane diameter is initially 50-100mm.

Claim 2: A true change in a lesion characteristic has occurred with 95% confidence if the measured measurand change is larger than 29% when the longest in-plane diameter is initially 35-49mm.

Claim 3: A true change in a lesion characteristic has occurred with 95% confidence if the measured measurand change is larger than 39% when the longest in-plane diameter is initially 10-34mm.

Claim 4: The lesion characteristic measurement performance, expressed as within-lesion within-subject standard deviation (wSD), is 0.085, 0.103, and 0.141 respectively for lesions with diameters of 50-100mm, 35-49mm, and 10-34mm. The resulting 95% confidence interval for the true change in area for several example measured lesions is <fill in>

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

These claims hold when:

- the lesion is measurable at both encounters (i.e., lesion margins are sufficiently conspicuous and

geometrically simple enough to be recognized on all images in both encounters; the lesion is unattached to other structures of equal density)

- the lesion longest in-plane diameter is between 10 mm (area 0.5 mm²) and 100 mm (area 524 mm²) at both encounters

180 **DISCUSSION**

Confidence Thresholds: The 95% confidence thresholds ($\pm 24\%$, $\pm 29\%$, $\pm 39\%$) in Claims 1, 2 and 3 can be thought of as “error bars” or “noise” around the measurement of measurand change. If you measure change within this range, you cannot be certain that there has really been a change. However, if a lesion changes size beyond these limits, you can be 95% confident there has been a true change in the size of the lesion, 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 lesion characteristic, the measured change should be at least 24% for a lesion 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 measurand change value. (See Confidence Interval of Result in section 3.1.2 below). If you measured the area to be 34 mm² at baseline and 268 mm² at follow-up (corresponding to a diameter change from 40mm to 80mm), then the 95% confidence interval for the true change is an increase in area of 234 mm² \pm 45. A confidence interval that contains zero indicates one should not conclude a true change has occurred.

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

CLAIMS

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 lesion the same conformant Imaging Physician actor and image analysis tool actor must make the measurement at both encounters. If a different Imaging Physician and/or image analysis tool was used at the baseline, this means the current Imaging Physician and image analysis tool must repeat the baseline measurement for the result to be conformant with this profile. The profile permits the other actors (acquisition device, technologist, physicist, etc.) to differ at the two encounters, 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, 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 Imaging Physician 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 Differences for Lesion Measurand changes (Informative)

Lesion Diameter	Different Acquisition Device				Same Acquisition Device			
	Different Imaging Physician		Same Imaging Physician		Different Imaging Physician		Same Imaging Physician	
	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:

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

3. Profile Requirements

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

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

240 **Table 3-1: Actors and Required Activities**

Actor	Activity
Site	Site Conformance and Periodic QA
Acquisition Device	Image Data Acquisition
Reconstruction Software	Image Data Reconstruction
Image Analysis Tool	Image Analysis
Imaging Physician	Subject Handling
	Image QA
	Image Analysis
Physicist	Site Conformance and Periodic QA
Technologist	Subject Handling
	Image Data Acquisition
	Image Data Reconstruction

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

245 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 Imaging Physician 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
250 purposes is entirely up to them.

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

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

260 The method for assessing atherosclerosis may be described as a pipeline. Subjects are prepared for scanning, raw image data is acquired, and images are reconstructed and evaluated. Such images may be obtained at (only) one encounter, or multiple longitudinally. When multiple encounters are available, in addition to assessing the disease at each individual encounter (referred to as a “cross sectional” claim) image analysis may further assess the degree of change between the available encounters. When expressed as a percentage, change is the difference for a given measurand between the encounters divided
265 by that at encounter 1. Although this introduces some asymmetry (e.g., measurements of 50mm² and 100mm² represent either a 100% increase or a 50% decrease depending on which was measured first), it is

more familiar to clinicians than using the average of the two encounters as the denominator.

The Profile does not intend to discourage innovation, although it strives to ensure that methods permitted by the profile requirements will result in performance that meets the Profile Claims. The above pipeline provides a reference model. Algorithms which achieve the same result as the reference model but use different methods may be permitted, for example by directly measuring the change between two image sets rather than measuring the absolute measurands separately. Developers of such algorithms are encouraged to work with the appropriate QIBA committee to conduct any groundwork and assessment procedure revisions needed to demonstrate the requisite performance.

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

3.0. Site Conformance and Periodic QA

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

DISCUSSION

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

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

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

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

SPECIFICATION

Parameter	Actor	Requirement
Acquisition Devices	Site	Shall confirm all participating acquisition devices conform to this Profile.
Reconstruction Software	Site	Shall confirm all participating reconstruction software conforms to this Profile.
Image Analysis Tools	Site	Shall confirm all participating image analysis tools conform to this Profile.
Imaging Physicians	Site	Shall confirm all participating Imaging Physicians conform to this Profile.
Physicists	Site	Shall confirm all participating physicists conform to this Profile.
Technologists	Site	Shall confirm all participating technologists conform to this Profile.
QC	Physicist	Shall perform relevant quality control procedures as recommended by the manufacturer. Shall record the date/time of QC procedures for auditing.

3.1. Subject Handling

295 This activity involves handling each imaging subject at each encounter. It includes subject handling details that are necessary to reliably meet the Profile Claims.

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.

300 **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.

305 **Timing Relative to Confounding Activities:** This document does not presume any timing relative to other activities. Fasting prior to a contemporaneous FDG PET scan 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 lesion measurands. Non-contrast CT might not permit an accurate characterization of the malignant visceral/nodal/soft-tissue lesions and assessment of lesion contours.

310 However, 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 Imaging Physicians 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 lesions may still be measured but the measurements will not be subject to the Profile claims.

315 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 encounters 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 encounters 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
320 consistent for all abdominal imaging encounters (although the tolerances for oral timing are larger than for intravenous).

Note that using no contrast at both encounters would be considered to be consistent enhancement at the two encounters.

325 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 Acquisition Device. 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
330 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

- 335 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 midaxillary line is at the widest part of the gantry.
- 340 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 in the behavior 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.
- 345 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 Claims. 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.
- 350 When imaging head and neck lesions, 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 encounters for a given patient.
- 355 The Subject Handling specification does not place requirements on patient positioning directly, but rather has the Imaging Physician disqualify measurements from the profile when the positioning at the two encounters is different. Consistent positioning will help ensure the majority of studies are conformant and thus achieve the profile Claim.
- 360 Recording the 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 the diagnostic CT setting) increase image noise. The effects of breast shields on image quality may vary depending on the types of shields and their positioning on the chest. 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 things such as breast shields so they do not degrade the reconstructed images.
- 365 Artifact sources, in particular metal and other high density materials, can degrade the reconstructed measurand data such that it is difficult to determine the true contour of a lesion. 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 measurand 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 lesions near the esophagus, this is not addressed here.
- 370 Consistent centering of the patient avoids unnecessary variation in the behavior of dose modulation algorithms during scan.
- Breath holding** reduces motion that might degrade the image. Full inspiration inflates the lungs, which separates structures and makes lesions more conspicuous.

375 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.

380 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)
- 385 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"

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

Timing/Triggers: The amount and distribution of contrast at the time of acquisition can affect the appearance and conspicuity of lesions.

395 **SPECIFICATION**

Parameter	Actor	Requirement
Contrast Protocol	Imaging Physician	Shall prescribe a contrast protocol (which may be No Contrast) that achieves enhancement consistent with baseline.
Use of intravenous contrast	Imaging Physician	Shall determine whether the selected contrast protocol, if any, will achieve sufficient lesion conspicuity.
	Technologist	Shall use the prescribed intravenous contrast parameters.
Use of oral contrast	Imaging Physician	Shall determine whether the selected contrast protocol, if any, will achieve sufficient lesion 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 measurands.
Table Height & Centering	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter. Shall position the patient such that the "sagittal laser line" lies along the sternum (e.g. from the suprasternal notch to the xiphoid process).
Breath hold	Technologist	Shall instruct the subject in proper breath-hold and start image acquisition shortly after full inspiration, taking into account the lag time between full inspiration and diaphragmatic relaxation.

3.2. Image Data Acquisition

This activity involves the acquisition of image data for a subject at either encounter. It includes details of

data acquisition that are necessary to reliably meet the Profile Claims.

400 **DISCUSSION**

CT scans for lesion characteristic 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 platform (manufacturer, model and version) which we expect will further reduce variation.

405 Many scan parameters can have direct or indirect effects on identifying, segmenting and measuring lesions. 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 3.4.2). 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 may, for example, validate ALL protocols for a given procedure so that any protocol the technologist selects will have been validated.

415 **Consistency with the baseline** implies a need for a method to record and communicate the baseline settings and make that information available at the time and place that subsequent scans are performed. Although it is conceivable that the scanner could retrieve prior/baseline images and extract acquisition parameters to encourage consistency, such interoperability mechanisms are not defined or mandated here. Similarly, managing and forwarding the data files when multiple sites are involved may exceed the practical capabilities of the participating sites. Sites should be prepared to use manual methods instead.

420 **Image Header** recordings of the key parameter values facilitate meeting and confirming the requirements to be consistent with the baseline scan.

The goal of **parameter consistency** is to achieve consistent performance. Parameter consistency when using the same scanner make/model generally means using the same values. Parameter consistency when the baseline was acquired on a *different* make/model may require some “interpretation” to achieve consistent performance since the same values may produce different behavior on different models.

430 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 Conformance Statements for Acquisition Devices and Reconstruction Software may be helpful for those looking for more guidance.

435 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, the regions subject to these artifacts, and is not required for imaging of the head, neck, pelvis, spine, or extremities.

Pitch is chosen so as to allow completion of the scan in a single breath hold.

Total Collimation Width (defined as the total nominal beam width, NxT, for example 64x1.25mm) is often not directly visible in the scanner interface. Manufacturer reference materials typically explain how to

440 determine this for a particular scanner make, model and operating mode. 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.

445 **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.

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.

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

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

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

460 Many reconstruction parameters can have direct or indirect effects on identifying, segmenting and measuring lesions. 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.

465 **Spatial Resolution** quantifies the ability to resolve spatial details and scales the impact of partial volume effects. Increased spatial resolution typically comes with an increase in noise which may degrade segmentation. If the spatial resolution is significantly different between the two encounters, 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 kernel (over which the user has some choice).

470 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 lesions 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 lesions both in the lung and elsewhere in the

475 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 contour of lesions by humans and automated algorithms. If algorithms become uniformly more "noise tolerant", the maximum threshold may be raised.

480 Decreased image noise is not always beneficial, if achieved through undesirable image manipulation (e.g. extreme amounts of image smoothing), 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 Acquisition Device 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.

Coverage of additional required anatomic regions (e.g. to monitor for metastases in areas of likely disease) depends on the requirements of the clinical trial or local clinical practice. In baseline scans, the lesion locations are unknown and may result in a lesion not being fully within a single breath-hold, making it “unmeasurable” in the sense of this Profile.

For subjects needing two or more **breath-holds** to fully cover an anatomic region, different lesions may be acquired on different breath-holds. It is still necessary that each lesion 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 lesion. A vertical scan plane (no tilt) is expected for all imaging except some head and neck exams.

Recording of Anatomic Coverage by the Acquisition Device may or may not depend on attention and interaction by the Technologist.

SPECIFICATION COMMON TO ARTERIAL BEDS

Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Imaging Physician	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
Acquisition Protocol	Acquisition Device	Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.	
	Acquisition	Shall validate that the protocol achieves an f50 value that is between 0.3	

Parameter	Actor	Requirement	DICOM Tag
	Device	mm ⁻¹ and 0.5 mm ⁻¹ for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution	
	Acquisition Device	Shall validate that the protocol achieves: <ul style="list-style-type: none"> a standard deviation that is < 20HU. See 4.2. Assessment Procedure: Voxel Noise	
Acquisition Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose.	

PROTOCOL SPECIFICATION UNIQUE TO CORONARY ARTERIES

Parameter	Actor	Requirement	DICOM Tag
Total Collimation Width	Imaging Physician	Shall set to Greater than or equal to 40mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Imaging Physician	Shall set to Less than or equal to 1.0mm.	Single Collimation Width (0018,9306)
Scan Duration	Imaging Physician	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)
Revolution Time	Imaging Physician	<fill in spec>	Revolution Time (0018,9305)
ECG Triggering	Imaging Physician	Shall be enabled with trigger set for end diastolic	

PROTOCOL SPECIFICATION UNIQUE TO CAROTID ARTERIES

Parameter	Actor	Requirement	DICOM Tag
Total Collimation Width	Imaging Physician	Shall set to Greater than or equal to 16mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Imaging Physician	Shall set to Less than or equal to 1.0mm.	Single Collimation Width (0018,9306)
Scan Duration	Imaging Physician	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)
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.	

3.3. Image Data Reconstruction

This activity involves the reconstruction of image data for a subject encounter. It includes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claims.

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 to have validated the protocols that the technologist will be using and conformance with the protocol depends on the technologist selecting those protocols.

Reconstruction Protocol affects the image pixel characteristics. The selection and reporting requirements imply a need for a method to record and communicate the protocol selected and any significant

modifications and make that information available to the Imaging Physician for the QA Activity. The Profile does not dictate any specific method. Manual methods are acceptable.

Reconstruction Field of View 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 encounter. 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, its effect on the spatial resolution will have been evaluated by the f50 requirement when determining conformance.

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 discontinuous data is unacceptable as it may “truncate” the spatial extent of the lesion, degrade the identification of lesion contours, confound the precision of measurement for total lesion measurands, etc. Decisions about overlap (having an interval that is less than the nominal reconstructed slice thickness) need to consider the technical requirements of the clinical trial, including effects on measurement, throughput, image analysis time, and storage requirements.

Reconstructing datasets with **overlap** will increase the number of images and may slow down throughput, increase reading time and increase storage requirements. For 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 lesions in the reconstructed images, which may influence measurements. 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 lesion must be measured on images reconstructed using consistent kernels at each encounter.

SPECIFICATION

Parameter	Actor	Requirement	DICOM Tag
Reconstruction Protocol	Imaging Physician	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	Imaging Physician	Shall set to between 0.5mm and 2.5mm (inclusive).	Slice Thickness (0018,0050)

Parameter	Actor	Requirement	DICOM Tag
Reconstructed Image Interval	Imaging Physician	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 that is between 0.3 mm ⁻¹ and 0.5 mm ⁻¹ for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution	
Voxel Noise	Physicist	Shall validate that the protocol achieves: <ul style="list-style-type: none"> a standard deviation that is < 60HU. See section 4.2. Assessment Procedure: Voxel Noise	
Reconstruction Protocol	Reconstruction Software	Shall be capable of performing reconstructions and producing images with all the parameters set as specified "Protocol Design Specification".	
Image Header	Reconstruction Software	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance.	
Reconstruction Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose.	
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)
Reconstruction Protocol	Reconstruction Software	Shall be capable of performing reconstructions and producing images with all the parameters set as specified "Protocol Design Specification".	
Image Header	Reconstruction Software	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance.	

565

3.4. 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 Claims.

DISCUSSION

570 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.

575 The Imaging Physician 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 at reporting time and as a result some or all of the lesion measurements may then be identified as not falling within the performance Claim 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 encounter and prone at another, then the direction of gravity changes and some lesions 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 quantitative assessment are not isotropic, changing the orientation of the lesion relative to the scan plane from one encounter 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 lesion contours as discussed in section 3.5, resulting in poor change measures and repeatability.

Clinical conditions can also degrade the ability to assess lesion contours, or influence the structure of the lesion 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 lesion extent.

Lesion Size can affect the accuracy of measurements. Both theoretical considerations and the groundwork projects done by QIBA indicate that for lesions that are small, errors in measurement represent a greater percentage of the measured size. For lesions 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 lesions that are extremely large, the limitations on measurement are based less on imaging physics and more on anatomy. Such lesions are likely to cross anatomical contours and abut structures that make consistent segmentation difficult.

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

Lesion Measurability is a general evaluation that is essentially left to the judgement of the Imaging Physician, and it is their responsibility to oversee segmentation and disqualify lesions with poor measurability or inconsistent segmentation between the two encounters. If the lesion 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 encounters, the Imaging Physician should disqualify the lesion. Conversely, if the lesion is attached to another structure but the Imaging Physician is confident they can get consistent segmentation over the two encounters, they may allow a lesion that would be otherwise disqualified.

Lesion Shape is not explicitly identified as a specification parameter. No specific lesion 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 lesions), the parameters for lesion size, lesion margin conspicuity and lesion 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 quantitative assessment.

Keep in mind that this Profile is "lesion-oriented". If one lesion in a study is excluded from the Profile Claim because the lesion does not conform with the specifications in this section, that does not affect other

620 lesions in the same study which do conform with these specifications at both encounters. Further, if a future study results in the excluded lesion being conformant at two encounters, then the claim holds across those two encounters.

625 While the Imaging Physician is responsible for confirming case conformance with the Image QA specifications, 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 Imaging Physician 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 lesion margins are sufficiently conspicuous").

SPECIFICATION

630 The Imaging Physician shall ensure that the following specifications have been evaluated for each lesion being measured.

Parameter	Actor	Requirement
Patient Motion Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to patient motion.
Dense Object Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to dense objects, materials or anatomic positioning.
Clinical Conditions	Imaging Physician	Shall confirm that there are no clinical conditions affecting the measurability of the lesion.
Contrast Enhancement	Imaging Physician	Shall confirm that the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
Patient Positioning Consistency	Imaging Physician	Shall confirm that any lesion deformation due to patient positioning is consistent with baseline (e.g. lesions may deform differently if the patient is supine in one scan and prone in another).
Breath Hold Consistency	Imaging Physician	Shall confirm that the breath hold state and degree of inspiration is consistent with baseline.
Scan Plane Consistency	Imaging Physician	Shall confirm that the anatomical slice orientation (due to gantry tilt or patient head/neck repositioning) is consistent with baseline.
Reconstructed Image Thickness	Imaging Physician	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	Imaging Physician	Shall confirm that the image field of view (FOV) resulting from acquisition and reconstruction settings appears consistent with baseline.
Lesion Measurability	Imaging Physician	Shall disqualify any lesion they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the Imaging Physician is confident and prepared to edit the contour to eliminate the impact, then the lesion need not be judged non-conformant to the Profile.

3.5. Image Analysis

635 This activity involves quantitative assessment of vessel structure and tissue composition of atherosclerosis within a target vessel or vessel subtree. It includes criteria and procedures related to producing quantitative measurements from the images that are necessary to reliably meet the Profile Claims.

DISCUSSION

Segmentation may be performed automatically by a software algorithm, manually by a human reader, or semi-automatically by an algorithm with human guidance/intervention, for example to identify a starting

seed point, stroke, or region, or to edit contours. Values may or may not correspond to the total of all the segmented voxels. The algorithm may consider partial volumes, do surface smoothing, lesion or organ modeling, or interpolation of user editing. The algorithm may also pre-process the images prior to segmentation. If a human reader participates in the segmentation, either by determining while looking at the images the proper settings for an automated process, or by manually editing contours, the settings for conversion of density into display levels (window and level) should either be fixed during the segmentation process or documented so that readers can apply consistent display settings at future encounters (or a different reader for the same encounter, if multiple readers may read each encounter, as for a clinical trial).

Segmentation Object Storage Storing segmentations and measurement results that can be loaded by an Image Analysis Tool analyzing data collected at a later date is certainly a useful practice as it can save time and cost. For this to happen reliably, the stored format must be compatible and the data must be stored and conveyed.

Tool Version 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.

Lesion Marking Determination of which lesions 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. Lesions to be measured may be designated by the Imaging Physician at a clinical site, by a reader at a central reading facility, or they may be designated automatically by the software analysis tool.

Audit Trail and Provenance 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 lesion segmentation contour as a DICOM Segmentation or NRRD file. Systems based on models should be capable of recording the model and parameters.

Multiple Encounters The Image Analysis Tool should be prepared to process both the current data and previous data at the same time and support matching across encounters in order to derive change values.

SPECIFICATION

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

Parameter	Actor	Requirement
Vessel structure	Image Analysis Tool	When used by readers of average capability and having been trained on the tool, using phantom ground truth as outlined in the Assessment Procedures:
		Lumen Area , range X-Ymm ² <i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]
		Wall Area , range X-Ymm ² <i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]
Max Wall Thickness , range	<i>Bias</i> : Zmm [l, h], <i>Intercept</i> : Wmm l, h], <i>Slope</i> : V [l, h],	

Parameter	Actor	Requirement												
		<table border="1"> <tr> <td>X-Ymm</td> <td><i>Quadratic</i>: U [l, h]</td> </tr> <tr> <td>Plaque Burden, range X-Y (unitless)</td> <td><i>Bias</i>: Z [l, h], <i>Intercept</i>: W [l, h], <i>Slope</i>: V [l, h], <i>Quadratic</i>: U [l, h]</td> </tr> </table>	X-Ymm	<i>Quadratic</i> : U [l, h]	Plaque Burden , range X-Y (unitless)	<i>Bias</i> : Z [l, h], <i>Intercept</i> : W [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]								
X-Ymm	<i>Quadratic</i> : U [l, h]													
Plaque Burden , range X-Y (unitless)	<i>Bias</i> : Z [l, h], <i>Intercept</i> : W [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]													
Tissue Composition	Image Analysis Tool	<p>When used by readers of average capability and having been trained on the tool, using histology ground truth as outlined in the Assessment Procedures:</p> <table border="1"> <tr> <td>Calcified Area, range X-Ymm²</td> <td><i>Bias</i>: Zmm² [l, h], <i>Intercept</i>: Wmm² [l, h], <i>Slope</i>: V [l, h], <i>Quadratic</i>: U [l, h]</td> </tr> <tr> <td>LRNC Area, range X-Ymm²</td> <td><i>Bias</i>: Zmm² [l, h], <i>Intercept</i>: Wmm² [l, h], <i>Slope</i>: V [l, h], <i>Quadratic</i>: U [l, h]</td> </tr> </table>	Calcified Area , range X-Ymm ²	<i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]	LRNC Area , range X-Ymm ²	<i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]								
Calcified Area , range X-Ymm ²	<i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]													
LRNC Area , range X-Ymm ²	<i>Bias</i> : Zmm ² [l, h], <i>Intercept</i> : Wmm ² [l, h], <i>Slope</i> : V [l, h], <i>Quadratic</i> : U [l, h]													
Reader variability	Image Analysis Tool	<p>When used by readers of average capability and having been trained on the tool, on clinical data sets as outlined in the Assessment Procedures:</p> <table border="1"> <tr> <td>Lumen Area, range X-Ymm²</td> <td><i>Inter-reader wSD</i>: Ammm² [l, h], <i>Intra-reader wSD</i>: Bmm² [l, h]</td> </tr> <tr> <td>Wall Area, range X-Ymm²</td> <td><i>Inter-reader wSD</i>: Ammm² [l, h], <i>Intra-reader wSD</i>: Bmm² [l, h]</td> </tr> <tr> <td>Max Wall Thickness, range X-Ymm</td> <td><i>Inter-reader wSD</i>: Amm [l, h], <i>Intra-reader wSD</i>: Bmm [l, h]</td> </tr> <tr> <td>Plaque Burden, range X-Y (unitless)</td> <td><i>Inter-reader wSD</i>: A [l, h], <i>Intra-reader wSD</i>: B [l, h]</td> </tr> <tr> <td>Calcified Area, range X-Ymm²</td> <td><i>Inter-reader wSD</i>: Ammm² [l, h], <i>Intra-reader wSD</i>: Bmm² [l, h]</td> </tr> <tr> <td>LRNC Area, range X-Ymm²</td> <td><i>Inter-reader wSD</i>: Ammm² [l, h], <i>Intra-reader wSD</i>: Bmm² [l, h]</td> </tr> </table>	Lumen Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]	Wall Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]	Max Wall Thickness , range X-Ymm	<i>Inter-reader wSD</i> : Amm [l, h], <i>Intra-reader wSD</i> : Bmm [l, h]	Plaque Burden , range X-Y (unitless)	<i>Inter-reader wSD</i> : A [l, h], <i>Intra-reader wSD</i> : B [l, h]	Calcified Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]	LRNC Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]
Lumen Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]													
Wall Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]													
Max Wall Thickness , range X-Ymm	<i>Inter-reader wSD</i> : Amm [l, h], <i>Intra-reader wSD</i> : Bmm [l, h]													
Plaque Burden , range X-Y (unitless)	<i>Inter-reader wSD</i> : A [l, h], <i>Intra-reader wSD</i> : B [l, h]													
Calcified Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]													
LRNC Area , range X-Ymm ²	<i>Inter-reader wSD</i> : Ammm ² [l, h], <i>Intra-reader wSD</i> : Bmm ² [l, h]													
Confidence interval	Image Analysis Tool	The Imaging Physician shall be able to call up a display for each measurand the range of plausible values for the given measurement stated in terms of the completed validation for the tool as a 95% interval.												
Provenance records	Image Analysis Tool	The identity, timing, and processing parameter settings for steps taken in the analysis of images shall be recorded and available to both visual as well as programmatic query.												
Result Verification	Imaging Physician	Shall review & approve margin contours produced by the tool.												
Multiple Lesions	Image Analysis Tool	Shall allow multiple lesions to be measured. Shall either correlate each measured lesion across encounters or support the Imaging Physician to unambiguously correlate them.												
Multiple encounters	Imaging Physician	Shall re-process the first encounter if it was processed by a different Image Analysis Tool or Imaging Physician.												
Multiple encounters	Image Analysis Tool	Shall be able to present the reader with both encounters side-by-side for comparison when processing the second encounter. Shall be able to re-process the first encounter (e.g. if it was processed by a different Image Analysis Tool or Imaging Physician).												

4. Assessment Procedures

To conform to this Profile, participating staff and equipment (“Actors”) shall support each activity assigned to them in Table 3-1. Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement references an Assessment Procedure subsection here in Section 4.

4.1. Assessment Procedure: In-plane Spatial Resolution

This procedure can be used by a manufacturer or an imaging site to assess the In-plane Spatial Resolution of reconstructed images. Resolution is assessed in terms of the f50 value (in mm⁻¹) of the modulation

transfer function (MTF). Loosely speaking, the MTF represents the blur of an infinitely small feature of interest, f_{50} represents the spatial frequency at which the contrast of the feature has decreased by 50%, and the inverse of the f_{50} value represents the size of a feature that would be degraded 50%. So for an f_{50} value of 0.4 mm^{-1} , features that are 2.5mm (or smaller) would have their contrast degraded by 50% (or more).

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

The assessor shall scan a spatial resolution phantom, such as the ACR CT Accreditation Program (CTAP) Phantom's module 1 or the AAPM TG233 phantom, which has a series of HU-value cylindrical inserts including one with soft-tissue equivalence. The acquisition protocol and reconstruction parameters shall conform to this Profile. The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2, i.e., the noise level during resolution assessment should correspond to that measured during noise assessment.

The phantom shall be positioned with the center of the phantom at isocenter and properly aligned along the z-axis. For further details, refer to Section C, Step 3 of the CT Accreditation Testing Instructions:

<http://www.acraccreditation.org/~media/ACRAccreditation/Documents/CT/CT-Accreditation-Testing-Instructions.pdf>

When the scan is performed, the assessor shall generate an MTF curve, measured as an average of the MTF in the x-y plane along the edge of a target soft-tissue equivalent insert using AAPM TG233 methodology as implemented in manufacturer analysis software, AAPM TG233 software or equivalent.

The assessor shall then determine and record the f_{50} value, defined as the spatial frequency (in mm^{-1} units) corresponding to 0.5 MTF on the MTF curve.

The assessor shall also generate the MTF curve and determine the f_{50} 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 air edge to assess, it is permitted to use the edge of the phantom.

The procedure described above 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. Note that for iterative reconstruction, the manufacturer may have specific test methodologies appropriate for the given algorithm.

Sites may submit to QIBA a proposed alternative method and evidence that the results produced by the proposed method are equivalent to this reference method or to the manufacturer method. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.

This assessment procedure is applicable to conventional filtered backprojection and to iterative reconstruction.

Note that in addition to the x-y plane MTF, the AAPM TG233 phantom and software also provides an axial resolution measurement (MTF in the z-direction), which may be used as a confirmation of the axial resolution anticipated from the reconstructed image thickness.

4.2. Assessment Procedure: Voxel Noise

This procedure can be used by a manufacturer or an imaging site to assess the voxel noise of reconstructed

images. Voxel noise is assessed in terms of the standard deviation of pixel values when imaging a material with uniform density.

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

730 The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2. When the scan is performed, the assessor shall select a single representative slice from the uniformity portion of the phantom.

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

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

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

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

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

4.3. Assessment Procedure: Vessel structure Bias and Linearity

755 This procedure can be used by a manufacturer or an imaging site to assess the bias and linearity of vessel structure. The bias and linearity of vessel structure calculations is estimated using a set of phantoms where ground truth measurements assessed by micrometer are known. The phantoms must be fabricated according to specifications that mimic appropriate CT characteristics and in sizes that represented a range of vessel sizes and presentations of interest. The phantoms must be filled with contrast media utilized in practice and scanned in a range of scanner settings that is representative of current clinical practice but which meet the requirements of this Profile. Statistical measures of bias were estimated from these data.

760 OBTAIN TEST IMAGE SET

The test image set consists of scanned physical phantoms (Figure 1).

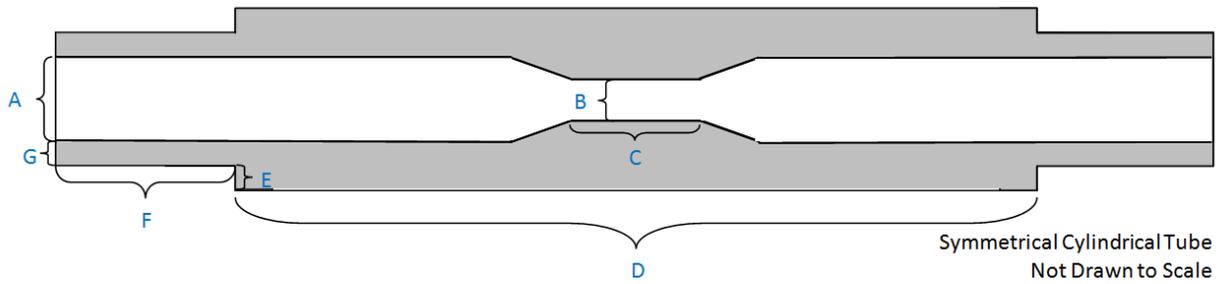


Figure 1: Physical Dimensions of Vascular Phantoms

An example material is Noryl, which has a density of 1.06 g/ml. The specifications for the phantoms that must be used are displayed on Table 1. If a given manufacturer wishes to support a subset rather than the whole range, then a note regarding the reduced scope needs to be made explicitly when representing conformance.

Table 1. Phantom Specifications

Phantom number	Surrogate artery	A Reference diameter (mm)	Reference area (mm ²)	B Stenosis diameter (mm)	Stenosis area (mm ²)	C Stenosis length (mm)	Diameter stenosis (%)	Area stenosis (%)	D Tube length1 (mm)	E Tube thick1 (mm)	F Tube length2 (mm)	G Tube thick2 (mm)
1	coronary	2.0	3.1	0.7	0.4	10.0	65.0	87.8	40.0	1.0	80.0	1.0
2	coronary	4.0	12.6	1.3	1.3	10.0	67.5	89.4	40.0	1.0	80.0	1.0
3	coronary/ vertebral	4.0	12.6	2.7	5.7	10.0	32.5	54.4	40.0	1.0	80.0	1.0
4	carotid	6.0	28.3	2.0	3.1	10.0	66.7	88.9	40.0	1.0	80.0	1.0
5	carotid	6.0	28.3	3.0	7.1	20.0	50.0	75.0	80.0	1.0	60.0	1.0
6	carotid	6.0	28.3	4.0	12.6	20.0	33.3	55.6	80.0	1.0	60.0	1.0
7	femoral	9.0	63.6	3.0	7.1	20.0	66.7	88.9	80.0	1.0	60.0	1.5
8	femoral	9.0	63.6	6.0	28.3	20.0	33.3	55.6	80.0	1.0	60.0	1.5
9	aorta	20.0	314.2	7.0	38.5	40.0	65.0	87.8	160.0	2.0	20.0	1.5

Each tube is a surrogate for at least one blood vessel. Phantom 1, 2, and 3 represent the size range of coronary arteries. Phantom 3 represents coronary and vertebral arteries. Phantom 4, 5, and 6 represent carotid arteries. Phantom 7 and 8 represent femoral arteries. Phantom 9 represents the abdominal aorta.

For the scans, the phantoms must be filled with diluted contrast agent (Omnipaque) between 10-12 mg iodine /ml to achieve the same contrast between vessel wall and lumen found in patient CTA scans at 100-120 kVp (based on published relationship of iodine concentration vs. HU for 80-120 kVp, ref. [14].

Suspend the phantoms in a plastic cage submerged in a box of vegetable oil, and scan at the same time. Acquire the test image set according to the requirements of this Profile (e.g. patient handling, acquisition protocol, reconstruction), to minimally include four admissible variations of scan parameters. By using a variance in CT scanning parameters, the performance analysis evaluates a spectrum of images rather than only one.

DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, recording how requirements as described in the Image Analysis Activity have been met.

The assessor is permitted to edit the segmentation or seed point if that is part of the normal operation of

the tool. If segmentation edits are performed, results should explicitly indicate whether they were achieved with and without editing.

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

When evaluating an Imaging Physician, a single tool shall be used for this entire assessment procedure.

The assessor shall calculate the measurands (Y) of each cross section (denoted Y_i) where Y denotes the measurand, and i denotes the i -th target.

790 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The natural log of the true measurements (X_i) as assessed by micrometer of each cross section are known and are provided in the dataset.

The assessor shall calculate the individual percentage bias (b_i) of the measurement of each cross section as

$$b_i = \ln Y_i - \ln X_i$$

795 The assessor shall estimate the population bias over the N cross sections as

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

The assessor shall convert to a percentage bias estimate as

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

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

The assessor shall divide the targets into a small vessel subgroup (vessels <4.5 mm) and a large subgroup (vessels ≥ 4.5 mm). The assessor shall repeat the percentage population bias calculation on each subgroup to estimate subgroup percentage bias, and then assess the ability to pool the results.

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

4.4. Assessment Procedure: Tissue Characteristics Bias and Linearity

810 This procedure can be used by a manufacturer the bias and linearity of tissue characteristics using histopathology as ground truth. Since annotation and positioning steps are performed with some degree of subjectivity, bias and linearity were estimated based on a random sample of pathologists and a random sample of radiologist/positioner combinations.

OBTAIN TEST IMAGE SET

815 Perform histology processing and assessment only at accredited centers and to ensure that ground truth processing be blinded to all other study data. Process sections at 2.0 mm throughout the length of the tissue specimen. It is acceptable to exclude sections (within reason and in no event cherry picking desirable sections) when the sample is too distorted, if it is missing significant portions due to specimen processing, if there is not enough visible tissue characteristics or distinct morphology to orient the *ex vivo* histology image to the *in vivo* radiology imaging, or if the pathologist marked tissue as a mixture of tissue types.

Correlate histology cross-sections with locations in the CT image volume. In one acceptable method, tissue portions of histopathologic images are converted into a mesh to facilitate returning its shape to its *in vivo* original using a finite element method (FEM) that factors in the tissue material type to simulate the stretching/compression of the relatively elastic material and then allow a positioner to rotate, tilt, and move the histology cross-section in 3D to provide a plausible alignment between the histopathology and radiology presentation. It is important to note that the matching must be performed using only raw CT, scrupulously avoiding use of the image analysis tool's computed segmentations to preserve objectivity in the matching.

Subjectivity of 3D placement must be systematically mitigated with consideration due to the sources of potential misalignment: (a) longitudinal displacement up or down the length of the vessel, (b) the angular tilt of the plane away from perpendicular to the vessel, and (c) the angular spin about the vessel.

DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, recording how requirements as described in the Image Analysis Activity have been met.

The assessor is permitted to edit the segmentation or seed point if that is part of the normal operation of the tool. If segmentation edits are performed, results should explicitly indicate whether they were achieved with and without editing.

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

When evaluating an Imaging Physician, a single tool shall be used for this entire assessment procedure.

The assessor shall calculate the measurands (Y) of each cross section (denoted Y_i) where Y denotes the measurand, and i denotes the i -th target.

CALCULATE STATISTICAL METRICS OF PERFORMANCE

The following must be performed in a strictly held-out set of subjects, and cannot be done iteratively. One the hold-out set has been used for evaluation, it may not be used for a later evaluation after the software changes, accept insofar as regression tests are performed where there is no material algorithm changes. It is highly advisable to anticipate this in advance when data is collected, and to pre-identify cohorts, and with sufficient numbers collected to support potentially many year development programs.

In order to properly account for sources of subjectivity, a minimum of three independent pathologist annotations and four positioned-radiologist reader combinations (that is, two independent positioning crossed with two independent radiology readings at each respective position) shall be collected and included in the analysis.

To assess bias, plot the value calculated by histopathologic examination versus the value calculated by image analysis tool. Inspect the resulting plot for associations between the magnitude of the histopathologic measurement and bias, associations between the magnitude of the histopathologic measurements and heteroscedasticity in the image analysis tool measurements, and limits of quantitation of image analysis tool measurements.

Fit a linear model, where the dependent variable is the image analysis tool measurement (Y) and the independent variable is the histopathology value (X). Generalized estimating equations (to account for the fact that subjects have more than one target) may be used to estimate the linear function, as follows: $E(Y|X) = \beta_0 + \beta_1 X$. An exchangeable working covariance may be used. Construct a 95% CI for the intercept

β_0 from the fitted model. CIs not containing 0 indicate constant bias. Also construct a 95% CI for the slope, intercept, and quadratic term. These calculations allow conclusions to be drawn regarding the linearity of the measurements (32).

Estimate the precision of the image analysis tool measurements by the standard deviation:

$$\sqrt{\frac{1}{n-1} \sum_{i=1}^n (Y_i - X_i - \bar{d})^2}, \text{ where } \bar{d} = \frac{1}{n} \sum_{i=1}^n (Y_i - X_i).$$

Construct a 95% CI for the standard deviation using bootstrap methods.

Present the bias profile (bias of measurements for various ranges of histopathology values versus the histopathology value) and precision profile (standard deviation of image analysis tool measurements from subjects with similar histopathologic values versus the histopathologic value) as summaries of image analysis tool measurement performance for the bias and precision components, respectively. Report the coverage probability at 80% coverage. The coverage probability is the probability that the absolute difference between the value calculated by image analysis tool measurements and the value calculated by histology is less than d_0 , ie, $\pi = \Pr(|Y - X| < d_0)$. Plot the coverage probability for a range of values for d_0 .

4.5. Assessment Procedure: Reader / Image Analysis Tool Variability

<fill in>

875 **Appendices****Appendix A: Acknowledgements and Attributions**

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

A more detailed description of the committee and its work can be found at the following web link:

<http://qibawiki.rsna.org/index.php?title=Committees>.

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890 **Appendix B: Conventions and Definitions**

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

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

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

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

906 Encounter: a discrete period during the course of a clinical trial when groups of imaging exams or clinical
907 exams are scheduled.

908 Lesion Definition Variability: the clarity of the lesion contour in the images. It originates from the biological
909 characteristics of the lesion, technical characteristics of the imaging process, and perhaps on the
910 perception, expertise and education of the operator.

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

914 Global Variability - partitioned as the variability in the lesion definition plus the "Technical" variability.

915 Intra-Reader Variability - is the variability in the interpretation of a set of images by the same reader after
916 an adequate period of time inserted to reduce recall bias.

917 Inter-Reader Variability - is the variability in the interpretation of a set of images by the different readers.

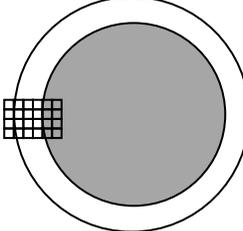
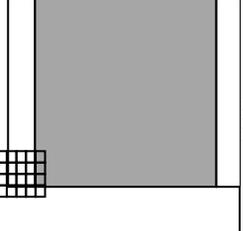
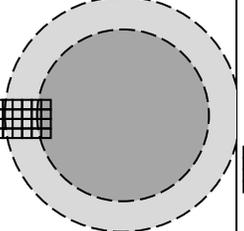
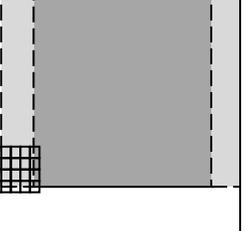
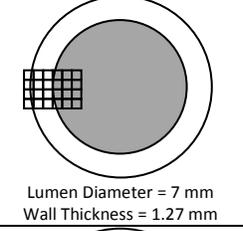
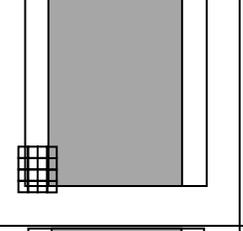
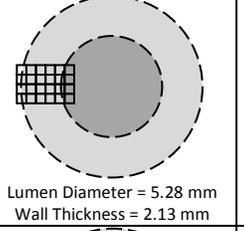
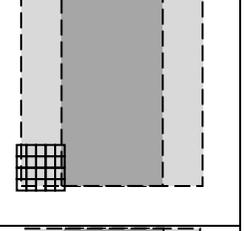
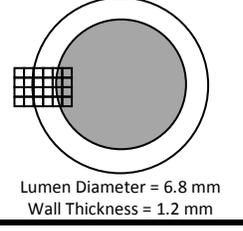
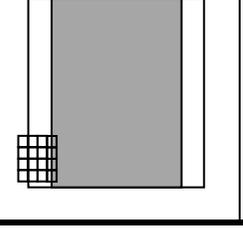
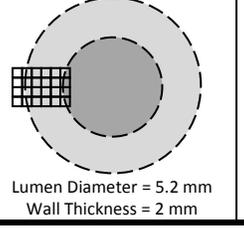
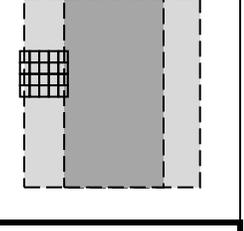
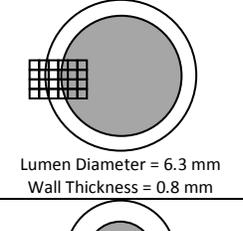
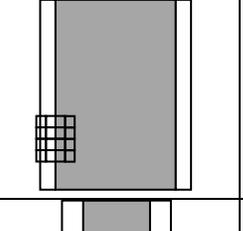
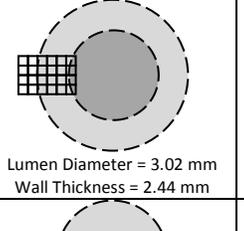
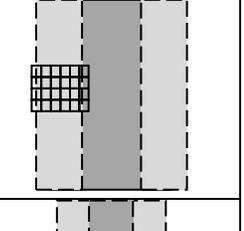
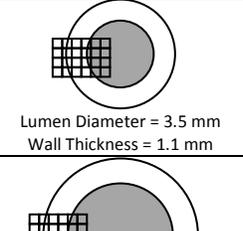
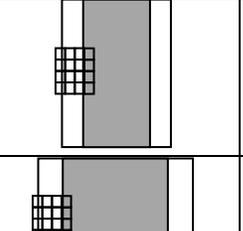
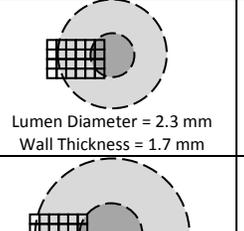
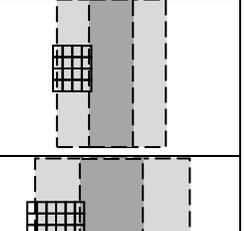
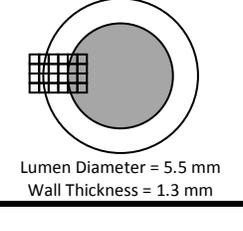
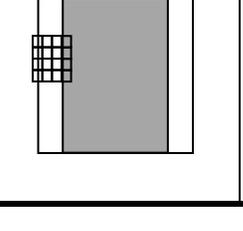
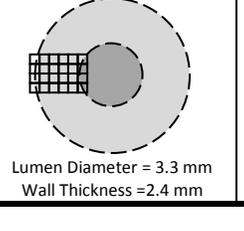
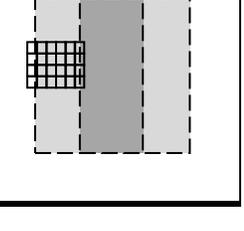
918 Repeatability – considers multiple measurements taken under the same conditions (same equipment,
919 parameters, reader, algorithm, etc.) but different subjects.

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

921

922 **Appendix C: Imaging Resolution Details**

923

Vessel	Resolution (mm)	Healthy (Axial)	Healthy (Coronal/Sagittal)	Diseased (Axial)	Disease (Coronal/Sagittal)
FEMORAL					
CT Axial Orientation Scan					
Common Femoral Artery ^{1,2}	0.5 x 0.5 x 0.63 	 Lumen Diameter = 9.5 mm Wall Thickness = 1.42 mm		 Lumen Diameter = 9.02 mm Wall Thickness = 1.66 mm	
Superficial Femoral Artery ^{3,4}	0.5 x 0.5 x 0.63 	 Lumen Diameter = 7 mm Wall Thickness = 1.27 mm		 Lumen Diameter = 5.28 mm Wall Thickness = 2.13 mm	
Deep Femoral Artery (profunda) ⁸	0.5 x 0.5 x 0.63 	 Lumen Diameter = 6.8 mm Wall Thickness = 1.2 mm		 Lumen Diameter = 5.2 mm Wall Thickness = 2 mm	
CAROTID					
CT Axial Orientation Scan					
Common Carotid Artery ^{1,9}	0.5 x 0.5 x 0.63 	 Lumen Diameter = 6.3 mm Wall Thickness = 0.8 mm		 Lumen Diameter = 3.02 mm Wall Thickness = 2.44 mm	
External Carotid Artery ⁹	0.5 x 0.5 x 0.63 	 Lumen Diameter = 3.5 mm Wall Thickness = 1.1 mm		 Lumen Diameter = 2.3 mm Wall Thickness = 1.7 mm	
Internal Carotid Artery ^{5,9}	0.5 x 0.5 x 0.63 	 Lumen Diameter = 5.5 mm Wall Thickness = 1.3 mm		 Lumen Diameter = 3.3 mm Wall Thickness = 2.4 mm	

CORONARY					
CT Varied Orientation					
Proximal RCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.4 mm Wall Thickness = 1.2 mm		 Lumen Diameter = 1.4 mm Wall Thickness = 2.2 mm	
Mid RCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.5 mm Wall Thickness = 1.1 mm		 Lumen Diameter = 1.3 mm Wall Thickness = 2.2 mm	
Distal RCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.1 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 1.3 mm Wall Thickness = 1.8 mm	
Left Main Coronary Artery ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 4.5 mm Wall Thickness = 1.85 mm		 Lumen Diameter = 2.8 mm Wall Thickness = 2.7 mm	
Proximal LAD Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.9 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 3.0 mm Wall Thickness = 2.0 mm	
Mid LAD Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.5 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	
Distal LAD Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 1.85 mm Wall Thickness = 0.79 mm		 Lumen Diameter = 1.85 mm Wall Thickness = 2.0 mm	
Proximal Circumflex Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.8 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	
Mid Circumflex Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.8 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	
Distal Circumflex Branch of LCA ^{6,7}	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.4 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	

- 924 ¹ Lumen diameter measurements taken from [15]
- 925 ² Wall thickness measurements taken from [16]
- 926 ³ Lumen diameter measurements taken from [17]
- 927 ⁴ Wall thickness measurements taken from [18]
- 928 ⁵ Lumen diameter measurements taken from [19]
- 929 ⁶ Lumen diameter measurements taken from [20]
- 930 ⁷ Wall thickness measurements taken from [21-23]
- 931 ⁸ Estimated
- 932 ⁹ Measurements taken from review of typical images
- 933

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Appendix D: Measurands with Description and Units

Measurand	Description	Units
Max Wall Thickness	Calculated by measuring the maximum cross-sectional wall thickness ("Max" refers to the maximum thickness of each cross section given that the wall thickness is not uniform)	Expressed in units of mm
Lumen Area	Calculated as cross-sectional area of blood channel at position along vessel centerline	Expressed in units of mm ²
Wall Area	Calculated as cross-sectional area of vessel at position along vessel centerline minus the LumenArea at that position	Expressed in units of mm ²
Plaque Burden	Calculated as WallArea / (WallArea + LumenArea)	Expressed as a unitless ratio
LRNC Area	The pathologic retention of lipids, particularly lipoproteins, by intimal/medial cells leading to progressive cell loss, cell death, degeneration, and necrosis. It is a mixture of lipid, cellular debris, blood and water in various concentrations.	Expressed in units of mm ²
Calcified Area	The physiologic defensive biological process of attempting to stabilize plaque, which has a mechanism akin to bone formation.	Expressed in units of mm ²

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Appendix E: CT Angiography Signal Applicability and Published Performance

The ability of standard CTA to reliably identify atherosclerotic plaque tissue characteristics and correlate them with cardiovascular events relative to the more widely reported use of MRI has not previously been well established in the literature. In principle, the Hounsfield Unit scale used by CT has the potential to be more quantitative than MRI due to the objective basis on which the voxel values are based, but terms like “soft plaque” instead of more specific terms like lipid-rich necrotic core are sometimes used in literature [24], suggesting less specificity. Ideal image processing would take this factor and partial volume effects into account. The speed and high-resolution of standard CTA scan protocols brings promise of more widespread adoption.

Examination of arterial beds using radiological imaging is common among three image modalities: ultrasound, CT, and MRI. A particularly thorough review paper [25] investigated the use of noninvasive imaging techniques in identifying plaque components and morphologic characteristics associated with atherosclerotic plaque vulnerability in carotid and coronary arteries. The review found 62 studies: 23 of which investigated ultrasound, 18 CT, 18 MRI, 2 that investigated both CT and ultrasound, and 1 that investigated both MRI and ultrasound. The 50 studies on the carotid arteries used histology as reference method, while the 12 studies on the coronary arteries used IVUS (but this would not be considered definitive as IVUS is itself not validated by histology).

VESSEL STRUCTURE

Source	Imaging Method	Reference	object	Structure measurement	Offset	Variability
de Weert 2006 [26]	CT	Inter-observer	7 Human carotid	Plaque Area (mm ²)	-5% constant over 74-111 mm ² range; poor below	8% constant over 74-111 mm ² range; poor below
de Weert 2006 [26]	CT	Inter-observer	13 Human carotid	Lumen Area (mm ²)	0% constant over 22-63 mm ² range; poor below	1% constant over 22-63 mm ² range; poor below
Kwee 2009 [27]	CT Auto	1.5T MR	14 Human carotid	Lumen Area	9% constant over 19-72 mm ² range; poor below	37% % constant over 19-72 mm ² range; poor below
Obaid 2013 [28]	CT	Intra-observer	22 Human coronaries	Lumen Area (mm ²)	-1% constant over 352-468 mm ² range; poor below	4% constant over 352-468 mm ² range; poor below
Papadopoulou 2013 [29]	CT	Intra-observer	162 Human coronaries	Lumen Area (mm ²)	2% constant over 12.8-23.2 mm ² range; poor below	10% constant over 12.8-23.2 mm ² range; poor below
Papadopoulou 2013 [29]	CT	Intra-observer	535 Human coronaries	Vessel Area (mm ²)	-1%	7%
Papadopoulou 2012 [30]	CT	Intra-observer	435 Human coronaries	Plaque Area (mm ²)	1% constant over 6.1-16.4 mm ² range; poor above	14% constant over 6.1-16.4 mm ² range; poor above
Rinehart 2011 [31]	CT	Inter-observer	85 Human coronaries	Minimum Lumen Diameter (mm)	-2% constant over 1.7-4.4 mm range; poor below	8% constant over 1.7-4.44 mm range; poor below
Rinehart 2011 [31]	CT	Inter-observer	179 Human coronaries	Minimum Lumen Area (mm ²)	0% constant over 1.6-21.2 mm ² range; poor below	14% constant over 1.6-21.2 mm ² range; poor below

TISSUE COMPOSITION

With a specific focus on CT, we quote a small illustrative sampling here to indicating the nature and utility of CT for characterizing atherosclerotic plaque:

- (quoted directly from introduction in [32]) In view of the limitations of [digital subtraction angiography], there is an increasing interest in CTA as a modality for assessing the carotid artery bifurcation. Computed tomography angiography is an imaging modality that can be used to accurately visualize the severity of luminal stenosis in 3D. With CTA it is extremely easy to detect calcifications in the carotid artery. CTA has also become an established method for successful artery calcium scoring in coronary arteries. With the introduction of Multi-detector CT (MDCT) in 1998 fast

964 imaging at high temporal and spatial resolution became possible. The main advantage of this
965 technology compared with conventional mechanical spiral CT scanner is that it consists of multiple
966 detector rows, which allow simultaneous acquisition of multiple slices. CT scanners using e.g. 16 and
967 64 – slice technology offer a very high spatial resolution and can generate very thin slices allowing
968 the acquisition of isotropic voxels. It has been shown, using 16-slice CT, that non-calcified coronary
969 lesions could be detected with a reasonable sensitivity of 78%. It has been also shown, with
970 comparison to histology, that assessment of carotid atherosclerotic plaque components is feasible
971 with MDCT using different plaque components Hounsfield units (HU) densities in vitro [20] and in
972 vivo [21]. In Figure 1.3 an illustration from of atherosclerotic plaques in MDCT cross-sectional slices
973 and corresponding histology samples are shown.

- 974 • (quoted directly from conclusions in [26]) The present study shows that MDCT is capable of
975 characterizing and quantifying plaque burden, calcifications, and fibrous tissue in atherosclerotic
976 carotid plaque in good correlation with histology, and that lipid core can be adequately quantified in
977 mildly calcified plaques. Furthermore the MDCT-based assessment of atherosclerotic plaque
978 component quantities was possible with moderate observer variability.
- 979 • (quoted directly from conclusions in [33]) Our study results indicate that [dual-source computed
980 tomography] angiography of the carotid arteries is feasible and the evaluation of carotid tissue
981 characteristics allows non-invasive assessment of different plaque components. Although some
982 limitations remain, [dual-source computed tomography] offers a high potential to non-invasively
983 assess the patients at a higher risk for stroke.

984 An often cited study supporting the use of CT to characterize plaques, while also documenting the factors
985 which can complicate overly simplistic methods [34], states:

- 986 • (from discussion) This study provides proof of principle that the tissue characteristics of
987 atherosclerotic plaques determined by CTA accurately reflects tissue characteristics of the lesion as
988 defined by histologic examination.
- 989 • (from results) The mean CT Hounsfield attenuation was measured for each of the 2x2-mm squares
990 that were electronically drawn on the CT reformatted images and considered in the linear
991 regression model with respect to the percentages of connective tissue, lipid-rich necrotic core,
992 hemorrhage, and calcifications in the corresponding histologic and micro-CT squares. The results of
993 the linear mixed model (i.e., mean Hounsfield attenuation for each histologic component and the
994 95% confidence intervals for these densities) are displayed in Table 2. There was significant overlap
995 in CT Hounsfield densities between lipid-rich necrotic core and connective tissue. There was also
996 some overlap between connective tissue and hemorrhage. Cutoff densities between lipid-rich
997 necrotic core and connective tissue, connective tissue and hemorrhage, and hemorrhage and
998 calcifications were determined as the halfway Hounsfield attenuation between the average
999 densities for each of the components: 39.5 Hounsfield units (HU) between lipid-rich necrotic core
1000 and connective tissue, 72.0 HU between connective tissue and hemorrhage, and 177.1 HU between
1001 hemorrhage and calcifications.

1002 Table 2 here reproduced for convenience (and with permission):

Table 2: Mean in-vivo CT Hounsfield density, SD, and 95% confidence interval for each histologic component*

Histologic Component	Mean (HU)	SD (HU)	95% Confidence Interval (HU)	
Lipid-rich necrotic core	32.6	20.0	-7.4	72.5
Connective tissue	46.4	19.9	6.6	86.2
Hemorrhage	97.5	22.0	53.5	141.6
Calcifications	256.7	30.2	216.3	297.1

Note:—HU indicates Hounsfield units.

* Determined by comparison of each 2×2 -mm square electronically drawn on the in vivo CT reformatted images with corresponding histologic and micro-CT squares.

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1004 Wintermark's Table 2, de Weert's result regarding cutoff values [26], and also work by Sieren [35] in lung
 1005 tissues considered for purposes of establishing the basic relationships between tissue types and their HU
 1006 values generally provide points of comparison with our work. These reference works highlight both what is
 1007 good about using HUs for characterization of lesion characteristics but at the same that which makes it
 1008 challenging. The principal challenge to QIBA-conformant image analysis tool is to mitigate limitations
 1009 gleaned from the various studies.

1010 More recently [36]:

- 1011 1. Tissue characteristics implicated in high risk atherosclerotic plaque may be quantitatively measured
 1012 from routinely available CTA in high correlation with histopathology (with Pearson correlation
 1013 coefficients for measurements greater than 5mm^2 of 0.973, 0.856, and 0.885 for Calcification, LRNC,
 1014 and Matrix respectively) and low reader variability (with Repeatability Coefficients $\leq 1.8\text{mm}^2$ and
 1015 Reproducibility Coefficients $\leq 4.4\text{mm}^2$), assessed on 2D cross-sections within calculated 3D
 1016 volumes.
- 1017 2. Overestimation of calcification on CTA may be successfully mitigated as evidenced by bias in
 1018 measurements of calcification area being -0.096mm^2 and demonstrating the property of linearity as
 1019 confirmed by histopathology when evaluated on held-out test data.
- 1020 3. Underestimation of lipid-rich necrotic core (LRNC) on CTA may be successfully mitigated as
 1021 evidenced by bias in measurements of LRNC area being 1.26mm^2 and demonstrating the property
 1022 of linearity as confirmed by histopathology when evaluated on held-out test data.
- 1023 4. Bias in measurements of tissue matrix area on CTA was -2.44mm^2 and demonstrating the property
 1024 of linearity as confirmed by histopathology when evaluated on held-out test data.

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