Clinical Trials Network: Facilitating Multicenter Trials

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Director
Clinical Trials Network
Society of Nuclear Medicine and Molecular Imaging

JSNM Annual Meeting
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Clinical Trials Network (CTN)

• CTN was founded in 2008

• Vision
  – The CTN will take a leadership role in advancing the use of radiopharmaceuticals and optimizing the use of molecular imaging in clinical trials and dissemination into clinical practice.
Clinical Trials Network

• Mission
  – Advance the use of molecular imaging radiopharmaceuticals in clinical trials through standardization of chemistry and imaging methodology. This includes using imaging agents during the course of drug development, as well as bringing new radiopharmaceuticals to regulatory approval.
Clinical Trials Network

• Goals
  – Ensure high-quality PET and SPECT imaging in the conduct of drug development clinical trials
  – Work towards use and approval of new radiopharmaceuticals
  – Facilitate access to investigational PET radiopharmaceuticals for multicenter clinical trials
  – Provide education and training for the use of molecular imaging in clinical research
CTN Organization and Structure
Clinical Trials Network Co-Chairs: Michael Graham, PhD, MD and John Hoffman, MD

CTN Operations Committee

Database  
Chair: John Sunderland

Scanner Validation  
Chair: Paul Christian

Site Education  
Chair: LisaAnn Trembath

Radiopharmaceutical Manufacturers  
Chair: David Dick

SPECT  
Chair: Jon Nye

Site Qualification & Monitoring  
Chair: James Mountz

Director: Bonnie Clarke
Asst. Dir.: Tina Kiss
Ass. Prog. Mgr.: Jina Kim

Assistance with Trial Design is available as an ad hoc service.
Scanner Validation

• CTN clinical simulator phantom
• Validation of scanners based on image quality, noise and contrast, lesion detectability, SUV accuracy, attenuation correction, PET/CT alignment, ability of technologist to follow directions
• Evaluation of entire imaging system: accuracy of dose calibration and reconstruction parameters

CTN Chest Phantom
Images courtesy of Paul Christian
Scanner Validation

CTN-Validated PET/CT Scanners (241)

Sites in Japan

- Dokkyo University School of Medicine (Tochigi)
- Institute of Biomedical Research and Innovation (Kobe)
- National Cancer Center (Tokyo)
From 201 individual scanners, we recorded 108 distinct reconstruction parameter sets. (GE and Siemens scanners)
Education

- A unique aspect of the CTN
- Educational offerings at live meetings, live webinars, and a library of recorded courses
- CME credits for technologists, physicians, and physicists are available
- Developing a ‘master level’ set of courses – RECIST measurements
Educational Offerings

CTN101: Source Documentation in Clinical Trials
CTN102: The Language of Clinical Trials
CTN103: Introduction to GCP and 21CFR312
CTN104: Adverse Events and Serious Adverse Events
CTN105: Vital Signs, ECG, and Other Physical Measurements
CTN106: The Importance of Following the Protocol in Clinical Trials
CTN107: Quality Control for Clinical Trials
CTN108: The Importance of SOPs in Clinical Trials
CTN109: A Close Up Look at the 1572
CTN110: PK and Biodistribution Sampling in Clinical Trials
CTN112: Conflict of Interest: Financial and Otherwise
CTN113: The Institutional Review Board [IRB]
CTN114: Site Inspections: Are You Ready?
CTN115: Phases of Drug Development
CTN116: Imaging in Clinical Research: Elements for Success

(4 additional courses are in progress; ready 1Q2015)
Radiopharmaceutical Manufacturers

- CTN manages the SNMMI-held FLT IND
  - Performs audits of sites manufacturing study doses of FLT
    - Desk top and on-site audits
  - Approves new manufacturers for inclusion in IND
- Assists with pharma company interactions relating to radiopharmaceutical manufacturing
- Available for audits of proprietary RP agents
Site Qualification and Monitoring

• Responsible for assessing each site’s capabilities
  – Research infrastructure
  – Access to required radiopharmaceuticals
  – Experience of staff with clinical trials
  – Appropriate imaging equipment available and access to it for study patients

• CTN reviews first 2 subject scans at each study site to assess protocol compliance and image quality
SPECT

• New committee, started August 2014
• Nearly 80% of nuclear medicine scans are single photon
• Many trials use SPECT agents
• Interest in quantitative SPECT is high
• First task is to evaluate/design a phantom that will allow for standardized quantitative measurements
Database

• The CTN database has a web-based interface for users
• Holds all data for both imaging and production sites including personnel information, equipment, RPs manufactured, and research infrastructure
• Sites are asked to update data yearly
• Reports can be generated: site status, scanner validations, and RPs
Database: Worldwide FLT Production

Red = Academic sites -- Blue = Commercial Sites
### Database

<table>
<thead>
<tr>
<th>Sites in Database</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging Only Sites</td>
<td>170</td>
</tr>
<tr>
<td>Production Only Sites</td>
<td>114</td>
</tr>
<tr>
<td>Imaging and Production</td>
<td>126</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>410</strong></td>
</tr>
</tbody>
</table>

Welcome to the Clinical Trials Network Database System
Facilitating Multicenter Trials
Role of the Sponsor

• The sponsor develops the clinical protocol and selects the study sites
  – Sites typically selected based on the oncologist, who is the principal investigator at the site
  – Imaging qualifications are a secondary consideration

• Pharmaceutical companies, or sponsors, request assistance with specific imaging components of the study

• The sponsor is responsible for all reimbursement of the site’s study activities
The Study Team

- Typically, an Imaging Contract Research Organization (CRO) is involved in the trial.
- A breakdown of responsibilities and communication plan between the sponsor, CRO, and CTN is written and signed.
- Conference calls with all team members occur monthly to discuss enrollment, scanner validations, any issues with the study or sites.
- A tracking log is jointly maintained by all parties.
Common Services Requested by Pharma

• Scanner validation
• Access to investigational radiopharmaceutical – This can impact site selection
• Assistance with imaging manual development (in the context of therapy protocol)
• Review of first patient images to ensure high quality and compliance with the protocol
Scanner Validation

- Send phantom and instructions to site
- Answer questions during the process
- Assist in image transfer
  - Images uploaded to Imagys® - a web-based clinical trial image management system
- Communicate validation results to site and sponsor; provide report and certificate
- Revalidate scanners, usually every 6 months
Access to Radiopharmaceuticals

- This is often NOT considered prior to site selection
- Work with sites and manufacturers to establish pricing, contracts, delivery schedules
- Site must schedule patients when the RP can be delivered, often late afternoon if investigational
- Educate sponsors on nuances of RPs
Imaging Manual Development

• Develop or edit the imaging manual
  – Patient preparation
  – Dose and uptake time
  – Image acquisition and reconstruction parameters
  – Patient positioning
  – Post-scan follow up
  – Therapy specific considerations (drug interactions)
• Train the site personnel on imaging details
• Develop source document worksheets for sites’ use
Review of Patient Images

• Sites upload the first two study patient images into Imagys®
• Reviewed by committee members to ensure protocol compliance and image quality
• If a problem exists, it is communicated to the sponsor and CRO
CTN Projects
FLT

• IND was opened in 2008
  – 2 studies total with one ongoing
  – 8 active sites in the trial
  – 72 patients enrolled in trials
  – 7 manufacturers are included in the IND
    • All major commercial vendors (4)
    • Small, independent pharmacy (1)
    • Academic institutions (2)
"Harmonized Reconstructions for Cancer Clinical Trials"

The Situation:
Clinical Trials involving PET Imaging in endpoint assessment, primarily (but not exclusively) for response to therapy applications, require accurate quantitation. FDA demands this.

The Problem:
The use of quantitative PET imaging in clinical trails is hampered by the large degree of variability arising from inconsistent and non-optimized image acquisition, processing and analysis. Efforts have been initiated to standardize protocols that impact PET quantitation. However, there has been ineffectual effort to harmonize image reconstruction methodologies to resolve the problem of the substantial variability in PET image accuracy in multi-center trials.
“Harmonized Reconstructions for Cancer Clinical Trials”

The Solution:

• The proposed project will provide quantitatively accurate and reproducible PET measurements for multicenter trials through performance-based reconstruction protocol specifications designed to harmonize reconstructions across a broad range of scanner makes and models.
Quantitative impact of different reconstructions on objects of different sizes

Even in the same scanner, substantial quantitative differences are seen depending upon the chosen reconstruction parameters.
Movember

- Coordinating two multicenter academic trials for prostate cancer imaging
- F-Choline
  - 10 centers in Australia, UK, and Canada
- F-DHT
  - 4 centers in Australia, US, Netherlands, UK
- Provide scanner validation, image upload, Case Report Form development, image QC
Gallium Users Group

• Users Group helps sites initiate $^{68}$Gallium-labeled somatostatin-receptor imaging for neuroendocrine tumor imaging (DOTATATE and DOTATOC)
  – IND template, imaging manual, CRF template
• In the US, there are 10 active sites and another 6 pending IND/protocol approval
• Many are funded with a cost-recovery IND
  – Allows hospitals to bill private payer
Gallium in Japan?

• GMP-grade $^{68}$GE/$^{68}$Ga generator available from Eckert & Ziegler
• Single-step kits for somatostatin receptor agents under development
• Prostate Specific Membrane Antigen (PSMA) for prostate cancer imaging under development in US and Europe
• Does this model work in Japan?
Future of CTN

- The first publication of the CTN scanner validation program results will be published in early 2015 (JNM)
- Harmonization results from R01 grant will be tested in a multicenter trial
- CTN is testing a new version of the oncology phantom containing the number and sized spheres that are in the NEMA phantom
Thank you