

Standards for Imaging Endpoints in Clinical Trials: Standardization and Optimization of Image Acquisition for CT

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The Use of CT in Clinical Trials

- UCLA involved w/ CT in Clinical Trials for > 10 yrs
 - NIH studies
 - FORTE and MESA studies from NHLBI
 - NLST from NCI
 - Private Sponsor Studies
 - > 450 sites
- Some have quantitative endpoints
 - % Emphysema or Calcium score
- Some have qualitative endpoints
 - Absence or Presence of Disease
 - Response to Therapy/ Dz Progression

The Use of CT in Clinical Trials

- Started with “Standard of Care”
- But what is that?

The Use of CT in Clinical Trials

Results tallied from one recent study in which
“Standard of Care” was used

- Requested (but did not require)
 - Thin section Chest CT
 - Post contrast Abdomen (Venous Phase preferred)
 - Scanned on an “Approved” scanner
 - A scanner we had them identify and test

The Use of CT in Clinical Trials

- Received:
 - 99% of studies were in DICOM format (!!)
 - 23% of cases were NOT anonymized
 - 26% were performed on unapproved scanner
 - 17% were not venous phase abdomen
 - 7% no contrast at all
 - 11% did not cover full chest
 - 8% did not cover full abdomen
 - 43% had motion artifacts
 - 61% were not thin section chest

An Example Program

- Start w/ statement of the goals of imaging task
 - Anatomic Region/ Disease Site(s)
 - Detection/Quantification/Assess Response/Etc.
- Translate into an imaging protocol
 - Acquisition parameters
 - Patient parameters – positioning, contrast, breathing instructions, etc.
- Credential the sites
 - Verify equipment and performance
 - Verify protocol
- Ongoing QA – even for Patient/Subject Scans

CT Protocol Chart – NLST Example

Parameter	GE QXi 4-slice/0.8 sec	GE LS Plus 4-slice/ 0.5 sec	GE Ultra 8-slice/0.5 sec	GE – LS 16 16-slice/0.5 sec	GE – VCT(64) 64-slice/0.5 sec
kV	120	120	120	120	120
Gantry Rotation Time	0.8 sec	0.5 sec	0.5 sec	0.5 sec	0.5 sec
mA (Regular patient-Large patient values)	50-100	80-160	80-160	80-160	50-100
mAs (Regular -Large) ¹	40-80	40-80	40-80	40-80	25-50
Scanner effective mAs ² (Reg-Lg)	26.7-53	26.7-53	29.6-59.2	29.1-58.2	27-53
Detector Collimation (mm) - T	2.5 mm	2.5 mm	1.25 mm	1.25 mm	0.625 mm
Number of active channels - N	4	4	8	16	64
Detector Configuration - N x T	4 x 2.5 mm	4 x 2.5 mm	8 x 1.25 mm	16 x 1.25 mm	64 x 0.625 mm
MODE (Thick/ Speed)	2.5/HS/15	2.5/HS/15	1.25/HS/13.5	1.25/1.375/ 27.5	.625/.984/ 39.37
Table incrementation (mm/rotation) - I	15 mm	15 mm	13.5 mm	27.5 mm	39.37 mm
Pitch ([mm/rotation] /beam collimation) - I/NT	1.5	1.5	1.35	1.375	0.984
Table Speed (mm/second)	18.75 mm/sec	30 mm/sec	22.5 mm/sec	55mm/sec	78.74 mm/sec
Scan Time (40 cm thorax)	22 sec	13 sec	18 sec	7.3 sec	5.1 sec
Nominal Reconstructed Slice Width	2.5 mm	2.5 mm	2.5 mm	2.5 mm	2.5 mm
Reconstruction Interval ³	2.0 mm	2.0 mm	2.0 mm	2.0 mm	2.0 mm
Reconstruction Algorithm ³	STD	STD	STD	STD	STD
# Images/Data set (40 cm thorax)	200	200	200	200	200
CTDI _{vol} Dose in mGy ⁴ (Regular – Large)	2.8 – 5.6 mGy	2.4 - 4.9 mGy	3.1 - 6.2 mGy	2.7 - 5.4 mGy	2.2 – 4.4 mGy

Site Credentialing

Several initial steps, some of which are listed here:

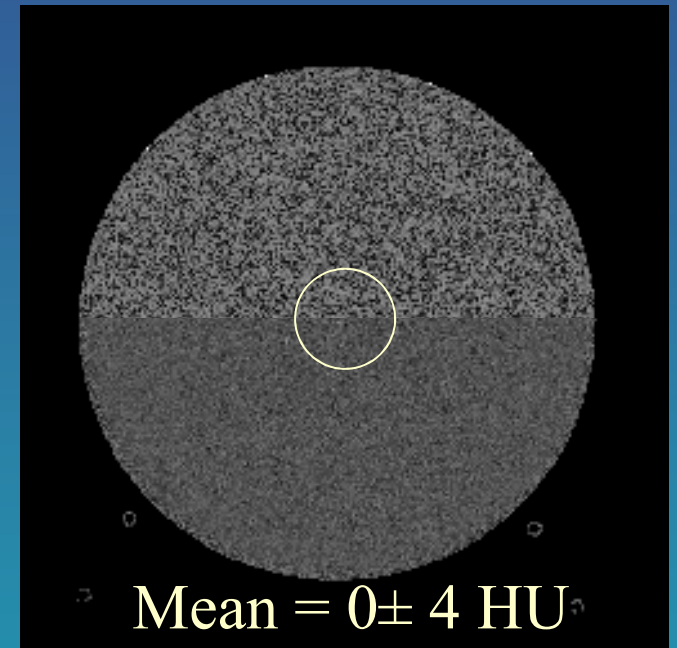
- **Prior to scanning any subject,**
- Candidate sites are REQUIRED to scan a phantom USING the prescribed protocol.
 - Submit image data to imaging core
- Imaging Core evaluates (Verifies):
 - Whether protocol was followed:
 - sites confirm values that cannot be obtained from DICOM header
 - Whether scanner is operating properly and in calibration
- If sites passes, then they are considered credentialed and are eligible to scan subjects.

Phantom = Test Object of Known Composition

American
College of
Radiology
CT
Accreditation



Manufacturer's
QA Phantom



Phantom Credentialing

- Not always straightforward
- Not enough to just specify protocol for trial and send it out
- Sites don't routinely use trial specific protocols
- Someone has to verify and give detailed feedback to sites

Recent Experience

- Study 1 – 14 sites, 5 failed on first submission, 3 failed more than once.
- Study 2 – 12 sites, 4 failed on first submission, 2 failed more than once.
- Study 3 – 14 sites, 8 failed on first submission, 3 failed more than once.

- 42.5% of sites fail on first attempt
- 20% require at least two attempts

Ongoing QA – Patient/Subject Images

- Even after credentialing, scans are reviewed
 - Initially by lab personnel, then with radiologist
 - Assess adequacy of study
 - Adherence to protocol
 - Correct coverage
 - Not excessive motion
- Provide timely feedback to site
 - Image Quality Score (IQS)

Emphasys:

Image Quality Score Criteria

- Maximum IQS is 5
- Points are allocated for following categories:
 - 1 for HIPAA compliance and use of correct study ID format in both “Patient ID” and “Patient Name” fields
 - 1 for TLC 10mm series
 - 1 for TLC thin section series (site-specific)
 - 1 for RV 10mm series
 - 1 for RV thin section series (site-specific)

Emphasys

Image Quality Score Criteria

- Points will be deducted for the following:
 - Images missing from any series
 - Apices or base cut off
 - Incorrect FOV
 - Breathing artifact
 - Incorrect breath hold
 - Incorrect Reconstruction Kernel
 - Effective mA is not within range
 - Others...

IQS scores

- 844 studies submitted from US sites
 - 42.6% received score of 5
 - 36.4% received score of 4
 - 15.2% received score of 3
 - 4.7% received score of 2
 - 1.1% received score of 1
- Nearly 80% received 4 or 5 (acceptable)
- Scores from EU slightly lower
 - Overall study (US + EU sites) 76% rec'd 4 or 5.
- Feedback is provided rapidly
 - usually within 48-72 hours
 - Idea is to correct any issues before next patient

Ongoing QA (Proactive Steps)

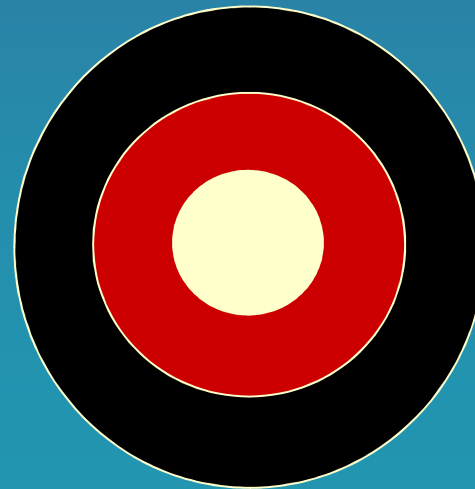
- Other steps taken can include:
 - Sending reminders to site BEFORE followup study for a specific subject
 - Remind them of acquisition protocol values
 - Any other issues that need to be addressed

RSNA's Quantitative Imaging Biomarker Alliance (QIBA) Activities

- What is needed if CT imaging is to be used as a biomarker of response in Clinical Trials
- Two Parallel Efforts
 - volCT: can volumetrics be used as a biomarker of response in therapeutic trials, esp. wrt. lung cancer Tx
 - COPD: can density (e.g. lung density) and morphometry (airway size) be used as biomarkers of response in trials for COPD

QIBA Activities

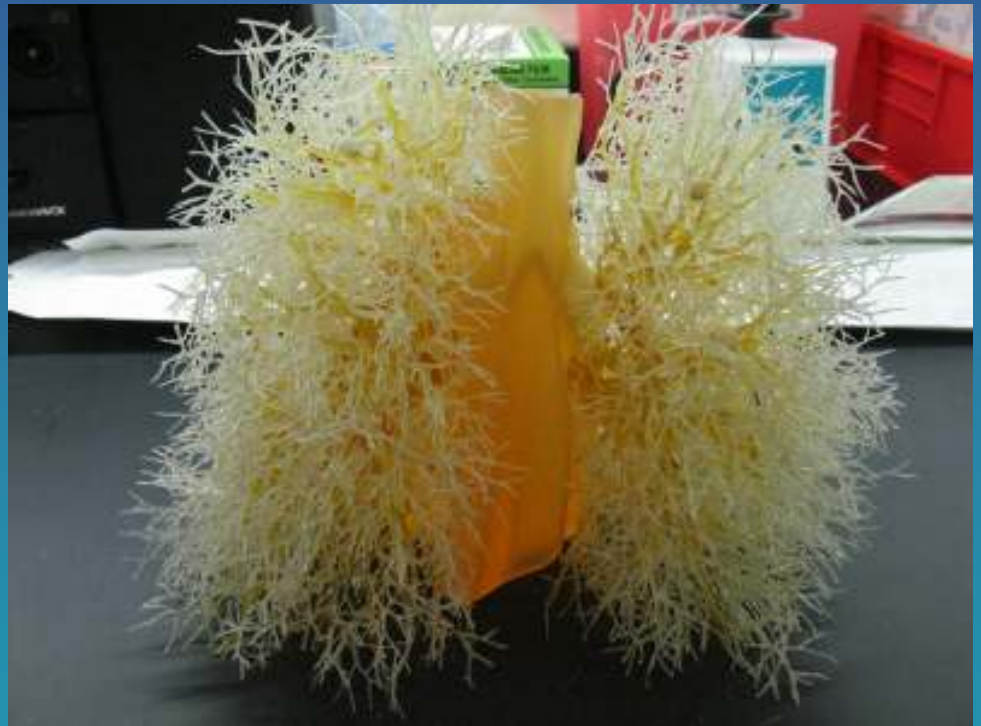
- Both groups
- QIBA profiles
 - Standardized descriptions of imaging in clin. Trials
 - Acquisition
 - Patient Prep
 - Analysis
- Bullseye Approach
 - Target
 - Ideal
 - Acceptable



QIBA Activities

- volCT group
- Ground work
 - Ongoing phantom and patient image studies to guide/inform the profiles
 - Investigating sources of measurement bias and variance
 - Nodule shape
 - Measurement method (Volumetric vs. 1-D diameter)
 - Slice thickness
 - Readers
 - Scanners
 - Strategies for Mitigation

Anthropomorphic Thorax Phantom



Courtesy of U.S. Food and Drug Administration CDRH/OSEL/DIAM

Aspherical Nodules

- Shapes
 - Elliptical
 - Lobulated
 - Spiculated
 - Random



Courtesy of U.S. Food and Drug Administration CDRH/OSEL/DIAM

CT of Thorax Phantom



1.5 Slices
16x0.75
200 mAs

Courtesy of U.S. Food and Drug Administration CDRH/OSEL/DIAM

Standardization and Optimization of Image Acquisition for CT

- Variability of imaging results will be minimized across multiple sites if we adhere to standards.
- Imaging results can be reproducible at multiple time points at a single site if we adhere to consistent methods for image acquisition and analysis.

Standardization and Optimization of Image Acquisition for CT

- Goal is to reduce measurement variation
- Even that does not *guarantee* that imaging is a good biomarker of disease.
- This requires validation studies with outcomes