

QIBA Profile:

Computed Tomography: Lung Densitometry

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# Change Log:

This table is a best-effort of the authors to summarize significant changes to the Profile.

|  |  |  |
| --- | --- | --- |
| **Date** | **Sections Affected** | **Summary of Change** |
| 2016.06.21 | All | First Draft |
| 2016.07.20 | Up to Section 3 | Per call discussion, modified specification for lung inflation volume. Completed changes through Section 2 with draft to be reviewed for internal comment. |
| 2016.07.24 | Section 3 | Assigned for discussion at next call (tentatively 2016.08.03) |
| 2016.08.31 | All | Cleanup of current discussions, additions to Section 3. |
| 2016.09.26 | Discussed Thru Section 3.2 | Took comments during call on organization, phantom specifications and statistics.  |
| 2016.11.16 | Updated Section 4.0, Assessment Procedures | Inserted text documenting detailed harmonization calculations provided by Dr. Chen-Mayer |
| 2016.11.16 | Addressed Call Comments Through Section 3 | Final approval from group on call. |
| 2017.02.01 | Updates to Calibration Sections for Scanner Qualification (3.1) | Stephen Humphries |
| 2017.03.29 | Revisions to Clinical Interpretation Sections and to finalize profile | David Lynch and Sean Fain |
| 2017.08.13 | 1. Added example of clinical context of claims
2. AEC moved to closed issue.
3. 3.3.2 and 3.6.2 specifications made consistent with text
4. References updated.
5. Appendix D added
6. Modifications to section 3.8 (software analysis)
7. Created Section 4.3 and place holder for Appendix E.
 | Sean Fain - Modifications in response to face to face meeting suggestions and 6/28/17 call.  |
| 2017.08.30 | 1. Moved AEC back to “Open Issue”2. Created a Clean Version for Distribution |  |

# Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage.

|  |
| --- |
| **Q.** What is the effect of iterative reconstruction (IR) methods on RA-950 HU and Perc 15 measures of lung parenchymal density?**A.** The resolution of this question is actively under investigation as part of a development/ground work project. The use of IR would be desirable to reduce CT dose to research subjects and patients undergoing quantitative CT of the lungs. Several published works have emerged, one in Medical Physics from this committee, demonstrating that IR methods reduce noise and have non-linear effects on texture and other low contrast structures. Further complicating this issue, vendors use different statistical and model-based IR methods in their commercial software that may affect image noise differently and would thus need to be harmonized across vendors. Additionally, IR methods are likely to continue to evolve, and continued ongoing assessment will be needed. We anticipate that after further study, recommendations for integration of IR methods into the Profile can be added to later versions. |
|  |
| **Q.** What is the best reference standard for harmonizing systematic differences in quantitative CT number (Hounsfield Unit – HU) across scanner make and model?**A.** Two rounds of scans conducted with engineers from 4 major vendors (Siemens, GE, Toshiba, and Philips) using the QIBA-SRM phantom to establish bias and precision of HU measure have been completed. A method to empirically correct to a common reference scanner has been shown to reduce bias and improve precision of qCT measures in this phantom. A model-based correction method based on the composition (best-knowledge) and the certified physical densities of the constituent materials of the QIBA-SRM phantom has also shown promise as an absolute correction (standardization) method, and a manuscript is under review by Medical Physics. The standardization method is being actively pursued and tested in the Round 2 analysis, with data acquisition completed and analysis pending.  |
| **Q.** There is a concern that a subject with 2 weak efforts, but less than 10% difference in lung inflation would still be accepted by this profile. Is a subject with this type of effort adequately quantifiable by this profile?Previous Comments: On the 2016.07.20 call discussed having Dr. Fain and Dr. Heather Chen-Mayer modify this threshold based on the observed standard deviation of volume changes from the studies included in the meta-analysis. Will hold this to smaller than 10% difference in lung inflation for now to be adjusted once information from the meta-analysis is known.From Dr. Chen-Meyer: Based on review of Dr. Park’s study in the meta-analysis, the range of fractional change of volume, V2/V1, is [0.90, 1.11], i.e. [-10%, +11%]. This was the study with the longest time interval between baseline and follow-up scans. For Dr. Chong’s study there is no direct data but it is possible to infer from their repeatability coefficient that the variation in lung volume was within 0.67 L, which for an average 7L total lung capacity fits nicely within the 10% threshold.Dr. Fain proposes that this case is well addressed by the current Profile in “Section 3.3 Subject Handling” where we explicitly describe the breath-hold coaching required to obtain a scan that conforms to a lung inflation standard that would meet the claims. Because we are assessing longitudinal change, it is less important (but still desirable) that the subject be within 90% of vital capacity. However published works do not in practice require spirometric gating (see Gierada et al., Radiology 220(2):448-454.), nor was spirometric gating of breath-hold used in the studies included in the meta-analysis. **A.**  Request a motion that this issue can be closed based on discussion above. |
| **Q.** Should the acquisition parameters include specification of matrix size or display FOV? **A.** This is specified if the in-plane spatial resolution is met. |
| **Q.** Does this profile meet any standards for airway morphology (e.g. wall thickness and lumen area) measurement?A. This profile meets claims for parenchymal density analysis only, but spatial resolution specifications under acquisition and reconstruction are also consistent with current methods in the literature for measurement of airway morphology assuming commercially available software analysis methods. A claim for airway measures is left for future versions.  |
| **Q.** Should the measurement methods specify regional measures (e.g. upper, middle, lower thirds) or lobar segmentation and density measurement methods used to guide lung volume reduction interventions?**A.** There is currently inadequate evidence to evaluate this issue, but there is little doubt that lobar segmentation is an emerging application for targeted lung volume reduction (by valve placement or surgically). While lobar specific density analysis is not part of the current profile, we expect to address this directly in future versions. However, it should be noted that there is no reason to think that the proposed protocols, including acquisition and reconstruction would not still serve this application equally well with the same quality assurance processes, not including software analysis. The main challenge preventing us from including this application in the claims is that some software analysis and measurement steps would need to be performed at the lobar level raising new challenges for accuracy and precision of segmentation, especially using automated techniques. More effort to characterize consistency and consequences of errors in lobar segmentation for lung volume reduction applications are needed to define claims for this application.  |
| **Q.** What is the effect of automated exposure control (AEC) on RA-950 HU and Perc 15 across scanner make and model?**A.** The use of AEC is desirable as a method that reduces dose and makes noise behavior more consistent throughout the image by matching tube current to achieve similar photon counts across varying structural attenuation. However, different vendors match performance to the selected AEC parameter to emphasize different features in the image and proprietary models are used to predict tube current modulation based on initial scout scans. Ground work performed by the Lung Density Biomarker Committee has led to harmonized protocols that match CT dose for AEC parameter selection across scanner makes and models (see protocol examples in Appendix D). More study is needed to resolve this issue in general, but the committee considers that AEC is sufficiently mature and resolved by empirically matching settings across scanner makes and models for inclusion in study protocols. Recommendations will be updated in later versions of this profile as more general solutions become available. |

# Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

|  |
| --- |
| **Q. Is this template open to further revisions?**A. Yes.This is an iterative process by nature.Submit issues and new suggestions/ideas to the QIBA Process Cmte. |
| **Q. Choice of key biomarkers of lung density resolved?**A. Yes, RA-950 HU and Perc 15 are the most established measures of emphysema, as both are validated against tissue histology. Perc 15 is used most ubiquitously in clinical research trials. |
| **Q. Whole lung or regional (e.g. lobar) measures of density recommended?**A. Whole lung at present. Regional measures may be introduced in later versions. |
| **Q. Will airway measures be included?**A. No. |
| **Q. Will density measures of air trapping be included?**A. No. |
| **Q. Will lung volume adjustment of RA-950 HU and Perc 15 be included in the Profile?**A. Yes, but no specific method will be recommended in this version of the Profile as this remains a developing area of research. |
| **Q. There is a concern that a subject with 2 weak efforts, but less than 10% difference in lung inflation would still be accepted by this profile. Is a subject with this type of effort adequately quantifiable by this profile?** A. Yes. Based on review of Dr. Park’s study in the meta-analysis, the range of fractional change of volume, V2/V1, is [0.90, 1.11], i.e. [-10%, +11%]. This was the study with the longest time interval between baseline and follow-up scans. This case is well addressed by the current Profile in “Section 3.3 Subject Handling” where it is explicitly described that the breath-hold coaching required conforms to a lung inflation standard that would meet the claims. Because we are assessing longitudinal change, it is less important (but still desirable) that the subject be within 90% of vital capacity. Published works do not in practice require spirometric gating (see Gierada et al., Radiology 220(2):448-454.), nor was spirometric gating of breath-hold used in the studies included in the meta-analysis. |
| **Q. Will there be a cross-sectional claim?**A. No, there is not sufficient data at the present time to support a cross-sectional claim. Both current claims are longitudinal, reporting change in emphysema extent. |
|  |

# 1. Executive Summary

The goal of a QIBA Profile is to achieve a repeatable and useful level of performance for measures of lung density from quantitative CT using the RA-950 HU and Perc 15 biomarkers of emphysema. Please see Appendix B for more detailed information on the calculation of and rationale for RA-950 HU and Perc 15 as the biomarkers of choice.

The **Claim** (Section 2) describes the performance in terms of bias and precision of RA-950 HU and Perc 15 for detecting change in lung density.
The **Activities** (Section 3) describe how to generate RA-950 HU and Perc 15 for longitudinal studies of the change in lung density. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim in Section 2.
**Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.

This QIBA Profile (Computed Tomography: Lung Densitometry) addresses RA-950 HU and Perc 15 for longitudinal studies which are often used as biomarkers of emphysema progression in chronic obstructive pulmonary disease (COPD) or as a response to cessation of smoking and possible future treatment approaches. It places requirements on Acquisition Devices, Technologists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis.

The requirements are focused on achieving negligible bias and avoiding unnecessary variability of the RA-950 HU and Perc 15 measurements by compensating for variations in CT number due to inconsistency of lung inflation volume and calibration of the CT scanner, and vendor-specific bias due to CT scanner make and model. To meet the claims, scanner calibration is performed using a well characterized imaging phantom ideally containing lung equivalent density foams as described in Section 4.1.

The clinical performance targets are to achieve a minimum threshold for change in RA-950 HU of 3.7% of the normalized lung volume, or a minimum threshold for change in Perc 15 of 11 HU.

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 document only states requirements to achieve the claim, not “requirements for standard of care.” Conformance to this Profile is less important than providing appropriate patient care.

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

# 2. Clinical Context and Claims

Clinical Context

The clinical context for this profile includes studies of quantitative longitudinal change in lung parenchymal density using image processing of CT scans acquired at different time points to quantify progression of emphysema in COPD. These studies specifically evaluate increase or decrease of lung relative area falling below a threshold of -950 HU (RA -950 HU) or the HU corresponding to a threshold at 15% of the lung relative area (Perc 15).

Volume adjustment (VA) refers to techniques to correct for differences in lung inflation volume between time points. The literature has noted that differences in lung inflation volume are present in longitudinal studies and thus repeatability is improved using some type of VA as discussed in more detail below and in Appendix B. That said, achieving consistent lung inflation volume through consistent breath-hold coaching and communication as described in Section 3.3.1 is required (and one of the most under appreciated procedures in the workflow) to achieve the claims. To further guide the various stakeholders interested in quantitative lung density measures using CT, we include protocols in Appendix D that meet or exceed the stated claims.

**Conformance to the requirements of this Profile supports the following claims:**

Claim 1: Without lung VA, an increase in RA -950 of at least 3.7%, or a decrease in Perc 15 of at least 18 HU, is required for detection of an increase in the extent of emphysema, with 95% confidence.

Claim 2: With lung VA, a decrease in Perc15 of at least 11 HU, is required for detection of an increase in the extent of emphysema, with 95% probability.

**These claims hold when:**

* **The thoracic cavity is fully represented in the field of view and readily segmented from the chest wall.**
* **Contrast agent is not present. Contrast agents shall not be used in the CT assessment of parenchymal lung density.**
* **The subject is scanned on the same CT scanner with the same acquisition and reconstruction parameters for baseline and followup scans**
* **The difference in lung inflation is smaller than 10% of baseline lung inflation.**
* **The lung parenchyma is devoid of respiratory motion artifact (unavoidable artifact due to cardiac motion is acceptable), and does not show underlying parenchymal infiltrates.**
* **Voxel noise, spatial resolution, and CT dose meet the specifications described in Section 3.4.2.**

**Discussion**

The confidence intervals defined for the claims, e.g. -18 and +18 HU in Claim 1 for the Perc15 measure, define boundaries that can be thought of as “error bars” or “noise” around the measurement of lung density. If one measures change within this range, one cannot be certain that there has really been a change. However, if lung density changes beyond these limits, one can be 95% confident there has been a true change in lung density, and the perceived change is not just measurement variability. Examples of scenarios for measures that are considered within the variability expected, and thus not a true change, vs a measure that exceeds the threshold for a true change are illustrated in **Figure 1**.



**Figure 1**: Example Bland-Altman plot for perc15 without VA; the LOA (or RC) are the thresholds required for detection of a true increase in the extent of emphysema. The first step is to assess whether a measurement meets the threshold for a true change (red crosses above the LOA’s above would be considered subjects showing true change).

 Determination of the magnitude of the change is then made relative to the standard error of the repeatability coefficient.

Note that this does not address the biological significance of the change, just the likelihood that the measured change is real. Once a real change has been identified, the magnitude of the change relative to the standard error of the repeatability coefficient is determined. For a protocol without VA and given a measured change of x HU in Perc15, the range for the true change is expected to lie in the interval [x -18 HU, x +18 HU] with 95% confidence; and for a measured change of y% in RA950, the range for the true change is expected to lie in the interval [y -3.7%, y +3.7%] with 95% confidence. For a protocol with VA, repeatability is improved such that given a measurement of x HU in Perc 15, the range for the true change is expected to lie in the interval [x -11 HU, x +11 HU] with 95% confidence. More detail on how these limits are calculated is described below and provided in Appendix B. However, it bears emphasis that VA should not be thought of as an alternative to breath-hold coaching and control. Consistent breath-hold coaching followed by simple visual inspection to confirm chest inflation by the coordinator or technologist is required to meet the claims. VA is an analysis tool to further improve repeatability in addition to prospective breath-hold coaching and control.

These claims are based on estimates of the repeatability coefficient (RC) of the RA -950 HU and the Perc 15, measured from the histogram of both lungs after segmentation of the thoracic cavity and removal of blood vessels and airways as described in more detail in Section 3.8. The repeatability coefficient (RC) is defined as 1.96 2 wSD, where wSD is the within-subject standard deviation. Specific definitions used to calculate the expected range for RA -950 HU and Perc 15 are defined in Appendix C. The claim assumes that there is negligible proportional bias in the measurements (i.e. bias < 5% of the measurement), and is supported by a meta-analysis (Appendix B) of studies conducted at the same site using the same scan protocol and CT scanner make and model. Further adjustment to remove bias is required when scanning subjects longitudinally on different CT scanner makes and models. Future versions of the Profile that seek to harmonize CT number or HU across different scanner makes and models may address this limitation, but this remains an open issue.

The method of VA refers generally to techniques to correct for differences in lung inflation volume between time points. The meta-analysis study in Appendix B supports the generally recognized fact that VA is useful for improving the precision of repeat CT measurements of lung density. The claim language is separated into without and with VA to reflect a narrower 95% confidence limit as a result of VA. For RA -950, only 2 repeatability studies were available, which was insufficient to support a meta-analysis to inform the impact of VA on the claim for the RA -950 metric. For the studies supporting the stated claims, the method of VA varied. Because more advanced techniques for VA continue to emerge, this document does not intend to suggest any particular model or method for VA. Appendix B provides a description of VA methods that fit the selection criteria.

Clinical interpretation with respect to the magnitude of true change:
Measurement of whole lung parenchymal lung density with CT has been used for several decades in clinical research as a marker of emphysema. For repeat CT examinations that are performed primarily for emphysema quantification, a decrease in Perc15 of at least 11 HU or an increase in RA -950 of at least 3.7%, is required for detection of an increase in the extent of emphysema, with 95% probability. Both of these measures reflect specific thresholds of the histogram of lung densities in HU and reflect loss of lung tissue based on a combination of comparisons to microscopic histology and associations with known measures of whole lung function. The committee recognizes that these limits of variability are substantially greater than the average change in lung density identified in individual subjects with emphysema. In untreated subjects with alpha-1 anti-trypsin deficiency, the average annual decline in 15th percentile lung density (adjusted for lung volumes) is about 2.2 g/L per year (corresponding to 2.2 HU) 1,2*.* In cigarette smokers with COPD, the average annual decline in lung density is about 1.1 g/L, or 1.1 HU 3. Given this discrepancy, the chief value of measuring change in lung attenuation will be in research cohorts in clinical trials; changes measured in individual subjects are unlikely to exceed the limits of variability. It is hoped that in the future, with greater adherence to this profile, the limits of variability can be narrowed to be more compatible with the changes expected in individual subjects.

These longitudinal claims have been informed by an extensive review of the literature and expert consensus, but have not yet been 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 any appropriate changes made to the claim or the details of the Profile. At that point, this caveat may be removed or re-stated.

The performance values in the reported claims reflect the likely impact of variations permitted by this Profile since the meta-analysis was based on studies that incorporated variable methods of CT reconstruction, image analysis software, and method of VA used. The Profile thus allows for the possibility of using variable approaches to attaining lung inflation volume, CT scanner protocol and analysis tools. However, in its current form the Profile would not permit different compliant actors (acquisition device, radiologist, image analysis tool, etc.) at the two time points (i.e. it is required that the same scanner or image analysis tool be used for both exams of a patient). Again, future versions of the Profile that seek to harmonize CT number or HU across different scanner makes and models could potentially relax this requirement, but this remains an open issue.

# 3. Profile Activities

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

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

Table 1: Actors and Required Activities

|  |  |  |
| --- | --- | --- |
| **Actor** | **Activity** | **Section** |
| Acquisition Device | Scanner Qualification | 3.1. |
| Periodic QA | 3.2. |
| Subject Handling | 3.3. |
| Image Data Acquisition | 3.4. |
| Physicist/Technologist | Scanner Qualification | 3.1. |
| Image QA | 3.6. |
| Technologist | Subject Handling | 3.3. |
| Image QA | 3.6. |
| Image Data Acquisition | 3.4. |
| Image Data Reconstruction | 3.5. |
| Image Distribution | 3.7. |
| Clinician or Statistician | Subject Handling | 3.3. |
| Image QA | 3.6. |
| Image Interpretation | 3.9. |
| Reconstruction Software | Image Data Reconstruction | 3.5. |
| Image Analysis Software | Image Analysis | 3.8. |

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a “shall” in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How users of this profile decide to handle deviations for analysis purposes is entirely up to them. The sequencing of the Activities specified in this Profile are shown in **Figure 2**.



**Figure 2: Computed Tomography: Lung Densitometry – Work flow**

## 3.1. Scanner Qualification

This activity describes performance assessment, calibration or standardization, and validations of equipment that are necessary to reliably meet the Profile Claim. These specifications are defined based on groundwork projects from vendor round 1 and 2 studies.

CT scans will be performed on equipment that complies with the specifications set out in Table 3.1.2. At present CT baseline and follow-up scans must be acquired using the same scanner make and model to meet the claims. Differences in scanner beam characteristics and calibrations by manufacturer and model are likely sources of systematic variation. A method to empirically correct to a common reference scanner has been shown to reduce bias and improve precision of qCT measures in phantom testing 4, although this is not strictly necessary to meet the current claims.

A model-based correction method based on the composition and the certified physical densities of the constituent materials of the QIBA-SRM phantom has also shown promise as an absolute correction method (i.e. standardization). The standardization scheme to be used across scanner platforms is currently being devised as part of active groundwork and remains an “open issues” for purposes of this version of the Profile. The goal of this work is to eliminate scanner dependent parameters and compare the results of the true material properties such as electron density across baseline and follow-up scans that can occur potentially with different scanner makes and models. Following initial scanner qualification specifications in Table 3.1.2, periodic quality assurance (QA) is necessary to ensure consistency over time as specified in Table 3.2.2.

### 3.1.1 Discussion

Initial qualification of a scanner involves verification that the equipment complies with specifications described in Table 3.1.2. Subsequent qualification of a scanner for evaluation of longitudinal change in lung density requires calibration of Hounsfield Unit (HU) values to improve precision and reduce bias. Modern scanners have the ability to achieve sub-HU standard deviations for intra-scanner repeat scans in the lung density region. It is desirable to confine the variations from different measurement systems to within 1 HU using an adequate test object.

This is accomplished by scanning a phantom test object, which includes reference material samples whose density and composition are known precisely. An example of a suitable reference phantom is the COPD Gene test object 5,6. However for more advanced studies in which standardization is required across a network of sites including different scanner makes and models, an ideal reference object would include a series of at least five foam standards whose density is in the range of lung parenchyma (64-321 kg/m3) that have been calibrated to their true densities. Such a phantom is introduced and described in Section 4.1 (**Figure 3**). Measurement of HU values within material samples whose composition is known establishes a HU-electron density relationship for a given scanner and protocol 4.

To perform the calibration procedure, five (N = 5) repeat scans of the phantom shall be acquired using a pre-determined, vendor optimized protocol. Acquisition parameters have been specified to allow completion of the scan of the whole lung volume in a single breath-hold of less than 10 seconds. Faster scan time can further reduce breath-hold duration and reduce the likelihood of respiratory motion artifacts. It is expected that scout (topogram, scanigram, etc.) images will be initially obtained to optimize positioning and coverage of an imaging phantom. Using a standard commercial software package 7, or published open source package [e.g. http://airwayinspector.acil-bwh.org/], regions of interest (ROIs) shall be placed within each material sample and mean HU values (within ROIs) averaged over repeated scans. The selected ROI’s must contain 10,000 voxels to be within ±0.2 HU error and centered within the material of interest to avoid artifacted regions expected near the periphery of the foam standards due to the known limits of the MTF for the scan.

Spatial resolution and noise thresholds will be identified using an appropriate test object (e.g. Catphan) with ability to estimate point or edge response function 8-12 and a phantom containing reference foams with lung equivalent densities (e.g. COPDGene phantom or equivalent).

### 3.1.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Standard Deviation’s (SD’s) as a measure of the noise in individual ROI’s drawn to encompass a water vial and air insert. | Acquisition Device | ≤ 20 HU for all ROI’s |
| In-plane spatial resolution  | Acquisition Device | Full-width at half-maximum (FWHM) ≤ 1.5 mm; Full width at tenth max (FWTM) ≤ 2.0 mm |
| Through-plane spatial resolution  | Acquisition Device | Full-width at half-maximum (FWHM) ≤ 1.05 mm; Full width at tenth max (FWTM) ≤ 2.0 mm9 |
| Acquisition speed | Acquisition Device | Sufficient for whole lung coverage in < 10 s (i.e. a table feed of 3 cm/s or greater).  |
| CT radiation exposure | Acquisition Device | CT Dose Index Volume (CTDIvol) ≤ 3 mGy |
| The absolute value of the Mean measured HU value within inside air (within phantom) and water (within phantom) shall be within this number of HU’s of their ideal values (-1000 HU and 0 HU) respectively. | Acquisition Device |  -1000 HU ± 6 HU for inside air |
|  |  |  |
| The Standard Deviation of the inside air (within phantom) and water (within phantom) for N = 5 acquisitions shall be Less than this Number of HU’s. | Acquisition Device |  ≤ 1 HU |
|  |  |  |

## 3.2. Periodic Quality Assurance

This activity describes calibrations, phantom imaging, performance assessments or validations performed periodically at the site, but not directly associated with a specific subject, that are necessary to reliably meet the Profile Claim.

### 3.2.1 Discussion

 The phantom shall be scanned monthly (or after equipment service that may alter scanner performance) to verify conformance with minimum standards outlined in Table 3.1.2. In the event of QA failure, the calibration procedure outlined in 3.1.1 shall be repeated in order to re-establish standardization. Additional action may be needed if equipment no longer passes performance assessment.

### 3.2.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Scanner Calibration | Physicist or Technologist | Shall assess the current CT conformance for HU value and standard deviation, encompassing scanning the COPD Gene phantom, and analyzing the images to prove conformance on a quarterly basis. |
| Acquisition Device | Shall meet the specifications in Table 3.1.2. |
| Qualification | Physicist or Technologist | Shall be a Qualified Medical Physicist (QMP) as defined by AAPM or trained radiation technologist as defined by ARRT. |
| Longitudinal (monthly) difference from baseline for air (within phantom) and water (within phantom) shall fall within this range. | Acquisition Device |  ± 4 HU |
|  |  |  |

## 3.3. Subject Handling

This activity describes details of handling imaging subjects that are necessary to reliably meet the Profile Claim. This constitutes consistent positioning of the subject and consistent breath-hold coaching.

### 3.3.1 Discussion

**Subject Positioning**

Consistent positioning avoids unnecessary variance in attenuation, location of subject within the scan gantry, and changes in anatomical shape due to posture, or body rotation that can affect image quality and consistency of HU value. The Technologist shall place the patient in a supine position, arms positioned comfortably above the head in a head-arm rest with lower legs supported. Using the laser positioning lights, the Technologist shall position the patient so the mid-axillary plane of the chest is at iso-center of the CT gantry and the “sagittal laser line” lies along the sternum (e.g. from the suprasternal notch to the xiphoid process). A lateral scout shall be performed and used to verify that the mid-axillary plane of the bronchial tree, at the level of the carina, is within 2 cm of iso-center. An AP (or PA) scout will be used to verify that the patient is correctly centered at horizontal iso-center within 2 cm.

**Lung Inflation**

Acquisition parameters have been specified so as to allow completion of the scan of the whole lung volume in a single breath-hold of less than 10 seconds. Faster scan time can further reduce breath-hold duration and reduce the likelihood of respiratory motion artifacts.

Consistency of lung inflation volume is also critical to lung density measures. The specification is to achieve a difference in lung inflation smaller than 10% of baseline lung inflation volume for longitudinal time points with the goal of achieving greater than 90% of predicted TLC at both time points. To achieve consistency of breath-hold it is essential that the technologist perform consistent coaching of the subject before the CT acquisition (so that the subject is prepared for the voice commands while in the scanner).

Before the scans are acquired, the coordinator (or trained CT technologist) will review the breathing instructions with the participant and emphasize the importance of following them as closely as possible during the actual imaging of the lungs. In summary, the participant will be instructed to inhale deeply and exhale 3 times and then hold their breath two different ways: with the lungs full of air (TLC scan). The technologist or coordinator should visually confirm that the subject is following the breath-hold coaching as intended (see script below). For example, as individual subjects will vary in their respiratory cycle and compliance with commands, it is important for the technologist or coordinator to give sufficient time for the subject to achieve full inspiration with visual confirmation that this is achieved by watching the subject’s chest before CT scanning commences. If additional expiratory scans are performed, please note that the cephalad/caudal coverage of the lungs from apex to base should be adjusted between the TLC and expiratory CT acquisitions to cover the lungs within the limits of the lung apex and base, e.g. no more than 2 cm cephalad to the apical or 5 cm caudal to the basal lung borders. An additional scout may be acquired between inspiratory and expiratory acquisitions, to prescribe each of the lung volume CT acquisitions separately so as to minimize CT dose to the subject.

In order to extract the desired information from the CT images, it is very important that the breathing instructions are followed closely.

An example of a breath-hold coaching script is:

* “Take a deep breath in” (watch the chest to ensure deep breathe is achieved)
* “Let it out” (watch chest to insure exhale is achieved)
* “Take a deep breath in” (watch the chest to insure exhale is achieved and timing of breath cycle for the subject)
* “Let it out”
* “Now breathe all the way IN, IN, IN…” (watch to confirm timing and inhalation is fully achieved and chest is still)
* “Keep holding your breath – DO NOT BREATHE”
* Visually confirm inspiratory breath-hold by watching subject’s chest and commence CT scan.
* “Breathe and Relax.”

### 3.3.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Subject Positioning | Technologist | Shall adjust the table height for the mid-axillary plane of the chest 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). |
| Scout Scans | Technologist | A lateral scout shall be performed and used to verify that the mid-axillary plane of the bronchial tree, at the level of the carina, is within 2 cm of iso-center. An AP (or PA) scout will be used to verify that the patient is correctly centered at horizontal iso-center within 2 cm.An additional scout may be acquired between inspiratory and expiratory acquisitions, to prescribe each of the lung volume CT acquisitions separately so as to minimize CT dose to the subject. |
| Lung Coverage | Technologist | The display field of view should be matched between time points to insure consistency of spatial resolution.Cephalad/caudal coverage of the lungs from apex to base should be adjusted between the TLC and expiratory CT acquisitions to cover the lungs within the limits of the lung apex and base, e.g. no more than 2 cm cephalad to the apical or 5 cm caudal to the basal lung borders.  |
| Breath-holdCoaching | Technologist | Breath-hold coaching as specified above. |
| Patient / Subject | Breath-hold for 10 s at within 10% of baseline lung inflation volume. |
| Use of intravenous contrast | Radiologist / Technologist | Intravenous contrast Shall NOT be used. |
| Use of oral contrast | Radiologist / Technologist | Oral contrast Shall NOT be used. |
| Artifact Sources | Technologist | Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads and other metal equipment) such that they will not degrade the reconstructed CT volumes. |

## 3.4. Image Data Acquisition

This activity describes details of the data acquisition process that are necessary to reliably meet the Profile Claim. It may also include calibrations, performance assessments or validations during acquisition (such as visual confirmation of breath-hold) that are necessary to reliably meet the Profile Claim.

### 3.4.1 Discussion

X-ray CT uses ionizing radiation and exposure to ionizing radiation increases health risks to the subject. The CT Dose Index Volume (CTDIvol) is used to specify radiation exposure across all scanner models. FDA and international conformance standards require CTDIvol to be available on all CT platforms. The radiation exposure is determined by tube potential, source filtration, tube current-rotation time product, and total collimation width. The general specifications of this profile are designed such that the CTDIvol be less than or equal to 3 mGy for an averaged size subject (75 kg) for each CT scan performed in order to minimize risk for longitudinal assessment of human subjects.

Generalizable image quality specifications are favored over narrow pre-defined parameter settings so as to allow flexibility in developing and supporting quantitative density measures within a specified CT dose. Therefore multiple possible parameter settings are allowed assuming that the acquisition protocol defined meets the specifications for Scanner Qualification and Calibration (Section 3.1) and periodic Quality Assurance (Section 3.2) and conforms to the specifications outlined in 3.4.2.

Spatial resolution and noise thresholds will be identified using an appropriate test object (e.g. Catphan) with ability to estimate point or edge response function 8,10-12 and a phantom containing foams standards with lung equivalent densities (e.g. COPDGene phantom or equivalent – See Section 4.1). A representative example of a phantom meeting or exceeding this standard is described under assessment procedures in Section 4.1 and **Figure 3**.

This approach is intended to enable different vendor architectures and reconstruction algorithms to meet the desired quantitative measurement standards while allowing ***flexibility*** to readily adapt protocols as CT systems continue to evolve.

### 3.4.2 Specification

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| Acquisition Protocol Selection | Radiologist | Select protocol |  |
| Acquisition Device | Qualified Device | Prospective “Quantitative Tag” |
| Total Collimation Width | Radiologist | ≥ 16 mm | (0018,9307)Total Collimation Width |
| Section Thickness | Radiologist | ≤ 1 mm | (0018,9306)Single Slice Collimation |
| Scan Plane | Technologist | Axial / Transverse | (0018,5100)Patient Position |
| Scout (Topogram, Scanogram) | Technologist | Confirm absence of metal or other artifact, verify centering of subject, constrain coverage to S/I, R/L extent of lung |  |
| Scan Duration | Technologist | ≤10 s | (0018,9309)Table Speed(DICOM Address?) Pitch |
| Anatomic Coverage | Technologist | Full Lung* Apex +2 cm;
* Base +5 cm
 | N/A (Confirmed by visual inspection) |
| Axial field of view | Technologist | Display field of view no more than 2 cm outside maximal lung extent. Matched to Baseline (if previous scan exists) | <Confirm DICOM Field>(0018,1100)ReconstructionDiameter |
| CT Dose | Radiologist/Technologist | ≤ 3mGy CTDIvol for a 75kg allowing for increased/decreased CT dose as appropriate based on BMI or chest size. | (0018,9345) CTDICTDIvol |
|  |  |  |  |

## 3.5. Image Data Reconstruction

This activity describes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim.

### 3.5.1 Discussion

The shape of the reconstruction kernel, or modulation transfer function (MTF), alters both the spatial resolution and noise characteristics of the image 13. The reconstruction is a weighted sample of the structures within the projection. A smoother reconstruction kernel emphasizes larger structures in a projection by increasing their relative weight at the expense of smaller structures but with the benefit of reducing noise. So there is also an inverse relationship between spatial resolution and noise that is dependent on choice of reconstruction kernel, necessitating that the reconstruction be carefully chosen to meet the specifications in Table 3.1.2 and as recapitulated in the context of human subject studies below in Table 3.5.2. Examples of kernels that would meet the specifications for the major vendors are described in Section 4.2.

### 3.5.2 Specification

| **Parameter** | **Requirement** | **DICOM Tag** |
| --- | --- | --- |
| Reconstruction Algorithm | A reconstruction algorithm shall be chosen such that both the spatial resolution, reconstructed slice thickness, and noise specifications are simultaneously satisfied as in Table 3.1.2.  | (0018,9323)Reconstruction Algorithm |
| Slice Thickness | ≤ 1 mm | (0018,0050)Slice thickness.(Conformance) |
| In-Plane Resolution | Full width at half maximum of line spread function shall be ≤ 1 mm. | To be measured as described in 3.1.2  |
| Noise performance | Consistent with requirements of Table 3.1.2. | To be measured as described in 3.1.2  |
|  |  |  |

## 3.6. Image QA

This activity describes criteria and evaluations of the images that are necessary to reliably meet the Profile Claim.

### 3.6.1 Discussion

Quality assurance

At the imaging console, subject images will be assessed for:

* Adequate coverage of the thoracic cavity; the lung volume must be fully represented in the field of view.
* Absence of respiratory motion artifact.
* Appropriate CT dose.
* Appropriate reconstruction algorithm and display field of view as specified.

In conjunction with image analysis, the images will be further reviewed for the above issues, and additionally for the following:

* Absence of intravenous (IV) contrast.
* (If followup scan) adequacy of lung inflation- no more than 10% difference from baseline scan.
* Specified DICOM fields shall be monitored to confirm adherence to protocol and CT Dose as well as between baseline and followup scans.

### 3.6.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Adequate coverage of the thoracic cavity | Physicist/Technologist  | The lung volume must be fully represented in the field of view |
|  |  |  |
| Verify that the lung parenchyma is sufficiently clear and uncorrupted by motion | Physicist/Technologist  | evaluate for respiratory motion (cardiac motion is unavoidable and acceptable) |
| Verify spatial resolution based on header tags. | Physicist/Technologist | Acquired and reconstructed resolutions ≤ 1 mm |
| Verify CT dose based on header tag.  | Physicist/Technologist  | CTDIvol “Per protocol” with average dose at 3 mGy |
| Verify repeat scans for longitudinal assessment conform to baseline. | Physicist/Technologist | Protocol is consistent.CT dose, and FOV within 10% of baseline allowing for changes in subject BMI or chest size. |
| Absence of IV contrast | Image Analysis Software | No IV contrast shall be present |
| Lung Inflation | Image Analysis Software | Measured lung volumes shall be within 10% |
| DICOM Fields | Image Analysis Software | Fields are consistent with Profile as specified. |

## 3.7. Image Distribution

Images must be transmitted in uncompressed DICOM format.

## 3.8. Image Analysis

This activity describes criteria and procedures related to producing quantitative measurements from the images that are necessary to reliably meet the Profile Claim.

### 3.8.1 Discussion

Automated computer image analysis programs shall use a consistent lung segmentation procedure throughout each clinical trial or for longitudinal evaluations and will share several basic processing steps including the following:

* Segmentation and removal of central pulmonary blood vessels.
* Segmentation and removal of the central airways.
* Generation of the image histogram for the remaining lung parenchymal tissues, and
* Calculation of the percentage of lung volume below -950 HU threshold (RA -950 HU), and/or
* Calculation of the HU value below which 15% (Perc15) of the total parenchymal tissue voxels fall,

With the advent of 3D volumetric CT, the field has moved towards full 3D volumetric segmentation of the lung. Given the typically large number of slices in a multi-slice volumetric CT lung scan, (400-600 slices), automated segmentation is a practical necessity. Accurate and reproducible automated segmentation of the lung structures requires combining several segmentation algorithms depending on the level of regional analysis required. For example, reproducible and accurate segmentation (compared to manual analysis) of the right and left lung can be readily performed using optimal thresholding followed by morphological operators and region growing as described by Hu and colleagues 14. Other methods, such as statistical shape modeling and atlas-based segmentation have been proposed 15.

Several commercial and prototype commercial packages are becoming available for these analyses (e.g. VIDA, Imbio, Thirona, MeVIS, etc…), each with their own proprietary segmentation method. As RA-950 and Perc15 are both straight-forward deterministic computational operations. Once an accurate segmentation mask of the lung volume is calculated, sources of variation will be entirely dependent on the quality of the segmentation assuming equal image acquisition and reconstruction settings.

Because of the multitude of software programs used by different commercial, open-source, and academic research labs, an evaluation is warranted to determine the degree of variation, if any, that different segmentation software applications have on the proposed lung density measurements used in this profile. Consensus repeatability compiled from commercial and academic analysis software for RA-950 and Perc15 from a common reference data set (made available on the QIDW website) are summarized in Section 4.3 and tabulated in more detail in Appendix E.

### 3.8.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Lung Density Analysis (Whole Lung) | RA -950 |  Output |
| Perc15 |  Output |
| Lung Density Histogram |  Output |
|  |  |  |

## 3.9. Image Interpretation

This activity describes criteria and procedures related to clinically interpreting the measurements and images that are necessary to reliably meet the Profile Claim.

### 3.9.1 Discussion

Measured changes in lung attenuation in individuals may be compared with the previously published mean changes; for example the mean change in volume adjusted lung density in untreated subjects with Alpha-1 antitrypsin deficiency is about 2.2 g/L/year 1, and the mean change in cigarette smokers with COPD is about 1.1 g/L/year 3. Important potential confounders in measurement of lung attenuation should also be considered. These would include significant changes in inspiratory lung volume, presence of other significant lung diseases on baseline or followup scans (e.g. pneumonia, interstitial lung disease), and change in smoking status. Importantly, smoking cessation decreases Perc 15 lung attenuation by a mean of 4.9 HU, simulating progression of emphysema 16.

### 3.9.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Real Change? | Clinician or Statistician | Meets the threshold identified in the Claims for change in lung density consistent with either disease progression or stability. |
| Magnitude of Change | Clinician or Statistician | Magnitude of the change *is* or *is not* significant with respect to the hypothesis of the proposed study. |

# 4. Assessment Procedures

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

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

Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement will reference an assessment procedure in a subsection here in Section 4.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. Vendors publishing a QIBA Conformance Statement shall provide a set of “Model-specific Parameters” (as shown in Appendix D) describing how their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing.

## 4.0. Assessment Procedure: Overview

Below are specific examples of procedures that would meet the standards of this profile. Several example protocols are also given in Appendix D that are derived from the proposed procedures and would meet the claims of this profile.

## 4.1. Assessment Procedure: Validation and Calibration of Density Measures

This procedure is recommended to be used by a physicist at the vendor origin or at an imaging site, to insure the linearity and repeatability of the measurement of CT number as a function of lung density for an acquisition device. An assessment is typically performed using a standard phantom with a defined range of reference foams, preferably with a calibrated density and known composition such that an expected HU value can be determined for a given energy. A phantom required to meet the minimum standards for scanner qualification (Section 3. 1) and periodic quality assurance (Section 3.2) is published and commercially available 5,6. As for any phantom calibration in CT, it is critical to position the phantom at the center of gantry rotation and in alignment with the axial scan plane such that the standards are minimally affected by differences in magnification and resolution. This can be achieved by using fiducial markers on the phantom and the alignment system of the scanner itself.

With a spread of the density values covering the entire lung foam range, a linear relationship can be established between the measured HU value and the physical density by a linear fit. This insures that the stated repeatability coefficient and true value of the HU is met for CT density measures for a given scanner make and model using a particular protocol. The QIBA-SRM phantom (Phantom Laboratory, Salem, NY), is an example of such a standard phantom and is shown in a CT image in **Figure 3**, consists of a suite of 5 reference foam inserts, as well as air, water and PEP, embedded in a larger oval shaped lung density equivalent foam and attenuated by a chest wall equivalent ring. The foam inserts, machined from commercially available sheet stock (General Plastics, FR-7104, 7108, 7112, 7116, and 7120, with the last two digits representing the nominal density in lb/ft3), have been certified for the physical density value in kg/m3 (Standard Reference Material SRM-2088, NIST).



**Figure 3. CT slice image of the QIBA-SRM phantom used in this study.** The phantom consists of (A) air, (B) PEP, (C) Water and a suite of 5 reference foam inserts (1) 16 lb/ft3, (2) 12 lb/ft3, (3) 20 lb/ft3, (4) 8 lb/ft3, (5) 4 lb/ft3, corresponding to SI units of 256.3 kg/m3, 192.6 kg/m3, 321.0 kg/m3, 128.1 kg/m3, and 64.2 kg/m3, respectively), all embedded in (D) a larger oval shaped lung density equivalent foam and attenuated by (E) a chest wall equivalent ring.

Using such a calibration system and well qualified foam standards, modern scanners also have the ability to achieve 1-3 HU standard deviations for inter-scanner repeat scans in the lung density region. For multi-center trials using different scanner makes and models a calibration procedure 4 is preferred as follows:

1. Perform air-water calibration using the air and water values from inside the phantom, by setting the CT number to -1000 and 0, respectively. An offset, determined by a linear combination of the deviation of air and water from their respective nominal value, is subtracted from the CT value of each foam. The CT numbers from this point on refers to the air-water corrected HU values.
2. Determine a protocol dependent parameter , by fitting the CT number from each foam as a function of the electron density ρe\*and effective atomic number Zeff\*, in this fashion: $H-ρ\_{e}^{\*}Z\_{eff}^{\*n} = αρ\_{e}^{\*}(1- Z\_{eff}^{\*n})$, where H is the shifted CT number,$ H=CT number (HU)/1000 +1$, ρe\*=0.956ρm, ρm is the certified mass density of each foam, and Zeff\*=0.871, calculated for the assumed composition based on best available information, and n=3.21 (reference: Martinez et al, 2012).
3. Use the calibration parameter  to obtain a relative electron density for the “lung foam” (large pink foam that filled the entire phantom) based on its measured CT number Hlung: $ρ\_{e,lung}^{\*} =\frac{H\_{lung}}{α \left(1- Z\_{eff}^{\*n}\right)+Z\_{eff}^{\*n}} $

Or, more directly, obtain a CT number at 80 keV (a monoenergetic value that represents the mean value of the attenuated CT spectrum):

$$H\_{80keV} =\frac{α\_{80keV} \left(1- Z\_{eff}^{\*n}\right)+Z\_{eff}^{\*n}}{α \left(1- Z\_{eff}^{\*n}\right)+Z\_{eff}^{\*}}$$

 where $α\_{80keV}=$0.9459 (Martinez 2012).

$H\_{80keV}$, shifted back to the HU representation, should be within the 95% confidence interval of -856 HU [-859 HU, -853 HU].

## 4.2. Assessment Procedure: Voxel Noise and Noise Power Spectrum

This procedure can be used by a vendor 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.

For the minimum standard the following procedure can be followed. 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 lung equivalent foam regions of the COPD Gene phantom 5,6. The phantom shall be placed at the isocenter of the scanner. The acquisition protocol and reconstruction parameters shall conform to this Profile (See Section 3.6.2 and 3.7.2). The same protocol and parameters shall be used when performing the assessments in 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. An approximately circular 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.

The procedure described above is provided as a reference method. Given the proprietary nature of CT reconstruction kernels, the preferred but more involved method is to calculate the noise power spectrum (NPS), the Fourier transform of the auto correlation function, which fully describes the spatial frequency dependence of the noise behavior. The preferred procedure for such a calculation to compare kernels is published 13. For multi-center protocols that use different CT vendors, in particular, this method would be preferred so as to match as best as possible the spatial frequency dependence of the noise behavior for different scanner makes and models. For example, typical smooth reconstruction kernels such as the GE Standard and Siemens B31f or B43f are well matched with respect to their NPS but other pairings could be selected assuming they meet the specifications outlined in Section 3.

Sites or vendors may also submit to QIBA a proposed alternative method (such as using the ACR CT Accreditation Program (CTAP) Phantom’s module 3, which is a 20 cm diameter cylinder of water equivalent material and air within a phantom or a lung equivalent foam portion of another manufacturer’s QA phantom) and evidence that the results produced by the proposed method are equivalent to this reference method. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.

The test procedure described here is based on the use of conventional filtered backprojection reconstruction methods; extreme care must be taken when iterative reconstruction methods are used as their use may invalidate some of the assumptions inherent in this method and are considered open issues for the present status of this Profile.

# 4.3. Assessment Procedure: Repeatability of Analysis Software

To determine level of variation, participating software vendor and research labs downloaded 100 cases from the QIBA website with varying degrees of airflow limitation, ranging from never-smokers with normal pulmonary function to GOLD IV COPD. Each vendor ran their version of segmentation following the guidelines outlined above, and submitted the full histogram profile and measures of -950HU and Perc15 in csv format to the University of British Columbia (Vancouver, BC, Canada), who volunteered to run the central analysis. Lung density measurements from each vendor were then compared to one another and to average measurements using Bland-Altman analysis, and the results were tabulated in Appendix E.

# Anticipate that we would make reference to images accessible on QIDW, and

# Add statistical analysis to establish conformance relative to other commercial and/or academic software packages. Reference Figure 4: Bland-Altman plot of repeatability of software analysis tools distinguished by academic and commercial vendors.

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# Appendices

## Appendix A: Acknowledgements and Attributions

This Profile is a joint effort of the QIBA Lung Density Biomarker Committee under the supervision of Phil Judy, Heather Chen-Mayer, Sean B. Fain, David Lynch, and Matthew K. Fuld. Discussions and feedback from Nancy Obuchowski greatly improved the statistical methods used in the meta-analysis. Discussions and editorial comments from Greg Kinney, and Ella Kazerooni improved the presentation to better support the profile.

## Appendix B: Background Information

1. **Introduction**

This Appendix reports details on how the specific claims were derived at the time of conclusion of literature reviews (8/4/2014) on the use of computed tomography (CT) measures of lung parenchymal density as a method for estimating severity and progression of emphysema in the lungs. Only whole lung measurements are considered. Regional and lobar measures of emphysema are increasingly being investigated and reported in the literature 17-22. However, the number of studies using regional measures is currently insufficient to assess emphysema severity, likewise their bias and repeatability for studies of emphysema progression.

 Measurement of whole lung parenchymal lung density with CT has been used for several decades as a clinical research marker of emphysema 19,23-26, but have not been widely adopted in clinical practice. With the advent of low dose lung cancer screening CT examinations, now recommended annually by the U.S. Preventative Services Task Force for 55-80 year olds with a 30 or more pack-year history of smoking, the value of serial emphysema CT measurements based on lung density as an important clinical data becomes immediately more relevant [11]. If repeat CT examinations were to be performed primarily for emphysema quantification, low dose techniques are important given the life expectancy of patients this could be applied to and the number of examinations they may undergo. Multiple but related measures of parenchymal density have been applied in clinical research, most prominently the relative area (RA), or low attenuation area (LAA), below specific thresholds of the histogram of lung densities in Hounsfield units (HU). Typically thresholds from -970 through -910 HU are used, at inspiratory lung volume coached to total lung capacity (TLC). The most common thresholds used are RA -950 HU, and RA -910 HU. The RAs are expressed in fractions or percentages. A second related class of measures inverts the relative area of lung below a threshold by specifying a single HU value below which a fixed relative lung area falls. For example, common measures of this class include the HU threshold below which 1% (Perc 1) or 15% (Perc 15) of the lung area falls, respectively.

Unfortunately only a limited number of studies have compared density measurement in the lungs to micro and macroscopic measures of histology derived from similar regions of diseased lung. Measures of tissue histology in the lungs are the gold standard for measuring severity and progression of emphysema but are necessarily limited themselves. Typically, such studies in human subjects or patients depend on obtaining resected tissue after lung surgery 23-25,27. Consequently, only limited agreement exists as to which of the related CT measures of lung parenchymal density is superior for detecting the presence and severity of emphysema. The more common measures have some empirical consensus based on a combination of comparisons to microscopic histology and associations with known measures of whole lung function. This consensus supports RA -950 HU 24,25,27 and Perc 1 27 as the measures best correlated to microscopic histology, and Perc 15 20 as the measure that has undergone the greatest degree of empirical validation and shown to be highly correlated to lung function 28,29. Therefore, RA -950 HU and Perc 15, being the most studied and best validated measures in clinical research studies, are hereby recognized as the reference standards and are used to determine the claims for bias and repeatability of lung parenchyma measures in this document.

Some general limitations of both RA -950 HU and Perc 15 should be recognized. RA -950 is especially sensitive to noise, which varies with choice of image reconstruction kernel and mA used for image acquisition. High frequency reconstruction kernels (so-called “hard” algorithms) result in higher absolute RA-950 irrespective of disease severity 30,31. The Perc 15 measure is less sensitive to image noise but is still affected 20. Both measures are sensitive to the state of lung inflation or inflation. There is strong underestimation by RA -950 and overestimation by Perc 15 (the two measures move in opposite directions) if lung inflation is less than 90% of TLC 32. This has necessarily focused significant research effort on lung volume adjustment (VA) methods 33. Lung VA appears to be justified for longitudinal studies where reduction in the limits of agreement in Bland-Altman analyses is substantial, e.g. on the order of 40% (Table 3), after correction using either statistical regression methods 34, or the constant lung mass assumption referred to as the “sponge” model 35,36. In Tables 2 and 3 we tabulate the bias and limits of agreement for a subset of longitudinal studies, both before and after performing VA, reported in the above selected studies using linear regression models with fixed and/or random effects. In particular, the sponge model represents the generalized approach to VA applicable to longitudinal studies, i.e. when correction of follow-up lung volume is made relative to a baseline scan. Expected improvements in bias and precision after lung VA are further discussed in Section 3.

1. **Study Inclusion and Exclusion Criteria**

The studies included for estimating the bias and precision of lung parenchymal density with CT had to meet the following inclusion criteria:

1. Publication year of the study after 2005 because CT scanner architectures and stability changed radically when these methods migrated from axial to multi-slice helical platforms and protocols.
2. A minimum of 16 slice detectors were used for CT acquisition to limit maximum breath-hold time to ~10 s with 3D whole lung coverage.
3. The same or similar CT platform was used for repeated scans.
4. The Study methods provided sufficient details regarding CT reconstruction and acquisition parameters to verify consistency.
5. Sufficient data for analysis was included to conduct Bland-Altman analysis to calculate bias and limits of agreement for one or both of RA -950 and Perc 15.
6. Subjects were scanned twice or more with less than or equal to a 4 month interval between CT scans with the intent of eliminating the influence of possible disease progression on the bias and precision estimates 37.

Studies were explicitly excluded if:

1. Repeatability data were not included.
2. Parenchymal density was not measured with either RA -950 or Perc 15.
3. The time interval between repeated CT scans exceeded 4 months or other inclusion criteria listed above were not met.

It is inevitable that even for the included studies variability remained, which was mainly in these four areas: CT scanner platform used, Number of subjects, severity of disease, and time interval between CT scans. The studies included are summarized and referenced in Table 1. The density metrics reported in this document are from studies on subjects assumed to be free of disease progression during the short time intervals between baseline and repeat scans. The primary sources of the within-subject variations in the apparent density of the lung parenchyma are attributed primarily to inspiration levels and scanner calibration/measurement error. This approach constrains sources of variation not due to the measurement method. Moreover, at the present time there are few studies that address repeatability with whole lung volume coverage in a reasonable breath-hold (<10 s) even over longer time intervals. There are two major reasons repeatability studies can be excluded: due to scanner architecture [20, 23-26], and due to excessive time between scans or inconsistency of methodology [14, 21, 27-29]. One exception to this is the Park et al study [21] that was included as a reference example in an “asymptomatic population” (GOLD stage 0) with a longer time interval between CT scans (8 months), but the subjects were deemed to have “no perceptual changes of disease progression”.

1. **Effect of VA on Bias and Precision Claims for RA -950 and Perc 15**

It is generally recognized that VA is useful for improving the precision of repeat CT measurements of lung density [25]. The cross sectional (inter-scanner) variation issue can be addressed by phantom studies [31]. In the current document we focus on longitudinal clinical studies from the same site using the same scan protocol, examining the sample mean bias and limits of agreement in the absence of disease progression after VA.

Generally the underlying physiological model-- the sponge model in which the lung mass is assumed to be conserved -- affords the simplicity of an inverse proportionality between lung density and volume. However, this model is not strictly followed in clinical data or even in phantom studies [32]. The more common approach is a statistical model that assumes a linear combination of effects that contribute to the density variation in repeat scans. The simplest is the linear fixed effect model in which the change in density metrics (dependent variable) is paired with the change in volume (independent variable), and the linear regression analysis returns a slope and intercept which are then used to correct the density metrics in the repeat scan, such that it may now be compared to the baseline scan free of inspiration related variation. The more advanced model adds random effects to address the individual level of variation, recognizing that the fixed effect model only takes into account the variation at the cohort level. Reference [33] has a detailed comparison of different models in the study of clinical data in the context of disease progression. For the studies compiled in this document, the method of VA varies, and is reported without any assessment of statistical or clinical merits. Because more advanced techniques for VA continue to emerge [34], this document does not intend to suggest any particular model or method, but rather provides an analysis of the sample studies available that fit the selection criteria. The results of the VA from the included studies are summarized in Table 3. The data, bias and limits of agreement (LOA) before and after VA are plotted in Figure 1.

1. **Mean Repeatability Coefficient Obtained by Meta-Analysis**

An initial assessment [35] was performed on a subset of data listed in Table 3 with a fixed effect linear model to test whether VA had an effect on the bias and LOAs of the change in Perc 15 and RA 950. For Perc 15, four studies were included, and the mean bias of -0.168 before VA and 0.090 after VA are statistically insignificant (p=0.46). Therefore, it was concluded that VA has negligible effect on the bias. Due to the lack of homogeneity in LOA exhibited by this set of studies, a more rigorous analysis was performed following the QIBA metrology working group guidelines [36]. QIBA statistical methods guidelines [37] and terminology guidelines [38] recommend use of the repeatability coefficient (RC) instead of the LOA for the technical performance assessment of repeatability of a quantitative imaging biomarker (QIB) . Therefore, the RC, which is a function of the within-subject variance, was first obtained based on the reported bias and LOA values for each study, and the meta-analysis was conducted using the random effects model [36]. The results of these analyses are summarized in Table 4 and in the Forest plots in Figure 2. The concept of Smallest Real Difference (SRD) is defined by the RC following the conventions of the published literature for test-retest assessments [39-41]. More details on the RC and the meta-analysis are in the Appendices of this document. The claim language in Section 5 is separated into without and with VA to reflect a narrower 95% confidence limit as a result of VA. For RA 950, only Ref. [15] fits the inclusion criteria, and despite making an exception to also allow the Park et al study [21], only 2 studies are insufficient to support a meta-analysis to inform the claim for the RA 950 metric. The committee will monitor the literature and make a more definitve claim when using the RA 950 metric in combination with VA when more data becomes available.

1. **Claims:**

For longitudinal studies with low-dose CT when monitoring patients who have smoking-induced emphysema:

* 1. Without lung VA, an increase in RA 950 of at least 3.7%, or a decrease in Perc 15 of at least 18 HU, is required for detection of an increase in the extent of emphysema, with 95% confidence.
	2. Without VA, for a measured change of x HU in Perc15, one can expect the true change to lie in the interval [x -18 HU, x +18 HU] with 95% probability; for a measured change of y% in RA950, one can expect the true change to lie in the interval [y -3.7%, y +3.7%] with 95% probability.
	3. With lung VA, a decrease in Perc15 of at least 11 HU, is required for detection of an increase in the extent of emphysema, with 95% probability.\*
	4. With VA, from a measured change of x HU in Perc 15, one can expect the true change to lie in the interval [x -11 HU, x +11 HU] with 95% probability.

\* No claim is made for the RA 950 measure with volume correction due to the lack of sufficient data at the time of this report.

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|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **Number of Subjects** | **Disease Severity** | **Time Interval (mean or median)** | **Scanner Manufacturer and Model** | **Density Measures** | **Reconstruction Kernel** | **Number of Centers & Vendor Platforms** | **Tube Current-Time (mAs)** | **Meets Study Inclusion Criteria? (Reason)** |
| Park 36 | 2012 | 52 | GOLD 0 | 8 mo | Siemens Sensation 16 | RA950, Perc 1, Perc 15 | B30f | 1, 1 | 40  | N (Time Interval)# |
| Chong 30 | 2012 | 44\* | Mild COPD (>GOLD 0) | 7 days | GE, Siemens, Toshiba | RA950, Perc 15 | Bone, B45f, FC51 (high freq.)♭ | 3, 3 | 80-150  | Y  |
| *Keller*  34 | *2011* | *105+* | *Mild assumed (cancer cohort)* | *< 4 mo, 78±27 days* | *GE Lightspeed Ultra (16 detectors)* | *RA910,* *Perc 15* | *Bone* | *1, 1* | *40*  | Y |
| Hochhegger 31 | 2011 | 50\*+ | No clinical emphysema or lung cancer; >20 pack-year smokers | < 3 mo, 78 days | Phillips Brilliance 64 | RA950 | D (Smooth) | 1, 1 | 200  | Y |
| Diciotte 38 | 2011 | 99\*o | NCE or lung cancer >20 pack years | 3 mo | Siemens Sensation 16 | RA950, Perc 15 | “Sharp”; 3X3 Gaussian♮ | 1, 1 | 30  | Y♮ |
| Gietema 37 | 2007 | 157 | “Heavy” Smokers | 3 mo | Phillips MX800IDT or Brilliance 16p | RA950 | B (moderately soft) | 1, 2 | 30 \*\* | Y\*\* |
| \*Subset of a multi-center, multi-platform study for which two baseline scans were obtained.+Subset of subjects with < 4 months between scans\*+Subset of 475 subjects screened for cancer\*oMILD trial only (16 slice)\*\* 140 kVp (vs. 120 kVp) for > 80kg weight♮Smoothing operation in image domain♭High frequency instead of smooth kernel used for reconstruction.#Note that Park et al is retained in subsequent analysis in spite of the longer scan intervals, factoring in that the study subjects were an “asymptomatic population” (GOLD stage 0) and the authors’ assertion that the subjects had no perceptual changes of disease progression. |

**Table 1. Summary of parameters for the selected studies used to determine the claims.**

**Table 2. Summary of repeated measures, bias, and LOA for RA950 and Perc15 for baseline and repeat scans from the selected studies without volume adjustment.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author** | **Year** | **Lung Volume (ml)**  | **RA950 (%)** | **Perc15 (HU)** |
|  |  | **Mean (SD) Time 1**  | **Mean (SD) Time 2** | **Mean (SD) Time 1**  | **Mean (SD) Time 2** | **Bias (SD)**  | **Limits of Agreement**  | **Mean (SD) Time 1**  | **Mean (SD) Time 2**  | **Bias (SD)** | **Limits of Agreement** |
| Park | 2012 | 4784 (908) | 4806 (978) | 8.7 (5.3) | 9.2 (5.1) | 0.5 (3.5) | -6.4, 7.4 | -933.4 (13.8) | -934.5 (13.7) | -1.1 (10.9) | -22.1, 20.7 |
| Chong | 2012 | 5770 (1540) | 5724 (NR) | 16.0 (11.7) | NR | 0.01 (1.17) | -2.33, 2.35 | -946.3 (28.3) | NR (NR) | 0.52 (5.29) | -10.07, 11.11 |
| Keller  | 2011 | NR  | NR | - | - | - | - | NR | NR | -0.39 (10.1) | -20.13, 19.35 |
| Hochhegger | 2011 | 2578 (584) | 2518 (591) | 0.53 (0.77) | 0.71 (1.19) | 0.39 (0.88) | -1.35, 2.15 | - | - | - | - |
| Diciotte | 2011 | 6290 (1220) | 6270(1180) |  6.2 (6.7) | 6.5 (6.8) |  0.3 (3.4)# | --6.8 , 6.6 | -925.2 (22.3) | -925.3 (21.8) | -0.1 (11.5) | -20.1, 25.0 |
| Gietema | 2007 | 6935 (1267) | 6945 (1322) | 0.17 (NR) | 0.08 (NR) | -0.09 (1.19) | -1.3, 1.1 | - | - | - | - |
| NR – “not reported.”For ‘-‘ the measure was not an end-point for the published study.# Diciotte did not report the SD for the RA 950 bias or LOAs; values here are estimated based on the pooled SD of the mean from time 1 and 2, assuming a correlation coefficient being comparable to the one given for the lung volume between time 1 and 2. |

**Table 3. Comparison of bias and LOA for RA 950 and Perc 15 for baseline and repeat scans from the selected studies *with* VA**

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** | **Method** | **RA -950 HU (%)** | **Perc 15 (HU)** |
|  |  | **Without VA** | **With VA** | **Without VA** | **With VA** |
|  |  | **Bias (SD)**  | **LOA** | **Bias (SD)**  | **LOA**  | **LOA** | **% ** | **Bias (SD)**  | **LOA** | **Bias (SD)**  | **LOA**  | **LOA** | **% ** |
| Park | Linear Regression | 0.5 (3.5) | -6.4, 7.4 | 1.1 (1.9) | -3.6, 3,7 | -5.2 | 47 | -1.1 (10.9) | -22.1, 20.7 | 0.3 (6.6) | -12.6, 13.2 | -8.5 | 40 |
| Chong | Linear Regression  | 0.01 (1.17) | -2.33, 2.35 | 0.22 (0.83) | -1.43, 1.87 | -0.69 | 29 | 0.52 (5.29) | -10.7, 11.11 | -0.42 (1.82) | -4.05, 3.21 | -7.3 | 67 |
| Keller1 | Univariate Linear Regression  | 0.22 (5.19) | -9.95, 10.38 | -0.27 (3.25) | -6.63, 6.10 | -3.8 | 37 | -0.39 (10.07) | -20.13, 19.35 | 0.48 (6.86) | -12.97, 13.94 | -6.3 | 32 |
| Multi-variate Linear Regression | -0.13 (2.99) | -5.98, 5.73 | -4.3 | 42 | 0.41 (5.67) | -10.7, 11.52 | -8.64 | 44 |
| Hochhegger | No VA | - | - | - | - | - | - | - | - | - | - | - | - |
| Diciotte2 | Linear Regression(log-transformed) | - | - | - | - | - | - | -0.1 (11.5) | -20.1, 25.0 | 0.0 (8.2)  | -14.7, 17.3 | -6.51 | 29 |
| Gietema | No VA | - | - | - | - | - | - | - | - | - | - | - | - |
| For ‘-‘ the measure was not an end-point for the published study.Shaded cells are not included due to missing data or if for RA-910 HU (as in Keller et al).1Keller et al shows data from RA -910 HU (omitted from Table 2) and Perc 15 (as reported in Table 2).2linear regression of the change in log-transformed Perc 15 vs change in log-transformed TLV. |

**Table 4. Summary of the results of meta-analyses for the repeatability coefficient (RC).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Summary table for meta-analysis of RC** | **#studies** | **mean**  | **SE**  | **95% CI (2-sided)** | **Lower bound** | **Upper bound**  |
| **Perc 15 (HU)** | **without VA** | 4 | 18.4 | 3.0 | 5.9 | 12.6 | 24.3 |
| **with VA** | 4 | 11.4 | 3.5 | 6.8 | 4.6 | 18.3 |
| **RA 950 (%)** | **without VA** | 5 | 3.7 | 0.7 | 1.4 | 2.3 | 5.1 |



Fig. 1. Bias and limits of agreement compiled from the selected 6 studies: Bias and 95% limits of agreement (hLOA, or half-width of the 95% LOA, defined as 1.96 SDbias) for RA -950 HU (left panel) and Perc 15 (right panel) both before (blue) and after (red) VA for selected studies (Table 1). The respective hLOAs are plotted as error bars. Study 3 reported RA -910 rather than RA -950. Studies 4, 5, and 6 did not perform VA for RA -950. Studies 4 and 6 did not report Perc 15 results. Meta-analysis was not performed for RA -950 after VA because there are only two data points (excluding study 3), and one of which (study 2) reported statistically insignificant improvement of precision as a result of VA. For Perc 15, meta-analysis was performed both before and after VA based on the 4 data points included.

Fig 2. Forest plots of the repeatability coefficient (RC) of the studies (blue) and their pooled RC (red), with the 95% CI (defined as 1.96 $√$SE\_RC) shown as error bars: (a) Perc 15 before VA, (b) Perc 15 after VA, (c) RA -950 before VA. For RA -950, only two studies performed VA, and the effect of VA on the bias and precision were statistically insignificant.

## Appendix C: Conventions and Definitions

**Constructing the repeatability coefficient (RC) based on reported bias and limits of agreement**

The studies reported either the standard deviation of the difference (SDbias) or the limits of agreement (LOA) where the half width of LOA (hLOA) is defined as 1.96 SDbias. Conceptually this represents the variability remaining when the between- and within- subjects variablity has been accounted for [38]. For the assessment of repeat measurements on N subjects, we use the total within-subject variance, wSD, defined below. The repeatability coefficient RC is defined as [36] 1.96 2 wSD. Based on the defintions, the following relationship can be used to calculate the RC given the bias and hLOA:

$$wSD=\sqrt{\sum\_{i}^{}\frac{1}{2N}(Y\_{i1}-Y\_{i1})^{2}}$$

$$RC=1.96\sqrt{2}wSD$$

$$hLOA=1.96\sqrt{\frac{1}{N-1}\sum\_{i}^{}(Y\_{i1}-Y\_{i1})^{2}- \frac{N}{N-1}[\overbar{\left(Y\_{1}-Y\_{2}\right)} ]^{2}}$$

where

$$\overbar{\left(Y\_{1}-Y\_{2}\right)}=\overbar{Y\_{1}}-\overbar{Y\_{2}}=bias$$

 and

$$\overbar{Y\_{1}}=\sum\_{i}^{N}\frac{Y\_{i1}}{N}$$

$$\overbar{Y\_{2}}=\sum\_{i}^{N}\frac{Y\_{i2}}{N}$$

are the means over N subjects for measurements 1 and 2, respectively.

Therefore,

$$RC^{2}=\frac{N-1 }{N}hLOA^{2}+1.96^{2} bias^{2}$$

Where subscript i = 1 to N represents the subjects, and subscripts 1, 2 represent measurements at time points 1 and 2, respectively. The mean values are taken over the sample size N. When the bias is small, and N is large, RC approaches hLOA. For these studies, the difference is negligible, but the conceptual distinction is asserted here.

In addition, an uncertainty has been assigned to the RC itself for each study, based on the gamma distribution with shape and scale parameters defined by the sample size and the RC value itself [35]. The variance of RC2 is Var(RC2)=kb2, where k =N(P-1)/2 is the shape parameter (P is the number of independent measurements, or studies included in the meta-analysis), and b=RC2/k is the scale parameter. Using the “delta method”, one can show that Var(RC)=Var(RC2)/(4 RC2).

**Meta-analysis of the performance metric from the four studies**

The goal of the meta-analysis is to derive a mean RC based on the four studies selected. Following [35], the Perc 15 or RA -950 metric data from the four studies were evaluated first using the fixed effects model assuming normal distribution as well as fixed effects model with exact maximum likelihoods. However, the heterogeneity test statistic I2 approaches 100, requiring that the random effects model be used. A variance  representing the underlying distribution of the RC’s is constructed based on the DerSimonian and Laird estimator for this group of studies [35], which is added to the variance of each study to modify the weighting factor for the mean RC. The standard error for the mean RC thus obtained is also modified accordingly. This task was performed using Excel (Microsoft, Redmond WA). The same method was also used on the bias of these studies, which were homogeneously small and therefore a simple fixed effect model sufficed. VA does not have any statistically significant effect on the bias.

## Appendix D: Model-specific Instructions and Parameters

For acquisition modalities, reconstruction software and software analysis tools, profile conformance requires meeting the activity specifications above in Sections 2, 3 and 4.

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

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

**IMPORTANT: The presence of a product model/version in these tables does not imply it has demonstrated conformance with the QIBA Profile. Refer to the QIBA Conformance Statement for the product.**

|  |  |
| --- | --- |
| **Subject ID** | **TEM05 PHANTOM** |
| **Scanner to be used:** |
| **Scanner ID** | **Scanner** | **Scanner Location** |
| **TEM05** | Philips Brilliance 256 | Boyer Pavilion |
| **Acquisition Parameters:** |
| **Effort** | **Pitch** | **kVp** | **Exposure** | **Slice Thickness** | **Interval** | **Protocol Details** |
| 1. Insp **Low­dose** | 0.923 | 120 | Modulated Ref 46mAs (85 mA) | 0.67 | 0.5 | Z­DOM or Dose Right |
| 2. Expiratory | 0.923 | 120 | 50 mAs | 0.67 | 0.5 | Z­DOM or Dose Right OFF |
| **Reconstruction Parameters:** |
| **Effort** | **Recon** | **Kernel** | **DFOV (cm)** | **Notes** |
| 1. Insp Low | Low1 | B | 36.5 cm |  |
| 1. Insp Low | Low2i | B iDOSE­L3 | 36.5 cm | Iterative Recon: iDOSE setting: L3 |
| 1. Insp Low | Low3i | D iDOSE­L3 | 36.5 cm | Iterative Recon: iDOSE setting: L3 |
| 1. Insp Low | Low4i | B iDOSE­L6 | 36.5 cm | Iterative Recon: iDOSE setting: L6 |
|  |
| 2. Exp | Recon 1 | B | 36.5 cm |  |
| 2. Exp | Recon 2 | Detail(D) | 36.5 cm |  |

**Visit 2 Scan ­ Information below to be filled out by CT Technologist**

**COPDGene Subject Id**

**CT Acquisition Date**

mm/dd/yyyy

**CT Dose Index (CTDI)**

(mGy)

**Insp Low**

**Exp**

**Imaging Technologist**

TEM05 PHANTOM

|  |  |
| --- | --- |
| **Subject ID** | **NJC04 PHANTOM** |
| **Scanner to be used:** |
| **Scanner ID** | **Scanner** | **Scanner Location** |
| **NJC04** | Siemens SOMATOM Definition AS+ | A342 |
| **Acquisition Parameters:** |
| **Effort** | **Pitch** | **kVp** | **Exposure** | **Slice Thickness** | **Interval** | **Protocol Details** |
| 1. Insp **Low­dose** | 1.0 | 120 | Modulated Ref 35 mAs | 0.75 | 0.5 | Care Dose ON Rotation rate: 0.3 s |
| 2. Expiratory | 1.0 | 120 | 50 mAs | 0.75 | 0.5 | Care Dose OFF |
| **Reconstruction Parameters:** |
| **Effort** | **Recon** | **Kernel** | **DFOV (cm)** | **Notes** |
| 1. Insp Low | Low1 | B31f | 36.5 cm |  |
| 1. Insp Low | Low2i | I31f SAFIRE­2 | 36.5 cm | Iterative Recon: SAFIRE setting: 2 |
| 1. Insp Low | Low3i | I44f SAFIRE­2 | 36.5 cm | Iterative Recon: SAFIRE setting: 2 |
| 1. Insp Low | Low4i | I31f SAFIRE­5 | 36.5 cm | Iterative Recon: SAFIRE setting: 5 |
|  |
| 2. Exp | Recon 1 | B31f | 36.5 cm |  |
| 2. Exp | Recon 2 | B45f | 36.5 cm |  |

**Visit 2 Scan ­ Information below to be filled out by CT Technologist**

**COPDGene Subject Id**

**CT Acquisition Date**

mm/dd/yyyy

**CT Dose Index (CTDI)**

(mGy)

**Insp Low**

**Exp**

**Imaging Technologist**

NJC04 PHANTOM

|  |  |
| --- | --- |
| **Subject ID** | **NJC02 PHANTOM** |
| **Scanner to be used:** |
| **Scanner ID** | **Scanner** | **Scanner Location** |
| **NJC02** | Siemens SOMATOM Definition | A344 |
| **Acquisition Parameters:** |
| **Effort** | **Pitch** | **kVp** | **Exposure** | **Slice Thickness** | **Interval** | **Protocol Details** |
| 1. Insp **Low­dose** | 1.0 | 120 | Modulated Ref 35 mAs | 0.75 | 0.5 | Care Dose ON Rotation rate: 0.33 s |
| 2. Expiratory | 1.0 | 120 | 50 mAs | 0.75 | 0.5 | Care Dose OFF |
| **Reconstruction Parameters:** |
| **Effort** | **Recon** | **Kernel** | **DFOV (cm)** | **Notes** |
| 1. Insp Low | Low1 | B31f | 36.5 cm |  |
| 1. Insp Low | Low2 | B45f | 36.5 cm |  |
|  |
| 2. Exp | Recon 1 | B31f | 36.5 cm |  |
| 2. Exp | Recon 2 | B45f | 36.5 cm |  |

**Visit 2 Scan ­ Information below to be filled out by CT Technologist**

**COPDGene Subject Id**

**CT Acquisition Date**

mm/dd/yyyy

**CT Dose Index (CTDI)**

(mGy)

**Insp Low**

**Exp**

**Imaging Technologist**

NJC02 PHANTOM

|  |  |
| --- | --- |
| **Subject ID** | **HAR02 PHANTOM** |
| **Scanner to be used:** |
| **Scanner ID** | **Scanner** | **Scanner Location** |
| **HAR02** | GE Revolution CT | CT Suite |
| **Acquisition Parameters:** |
| **Effort** | **Pitch** | **kVp** | **Exposure** | **Slice Thickness** | **Interval** | **Protocol Details** |
| 1. Insp **Low­dose** | 0.984 | 120 | Modulated max mA=100 Tgt NI\*=66.5 | 0.625 | 0.5 | Auto­mA, Smart­mA ON Rotation rate: 0.5 s\*Target Noise Index=66.5 |
| 2. Expiratory | 0.984 | 120 | 100 mA x 0.5s | 0.625 | 0.5 | Auto­mA, Smart­mA OFF |
| **Reconstruction Parameters:** |
| **Effort** | **Recon** | **Kernel** | **DFOV (cm)** | **Notes** |
| 1. Insp Low | Low1 | Std | 36.5 cm | Recon mode: Plus |
| 1. Insp Low | Low2i | Std ASIR­40% | 36.5 cm | Iterative Recon: ASIR setting: 40% Recon mode: Plus |
| 1. Insp Low | Low3i | Bone ASIR­40% | 36.5 cm | Iterative Recon: ASIR setting: 40% Recon mode: Plus |
| 1. Insp Low | Low4i | Std ASIR­100% | 36.5 cm | Iterative Recon: ASIR setting: 100% Recon mode: Plus |
|  |
| 2. Exp | Recon 1 | Std | 36.5 cm |  |
| 2. Exp | Recon 2 | BONE | 36.5 cm |  |

**Visit 2 Scan ­ Information below to be filled out by CT Technologist**

**COPDGene Subject Id**

**CT Acquisition Date**

mm/dd/yyyy

**CT Dose Index (CTDI)**

(mGy)

**Insp Low**

**Exp**

**Imaging Technologist**

HAR02 PHANTOM

Appendix E: Image Analysis Software **Comparison**