QUANTITATIVE IMAGING IN MULTICENTER CLINICAL TRIALS: PET

American College of Radiology Clinical Research Center
This module is intended to provide a brief overview of general and PET-specific issues relevant to quantitative imaging for clinical trials. For additional information related to quantitative imaging for clinical trials, please see USEFUL LINKS on the CQIE web page (address provided below). For additional CQIE program information and qualification materials (MOP, forms, etc.), please refer to the CQIE web page.

CQIE MOP and program information:

www.acrin.org/NCI-CQIE.aspx

After you have reviewed this module please let us know by submitting the learning module attestation. The link is provided at the end of this module.
What is Quantitative Imaging?

As defined by the Toward Quantitative Imaging (TQI) task force of the Radiological Society of North America (RSNA):

“Quantitative imaging is the extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal. Quantitative imaging includes the development, standardization, and optimization of anatomical, functional, and molecular imaging acquisition protocols, data analysis, display methods, and reporting structures. These features permit the validation of accurately and precisely obtained image-derived metrics with anatomically and physiologically relevant parameters, including treatment response and outcome, and the use of such metrics in research and patient care.”

Buckler, et al., A Collaborative Enterprise for Multi-Stakeholder Participation in the Advancement of Quantitative Imaging, Radiology; Volume 258: Number 3, March 2011
What is Quantitative Imaging?

Which imaging parameters are quantitative?

Morphology

- Volume, 3D techniques (vCT, vMR)
- Cellularity, density, composition of tissue

Function

- Perfusion (DCE-MRI and DSC-MRI)
- Metabolic activity (PET)
- Molecule movement (DWI)
- MR Spectroscopy (MRS)
What is an imaging biomarker?

“...any anatomic, physiologic, biochemical, or molecular parameter detectable with one or more imaging methods used to help establish the presence and/or severity of disease.” Ideally, a biomarker is an objectively measurable characteristic (versus a qualitative observation).

Why use biomarkers?

To speed the development of safe and effective medical therapies and procedures.

Imaging Biomarkers in Clinical Trials

Uses:

- Patient stratification in order to decide on alternative treatments
- Analysis of heterogeneity within and across lesions (can assess varying pharmacokinetics, receptor status, proliferative/apoptotic rates, ...)
- Early prediction of treatment response
- Basis for modifying therapy
- Monitoring for Treatment Efficacy
- Longitudinal monitoring and evaluation (can be done before then after treatment, substituting for longitudinal tissue biopsy)

Needs:

- **Standardization** - the consistent performance of imaging, and adherence to protocols, for every research study performed at a given clinical site.

- **Harmonization** - the identification and implementation of mechanisms to control for inconsistencies of data between the different sites, particularly to ensure that imaging data generated with different systems are comparable.

Facilitating the Use of Imaging Biomarkers in Therapeutic Clinical Trials, M.Graham, RSNA/SNM/FDA Two Topic Imaging Workshop, 2010
Why? Good Science

Reliable decision making based on medical imaging requires comprehensive standards and tools to maintain integrity and ensure quality of results. For results to be of benefit to researchers and patients, the results must be accurate, comparable and reproducible (across patients, time-points, and institutions).

- Standardize imaging equipment (when possible)
- Standardize image/data acquisition
- Standardize image/data reconstruction
- Standardize image/data processing
- Standardize image interpretation
Qualify NCI cancer centers in quantitative imaging methodologies:
- Static and dynamic PET, PET/CT (body and brain)

Standardized qualification process and assessment, across 58 NCI-designation Cancer Centers

Promote imaging standardization and harmonization within multi-center clinical trials.
Clinical Test Cases
- 2 Brain, 2 Body- AC, NAC and CTAC files
- Anonymized and submitted via sFTP

Phantoms
- Uniform Cylinder- AC, NAC and CTAC files
  - 2 bed position body FOV scan, using routine body protocol
  - 1 bed position brain FOV scan, using routine brain protocol
  - 1 bed position body FOV dynamic scan- 25 minute acquisition reconstructed in pre-defined time bins and summed
- ACR Phantom- AC NAC and CTAC files- Don’t forget to remove the 6 spheres and 6 mounting posts attached to the spheres
  - 2 bed position body FOV scan, using routine body protocol
  - 1 bed position brain FOV scan, using routine brain protocol
- Submitted via sFTP
Standardized QC helps to ensure the quantitative data generated within a clinical trial is comparable within an institution and across institutions.

Sites are expected to incorporate the CQIE standardized QC measures into their existing QC activities.

Sites are required to adhere to the CQIE standardized QC measures to maintain qualification status.
QC is an important function of image quality and patient safety. Benefits of routine QC include...

- Verification of operational integrity of imaging systems
- Early identification of technical issues
- Consistent, high image quality
- Consistent quantitative accuracy - SUV and Tracer Kinetics

Quantitative imaging increases importance of QC.

Participation in multicenter clinical research trials increases the importance of QC.
<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Inspection</td>
<td>To check gantry covers in tunnel and patient handling system.</td>
<td>Daily</td>
</tr>
<tr>
<td>Daily QC Check</td>
<td>To test proper operation of scanner (per manufacturer’s recommendations)</td>
<td>Daily</td>
</tr>
<tr>
<td>Normalization</td>
<td>To adjust system response to activity inside the field of view (FOV).</td>
<td>As recommended by manufacturer (at least every 3 months); after software upgrades and after hardware service</td>
</tr>
<tr>
<td>Uniformity</td>
<td>To assess Transverse and Axial Uniformity across image planes by imaging a uniformly filled object.</td>
<td>At least every 3 months, after new setups and after software upgrades,</td>
</tr>
<tr>
<td>Cross-Calibration</td>
<td>To monitor and identify discrepancies between the PET scanner and the dose calibrator.</td>
<td>At least every 3 months, after scanner upgrades, after new setups, and after modifications to the dose calibrator</td>
</tr>
<tr>
<td>Image quality</td>
<td>To check hot and cold spot image quality of standardized image quality phantom.</td>
<td>At least annually</td>
</tr>
</tbody>
</table>

Documentation of the tests are subject to audit on annual renewal for qualification
## Standardized QC - CT

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water CT Number &amp; Standard Deviation</td>
<td>Daily- Technologist</td>
</tr>
<tr>
<td>Artifacts</td>
<td>Daily- Technologist</td>
</tr>
<tr>
<td>Scout Prescription &amp; Alignment Light Accuracy</td>
<td>Annually</td>
</tr>
<tr>
<td>Imaged Slice Thickness-Slice Sensitivity Profile (SSP)</td>
<td>Annually</td>
</tr>
<tr>
<td>Table Travel/Slice Positioning Accuracy</td>
<td>Annually</td>
</tr>
<tr>
<td>Radiation Beam Width</td>
<td>Annually</td>
</tr>
<tr>
<td>High-Contrast (Spatial) Resolution</td>
<td>Annually</td>
</tr>
<tr>
<td>Low-Contrast Sensitivity and Resolution</td>
<td>Annually</td>
</tr>
<tr>
<td>Image Uniformity and Noise</td>
<td>Annually</td>
</tr>
<tr>
<td>CT Number Accuracy</td>
<td>Annually</td>
</tr>
<tr>
<td>Artifact Evaluation</td>
<td>Annually</td>
</tr>
<tr>
<td>Dosimetry/CTDI</td>
<td>Annually</td>
</tr>
</tbody>
</table>

Documentation of the tests are subject to audit on annual renewal for qualification.
# Standardized QC – Dose Calibrator

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constancy (precision)</td>
<td>Each day of use and after equipment repair</td>
</tr>
<tr>
<td>Clock Accuracy</td>
<td>Daily</td>
</tr>
<tr>
<td>Linearity</td>
<td>Quarterly</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Annually and after equipment repair</td>
</tr>
<tr>
<td>Geometry (position and volume)</td>
<td>Upon installation and after replacement or repair of the chamber</td>
</tr>
<tr>
<td>Accuracy of F18 Measurements</td>
<td>Upon installation; at least once since June 2009</td>
</tr>
</tbody>
</table>

Documentation of the tests are subject to audit on annual renewal for qualification.
Refresher - What is SUV?

- Standardized Uptake Value
- Semi-quantitative measure of the tracer uptake in a given region

\[
SUV_{Weight} = \frac{Conc_{Tissue}}{InjAct/Weight}
\]

- \( Conc_{Tissue} \) = Activity Concentration in Tissue (or region of a phantom) as measured in an ROI
- \( InjAct \) = Injected Activity at the start of the PET Emission acquisition
- \( Weight \) = Weight of patient (or active volume of phantom)
  - Weight is the most common method of SUV normalization but factors like Lean Body Mass and Body Surface Area can also be employed
Technical Factors Affecting SUV

- Strict adherence to research protocol
- Accurate recording of time, activity and weight
- Dose calibrator accuracy, constancy, low background
- Scanner normalization, calibration
- Image reconstruction algorithm
- PET corrections: attenuation, scatter, randoms, decay
- ROI definition/methods for SUV
- SUV Normalization factor (body weight, body surface, lean body mass)
Quantitative Accuracy

- With so many factors contributing to the accuracy of SUV calculation it is of the utmost importance to ensure all instruments are functioning within acceptable limits at all times.

- All times must be recorded to the minute and all clocks must agree with the PET scanner clock to the minute.
  - Assay Time, Injection Time, Residual Assay Time, Scan Start Time.
Strict Adherence to Protocol

- Deviation from protocol invalidates quantitative data.
  - Increase or decrease in circulation time alters SUV
  - Blood Glucose and Insulin levels alter SUV when using some tracers
  - Patient behavior before and during uptake period can affect tracer distribution and SUV
  - Moving the patient between scans when instructed not to may interfere with or invalidate core lab analysis
  - Failure to perform additional scans with IV contrast may interfere with or invalidate core lab analysis
Accurate Data Entry

- If weight, net injected dose, time of dose assay or injection are recorded or entered incorrectly, any SUV calculated for the resulting images will be incorrect.

- **Good Research Practice**
  - Weigh every person on the scale in the PET Facility; do not take the patient’s word.
  - Ensure all clocks in the PET Facility are synchronized to the PET scanner clock and to the minute.
The dose calibrator must be maintained and checked in accordance with NRC guidelines.

The dose calibrator clock must be in agreement with the PET scanner clock to the minute.

All doses must be assayed with the dose calibrator background at 0:

- Remove all radioactive sources from the area.
- Check to ensure background is 0 before and after the assay of every dose.
- Keep a spare dose calibrator dip stick handy at all times for use in the event of contamination.
- Clean even small amounts of radioactive material from the chamber if detected.
- If background above 0 is unavoidable record the background reading and the time measured before and after dose assay.
Image Reconstruction Algorithm

- Changing the reconstruction algorithm can affect the activity distribution visualized in the final image.
- In all research trials, it is important to use the same reconstruction algorithm with the same parameters for all patients.
  - This will help ensure data across patients and time points can be compared both qualitatively and quantitatively.
PET Corrections

- **Normalization** – Corrects for non-uniformities in detector response
- **Attenuation** – Corrects for decrease in detected events due to absorption and scatter
- **Scatter** – Corrects for detected events that underwent a scattering event
- **Randoms** – Corrects for detected events that originated from two different annihilation events
- **DeadTime** – Corrects for a reduction in detected counts caused by elevated count rate
- **Decay** – Corrects for the decreased activity during the scan due to radioactive decay.
- **Cross-Calibration/SUV** – Converts the reconstructed counts into concentration (or SUV) in the final image
Scanner Normalization

- Corrects for non-uniformities in event detection over the full scanner
- Sources of non-uniformities:
  - Variation in amount of scintillation light collected due to crystal non-uniformities and detector design (detector effect)
  - Difference in detection sensitivity due to angle of incidence
- Most manufacturers use a uniform cylinder acquisition to generate the normalization correction

Uniform cylinder
Routine Scanner QC

- Purpose of scanner QC is to ensure that the system performing as expected and expose any issue before they have a clinical impact.
- QC program should involve daily, weekly, monthly, quarterly and annual tests.
- QC programs should be reviewed regularly and updated should any deficiencies be found.
- Scanner QC helps ensure that resulting images are quantitatively reliable.
ROI Definition

- How the boundaries of an ROI are defined affects quantitative results

- A short Example:
  - Max – Max Pixel in ROI
  - Peak – Avg. in 1 cm ROI
  - CT – Avg. in ROI using boundaries defined on CT

- To the right:
  - Actual Diameter is 16 mm
  - Max = 2.110
  - Peak = 1.721
  - CT = 1.538
Normalization Factor - Body Weight

- It is essential to accurately record patient weight
- Ensure your scale is accurate
- Never record weight as reported by the patient or test subject.
Important Points

- Quantitative, multi-center clinical trials require reliable, quantitatively accurate image data.

- This is obtained by properly maintaining all imaging related equipment, strictly following the research protocol, and accurately recording all required patient related information.

- A small number of non-compliant cases can invalidate an entire trial.
Imaging & Research-Related Links

- RSNA/ACRIN Imaging Researchers Workshop (Sept. 2011), http://www2.rsna.org/re/CTSAIWGACRIN2011/Index.htm
Please follow the link below to report your review of this module
https://www.surveymonkey.com/s/CQIE_QuantitativeImaging_PET

CQIE PET questions should be directed to CQIE-PET@acr.org

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Thank you!