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/Subjetc Scans
## CT Protocol Chart – NLST Example

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GE QXi 4-slice/0.8 sec</th>
<th>GE LS Plus 4-slice/0.5 sec</th>
<th>GE Ultra 8-slice/0.5 sec</th>
<th>GE – LS 16 16-slice/0.5 sec</th>
<th>GE – VCT(64) 64-slice/0.5 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Gantry Rotation Time</td>
<td>0.8 sec</td>
<td>0.5 sec</td>
<td>0.5 sec</td>
<td>0.5 sec</td>
<td>0.5 sec</td>
</tr>
<tr>
<td>mA (Regular patient-Large patient values)</td>
<td>50-100</td>
<td>80-160</td>
<td>80-160</td>
<td>80-160</td>
<td>50-100</td>
</tr>
<tr>
<td>mAs (Regular -Large)¹</td>
<td>40-80</td>
<td>40-80</td>
<td>40-80</td>
<td>40-80</td>
<td>40-80</td>
</tr>
<tr>
<td>Scanner effective mAs² (Reg-Lg)</td>
<td>26.7-53</td>
<td>26.7-53</td>
<td>29.6-59.2</td>
<td>29.1-58.2</td>
<td>27-53</td>
</tr>
<tr>
<td>Detector Collimation (mm) - T</td>
<td>2.5 mm</td>
<td>2.5 mm</td>
<td>1.25 mm</td>
<td>1.25 mm</td>
<td>0.625 mm</td>
</tr>
<tr>
<td>Number of active channels - N</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Detector Configuration - N x T</td>
<td>4 x 2.5 mm</td>
<td>4 x 2.5 mm</td>
<td>8 x 1.25 mm</td>
<td>16 x 1.25 mm</td>
<td>64 x 0.625 mm</td>
</tr>
<tr>
<td>MODE (Thick/ Speed)</td>
<td>2.5/HS/15</td>
<td>2.5/HS/15</td>
<td>1.25/HS/13.5</td>
<td>1.25/1.375/27.5</td>
<td>.625/.984/ 39.37</td>
</tr>
<tr>
<td>Table incrementation (mm/rotation) - I</td>
<td>15 mm</td>
<td>15 mm</td>
<td>13.5 mm</td>
<td>27.5 mm</td>
<td>39.37 mm</td>
</tr>
<tr>
<td>Pitch ([mm/rotation] /beam collimation) - I/NT</td>
<td>1.5</td>
<td>1.5</td>
<td>1.35</td>
<td>1.375</td>
<td>0.984</td>
</tr>
<tr>
<td>Table Speed (mm/second)</td>
<td>18.75 mm/sec</td>
<td>30 mm/sec</td>
<td>22.5 mm/sec</td>
<td>55mm/sec</td>
<td>78.74 mm/sec</td>
</tr>
<tr>
<td>Scan Time (40 cm thorax)</td>
<td>22 sec</td>
<td>13 sec</td>
<td>18 sec</td>
<td>7.3 sec</td>
<td>5.1 sec</td>
</tr>
<tr>
<td>Nominal Reconstructed Slice Width</td>
<td>2.5 mm</td>
<td>2.5 mm</td>
<td>2.5 mm</td>
<td>2.5 mm</td>
<td>2.5 mm</td>
</tr>
<tr>
<td>Reconstruction Interval ³</td>
<td>2.0 mm</td>
<td>2.0 mm</td>
<td>2.0 mm</td>
<td>2.0 mm</td>
<td>2.0 mm</td>
</tr>
<tr>
<td>Reconstruction Algorithm³</td>
<td>STD</td>
<td>STD</td>
<td>STD</td>
<td>STD</td>
<td>STD</td>
</tr>
<tr>
<td># Images/Data set (40 cm thorax)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>CTDI\textsubscript{vol} Dose in mGy ⁴ (Regular – Large )</td>
<td>2.8 – 5.6 mGy</td>
<td>2.4 - 4.9 mGy</td>
<td>3.1 - 6.2 mGy</td>
<td>2.7 - 5.4 mGy</td>
<td>2.2 – 4.4 mGy</td>
</tr>
</tbody>
</table>
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

Mean = $0 \pm 4$ HU
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
Anthropomorphomorphic 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