State of the Network

A communication from CTN Co-Chairs:
Michael M. Graham, PhD, MD; Peter S. Conti, MD, PhD; John M. Hoffman, MD; and Alexander J.B. McEwan, MD

After years of planning and strategizing, SNM launched the Clinical Trials Network (CTN) in August 2008. We believe that the results that the CTN has delivered to date have far exceeded our initial expectations.

The Clinical Trials Network has five overarching goals:
• Organize multisite clinical trials to gather standardized imaging data that will lead to expanded use and validation of molecular imaging biomarkers for Phase 1, 2 and 3 therapeutic trials;
• Provide safety and efficacy data of molecular imaging biomarkers through a centralized IND;
• Organize a manufacturing registry for production of and access to molecular imaging biomarkers;
• Provide an international registry of qualified and certified imaging centers through phantom utilization and ongoing assessment and monitoring;
• Provide site orientation and training programs to increase adherence to protocols and drive quality in imaging-based clinical research.

Some key deliverables that we can celebrate after the first year of operations include:
• Three pharmaceutical partners have now joined with the CTN and have agreed to provide financial support of the required infrastructure and processes;
• Initial launch of manufacturer’s registry with 135 sites to date;
• Expansion of our imaging site registry database, which currently includes more than 200 sites worldwide who have expressed interest (>25% participation from outside the U.S.);
• First CTN SNM-centralized IND for an imaging biomarker: [F-18] FLT;
• Collection of DMF letters of cross-reference from all major FLT manufacturers in the U.S. (PETNet Solutions, Cardinal Health and IBA Molecular);
• Near completion of initial FLT phantom demonstration project (with several other opportunities on the horizon);
• Selection of FMISO as the next imaging agent for submission of an CTN SNM-Centralized IND;
• Development of a supply of oncology phantoms to support upcoming site qualification work;
• Development of a brain phantom prototype, with a cardiac phantom planned for 2010;
• Completed demonstration of the initial functional version of the database at the SNM Annual Meeting (should launch in 1Q 2010);
• The recruitment of two full-time staff members experienced in pharmaceutical and academic clinical trials work;
• Multiple ongoing CTN-supported educational activities to advance awareness and understanding of the “Practice of Clinical Trials” within the imaging community.

At this time, we are identifying a small number (20-25) of sites, based on the needs of the CTN.
and our pharmaceutical members, who will enter the scanner validation and site qualification process. Our goal is to have at least ten U.S. and five non-U.S. (three Canadian and two European/other) sites validated via the CTN Phantom Program and qualified prior to the SNM Conjoint Mid-Winter Meetings on February 1, 2010. Qualified sites will have completed a series of on-line forms that include a listing of site personnel and qualifications, equipment, experience and quality assurance routines. A site is considered “fully qualified” for conducting imaging studies after successfully completing our scanner validation and site qualification process. Such sites can then move on to qualify for participating in specific clinical trials at the individual sponsor’s discretion.

Working from the strong foundation of our early successes, we can now reflect upon what has been effective and where we need increased focus going forward.

THE TOP THREE CRITICAL-TO-SUCCESS FACTORS FOR FY2010

• **Imperative #1: Drive understanding of the importance and need for standardization and harmonization in clinical trials.** When pharmaceutical companies apply to the FDA for approval of a new therapeutic drug, they must often demonstrate a defined level of disease identification and response as evidenced by an imaging measurement or assessment. Denials of new drug applications are often based on data rejection due to non-standardization of imaging techniques across clinical trial sites. Sites interested in participating in multicenter therapeutic clinical trials must demonstrate an ability and willingness to follow standardized imaging protocols and procedures that are essential for harmonizing the data at the end of the trial.

• **Imperative #2: Create a community of trained and certified molecular imaging research technologists.** Growing feedback from pharmaceutical companies and clinical sites indicates that there are fewer errors, lower costs, more reliable data and greater safety in trials when properly trained and certified personnel are involved. We believe that nuclear medicine technologists have a critical role to play in the evolution of this field and, by providing certification and training opportunities within the CTN structure, we will ensure the highest standards of compliance when performing clinical research. The CTN demonstrates a commitment to the public and to sponsors of clinical trials to assure that the molecular imaging studies performed as part of therapeutic clinical trials will be of the highest quality.

• **Imperative #3: Deliver high-quality programs and services.** As we approach each definitive phase of CTN’s plans, we should keep our available resource level in mind and determine just which capabilities we can manage ourselves and what must be outsourced or not done at all. As we face tough choices and trade-offs in the future, we will continue to be best served by refusing to compromise on quality and avoid doing more than what we can do well.

LOOKING AHEAD

As co-chairs of the Clinical Trials Network, we are very enthusiastic about the progress we have made to date and the momentum we have heading into 2010. Thank you for your tireless efforts to launch the SNM Clinical Trials Network. It is our belief that just the act of completing the validation and qualification processes will benefit each site and their personnel. Feedback the sites receive as a result of completing these procedures will likely lead to improvements that will benefit your technologists, doctors and, most importantly, your patients immediately. As you know, this important initiative is destined to markedly expand the role of molecular imaging and will bring the right treatment to the right patient at the right time. There can be no better outcome than that.

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**SNM Clinical Trials Network Co-Chairs**

[Images of co-chairs]

Michael Graham  Peter Conti  John Hoffman  Sandy McEwan

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**Isotope Shortage and Availability**

Jeffrey P. Norenberg, PharmD
Robert W. Atcher, PhD, MBA

As most people in the nuclear medicine community are now aware, there is a critical shortage of the medical radioisotope, Technetium-99m (Tc-99m), a product derived from Molybdenum-99 (Mo-99). There are only five reactors in the world that are approved to produce and ship this isotope to the U.S.

The U.S. capacity for domestic medical radioisotope production had declined sharply over the past 10 years, and there are currently no facilities in the U.S. that are producing Mo-99. Both domestic and worldwide shortages of Mo-99 have been widely reported since late 2007. The most recent extended shortage began in May 2009, when the NRU reactor in Chalk River, Canada—the world’s largest reactor that produces Mo-99—went offline for maintenance. The NRU reactor is expected to remain offline through the first quarter of 2010. This, combined with recent efforts to limit the use of highly-enriched uranium (HEU) in radioisotope production, now poses a significant threat to Mo-99 availability within the U.S. The U.S. House of Representatives has taken an important step forward by passing the “American Medical Isotope Production Act” (H.R. 3276)—a bill that would create a stable and reliable supply of medical isotopes in the U.S. The bill will now head to the U.S. Senate for approval.

Tc-99m is used in more than 16 million nuclear medicine tests each year in the United States. A significant number of clinical trials depend on Tc-99m for their conduct, yet a small fraction — approximately 2% — of the Tc-99m is actually consumed for research purposes within the U.S.
What’s Happening

DATABASE COMMITTEE
John Sunderland, PhD

The Database Committee was established to design and implement a Web-accessible database that provides tools to help manage the imaging and production components of the Clinical Trials Network. Equally important, the database is designed to provide pharmaceutical partners with complete, accurate and up-to-date structured access to imaging and production capabilities of all CTN member sites. The database will store complete information about on-site personnel, as well as both departmental and institutional research infrastructure. An inventory of PET and PET/CT scanners at each site will be collected and maintained, along with QA/QC programs associated with each scanner. Information on all scanners validated through the CTN phantom validation program will be accessible through the database. Although the database will not store images, it will record results of qualification and validation testing, in addition to the items mentioned above. Version 0.9 of the database application has been authored and is presently in beta testing with select CTN sites. CTN member sites can access the database entry portal through the SNM Web site. In its present incarnation, the database consists of approximately 150 fields of data entry for each site.

By January 2010, the day-to-day operations and management of the database will be outsourced to a Web-based group with the expertise and personnel to handle this large and comprehensive database. This committee will continue to address requests by pharmaceutical and CTN members regarding updates, revisions to existing reporting features and overall content of the database.

TRIAL DESIGN
Anthony Shields, MD, PhD

The Trial Design Committee promotes standardization of molecular imaging protocols and development of centralized INDs for use in multicenter imaging-based clinical research studies. As such, they assist pharmaceutical sponsors in writing imaging protocols for the development of new therapeutic agents and to test and validate new imaging approaches. An accurate and appropriate imaging protocol design, or lack thereof in most cases, has led to conducting trials that produce uninterpretable data for some in the pharmaceutical industry. Standardization will help to ensure precise reporting, thus enabling a higher probability for quality data at study’s end. It is the goal of the CTN that involving the Trial Design Committee in developing an imaging protocol at the inception of the overall study design will increase the sponsor’s chance for FDA approval of their NDA/ANDA (providing others areas of the application are complete and acceptable).

In addition to writing protocols for centralized INDs and providing sponsor protocol support, one of the committee’s goals includes writing a standardized imaging protocol using FDG; not as a centralized IND submission but as a template with uniform guidelines that sponsor/sites can follow when using FDG in clinical research. The main purpose of this endeavor is to obtain accurate and homogeneous imaging datapoints, a key factor in the FDAs review process. To date, the committee has facilitated execution of a successful FDA-approved FLT biomarker IND available for cross-reference in pharmaceutical clinical trials, with a second one in preparation. Standardized imaging protocols are also being developed for specific multicenter clinical research trials.

Continued on page 5. See HAPPENING.

BIOMARKER SPOTLIGHT

CTN’S NEXT CENTRALIZED IND—FMISO

Hypoxia is recognized to be an independent predictor of clinical outcome in oncology. Hypoxic, or poorly oxygenated tumor cells are more resistant to radiation therapy than well-oxygenated cells. PET, using the radiotracer 18F-fluoromisonidazole (FMISO), binds to hypoxic tissue and is useful for the non-invasive assessment of hypoxia in cancer. Hypoxia is one of the most important prognostic factors in cancer of the head and neck (HNC) and non-small cell lung cancer (NSCLC). FMISO-PET represents a valuable tool for identifying those patients with increased risk of relapse, who may then be treated with an intensified therapeutic regimen sooner in the course of treatment. Other important potential uses of FMISO are to identify patients with hypoxic tumors who might benefit from treatment using hypoxic radiosensitizers, such as tirapazamine, and to assess the success of tumor reoxygenation schemes.

The CTN has identified FMISO as the next centralized IND radiopharmaceutical. Its value as a prognostic indicator of hypoxia is essential in treating patients with HNC and NSCLC and may provide a powerful non-invasive tool that is not available to clinicians today. Members of the Trial Design Committee and CTN Leadership will begin assembling information and writing of the IND application, with a goal for submission to the FDA in Spring 2010.

FMISO in glioblastomas
As the Clinical Trials Network moves into full operation, nuclear medicine and molecular imaging technologists are taking on a greater role in the execution of imaging trials. Some of us have participated in clinical trials for years, but have struggled with the regulatory and practical application of strict imaging protocols. How do we follow the clinical trial protocol if it differs from our clinical practice? What regulations apply to our practice in research?

With this need in mind, the Clinical Trials Network has designed an educational series specifically geared toward technologists who are currently participating, or desire to participate in, radiopharmaceutical trials. This series will provide both beginner and advanced sessions in the administration of clinical trials; specifically in the areas of: Following the Protocol, Standard Operating Procedures and Quality Assurance.

These educational sessions also provide the opportunity to network with fellow technologists and benefit from each other’s knowledge and experience. I encourage you to embrace this opportunity to advance your practice. Participation in the Clinical Trials Network will not only benefit our patients, but will also allow us to play an important role in the advancement of nuclear medicine and molecular imaging technology.

**TECHNOLOGIST COURSE CURRICULUM AVAILABLE COURSES:**

- **Course Number: CTN106**
  **Course Title: The Importance of Following the Protocol in Clinical Trials**
  **Target Audience:** Nuclear med techs, imaging techs, investigators
  **Time:** 60 minutes
  **Credit:** 1.0 VOICE credit
  **Objectives:** Upon completion of this presentation, participants should be able to:
  1. Describe the following terms: protocol deviation, protocol violation, protocol exception
  2. Recognize the importance of following the clinical trial protocol to exact specifications
  3. Create a list of questions that should be answered by the sponsor or trial organizers prior to patient enrollment.

- **Course Number: CTN107**
  **Course Title: Quality Control in Clinical Trials**
  **Target Audience:** Nuclear med techs, imaging techs, investigators, radiopharmacists
  **Length:** 30 minutes
  **Credit:** 0.5 VOICE credits
  **Objectives:** Upon completion of this presentation, participants should be able to:
  1. Describe quality control standards for imaging equipment and radiopharmacy equipment in clinical practice and how they may differ for clinical trials.
  2. List the most commonly requested QC procedures for clinical trials.
  3. Create a list of questions about QC that should be answered by the sponsor or trial organizers prior to patient enrollment.

- **Course Number: CTN108**
  **Course Title: The Importance of SOPs in Clinical Trials**
  **Target Audience:** Nuclear med techs, imaging techs, investigators, radiopharmacists
  **Length:** 30 minutes
  **Credit:** 0.5 VOICE credits
  **Objectives:** Upon completion of this presentation, participants should be able to:
  1. Describe what institutional or site SOPs are pertinent to clinical trials.
  2. List appropriate SOP documentation that may be requested by the trial sponsor or organizer.
  3. Explain the difference between a clinical trial SOP and a departmental SOP.

The following courses are being considered for further implementation:

- The Language of Clinical Trials: Who is Who and What is What
- ABCs of GCPs: Regulatory Basics for Clinical Trials
- Adverse Events and Serious Adverse Events
- Vital Signs, ECG, and Other Physical Measurements in Clinical Trials
- A Close-up Look at the 1572: The Investigator’s Responsibilities in Clinical Trials
- Pharmacokinetic Sampling: Blood and Urine Collection Techniques
- RECIST and Other Response Measurement Criteria
- Conflict of Interest: Financial and Otherwise
- The IRB Review Process
What’s Happening  Continued from page 3.

TECHNOLOGIST EDUCATION
LisaAnn Trembath, MSH, CNMT, CCRA

Image standardization and accuracy of data recording are two things that are a high priority for pharmaceutical and device company sponsors. While each protocol is unique, and specific documentation requirements vary among companies, all of these sponsor requirements originate from the same regulations and guidelines. Every nuclear medicine technologist who has participated in a research protocol can share a story about how complicated it is to accomplish every task in the protocol, collect every single data point over the length of the study, and document the project in the way that the sponsor requires. The Technologist Education Subcommittee of the CTN has been created to provide resources and training for technologists who perform sponsored clinical trials, and who want to enhance their research skills and learn about the regulations behind the sponsors’ requests.

The CTN Technologist Education Series currently contains four programs complete with knowledge assessments, handouts, speaker slide kits and VOICE credits appropriate to the length of the program. Additional topics are “under construction” and are projected to be available later in 2010. Members of the Technologist Education Subcommittee have been trained to present these lectures, which will debut at the CTN Workshop during the SNM Conjoint Mid-Winter Meetings and then subsequently be available via webinars.

Clinical Trials Network
Webinar Series—2010

The Clinical Trials Network is pleased to present a monthly webinar series aimed at advancing the “Practice of Clinical Trials” for all personnel involved in clinical research. The series begins in February 2010 and will occur once each month. Listed below are proposed topics and dates, but please check the CTN Web site for ongoing information and updates.

February 22, 2010  Overview of the Clinical Trials Network
March 23, 2010  The Language of Clinical Trials
April 27, 2010  Why Use the CTN?—An Industry Perspective
June 22, 2010  Standardization in Clinical Research Imaging Trials
July 27, 2010  CTN: Site Qualification and Scanner Validation
August 24, 2010  The Importance of Following the Protocol in Imaging Trials
September 28, 2010  Surrogate Endpoints in Imaging Trials
October 26, 2010  Ethical Concerns and Human Subject Protection
November 23, 2010  Accessing the SNM Centralized INDs
December 16, 2010  Clinical Research Site Inspections: Are You Ready?

The Nanomedicine and Molecular Imaging Summit
January 31–February 1

Nanotechnologies have tremendous promise in benefiting medical and consumer products; however, uncertainties regarding health, safety and environmental issues must be resolved. Molecular imaging is the best tool for improving our tracking, understanding and management of nanomaterials.

This agenda includes talks that:

- Examine key issues related to expanding the medical use of nanotechnologies
- Explore ways in which molecular imaging and therapy currently use nanotechnology
- Discuss how these methods can facilitate advancements in the understanding and proper management of nanomaterials for the environment and human health

Please plan on attending this important summit to gain insight into these pioneering areas of imaging. The complete agenda is posted on the SNM Web site: www.snm.org via the orange SNM Conjoint Mid-Winter Meeting icon in the center of the page.
SITE QUALIFICATION AND MONITORING
James Mountz, MD, PhD

The Site Qualification and Monitoring Committee of the SNM Clinical Trials Network was organized to perform the critical role of gathering information in assessing a site’s resources, abilities and expertise to perform the highest quality of imaging in clinical trials. The committee, through frequent teleconferences and face-to-face meetings, has developed a set of questionnaires designed to provide pharmaceutical sponsors with the critical information needed to assure that a site is capable of performing the imaging assessments required for their therapeutic drug studies. This includes assessing site personnel training including technologists, physicians, research associates and the clinical coordinators who would be involved in imaging trials. These questionnaires will eventually be Web-based and accessible to pharmaceutical sponsors to aid in site selection and to existing clinical trial site members to update their information.

In addition to personnel, the available nuclear medicine and PET imaging device(s) at each site and the QA program used to maintain the device(s) will also be recorded. Representative image sets will be reviewed to assure that the site’s imaging device(s) are functioning optimally and providing reproducible quantitative data. Once a site participates in a clinical trial using the CTN services, the committee will monitor these sites to assure that the imaging component of the protocol is being followed and that the sites are adhering to all FDA regulatory rules related to imaging-based clinical trials.

SCANNER VALIDATION
Paul Christian, CNMT, BS, PET

The Scanner Validation Committee via the SNM Clinical Trials Network Phantom Program is charged with evaluating the image performance capabilities of participating sites. The initial work by this committee was to develop and test a phantom that acts as a clinical simulator and creates challenges for PET/CT oncology studies. The committee used this phantom to evaluate both image quality and lesion detectability while measuring quantitative accuracy of images generated at participating clinical trial sites. Initial testing and modification of the phantom has been ongoing to ensure that this precision phantom could measure the performance of various PET/CT scanners under different environments and still obtain standardized accuracy in lesion detection and measurement. Once sites become qualified through this process, the committee is also responsible for ongoing re-qualification of these sites. An initial demonstration project, which included 10 sites that are currently participating in a clinical trial, is closing in 1Q 2010. Summary experience and data from this project will be used for larger oncology studies and in other areas of need, such as brain and cardiac disease.

Design and development of additional phantoms are underway, including a phantom for neurological PET studies. The brain phantom will be used to evaluate PET scanner image uniformity and resolution capabilities. The phantom is designed to provide both qualitative and quantitative evaluation of scanner performance. The phantom also has a section for simulating the normal distribution of FDG in brain imaging. The neurologic PET phantom provides a cost-effective manner of evaluating PET scanner performance that is not provided with commercially available phantoms. When development is complete, sites will be able to use the phantom for validation as part of the CTN. Look for updates in future editions of Pathways.

CTN
Developing a Brain Phantom
Paul Christian, CNMT, BS, PET

The CTN is in the process of developing a phantom for neurologic PET studies. The brain phantom will be used to evaluate PET scanner image uniformity and resolution capabilities. The phantom is designed to provide both qualitative and quantitative evaluation of scanner performance. The phantom also has a section for simulating the normal distribution of FDG in brain imaging. The neurologic PET phantom provides a cost-effective manner of evaluating PET scanner performance that is not provided with commercially available phantoms. When development is complete, sites will be able to use the phantom for validation as part of the CTN. Look for updates in future editions of Pathways.

Cardiac Phantom and perfusion scans

Brain Phantom
Pre- and post-scanning images

Chest Phantom and Scan

All images on this page are courtesy of Paul E. Christian
The United States Pharmacopeia (USP) is a non-governmental, not-for-profit public health organization. Since its inception in 1820, it has become the official public standard-setting authority for drugs manufactured or sold in the United States. USP sets standards for the quality, purity, strength and consistency of these products, critical for public health. These standards can be enforced by the FDA, the Joint Commission and state agencies. Part of the USP’s role in drug standards development and informational activities relates to PET radiopharmaceuticals (RP). With the passage of the FDA Modernization Act of 1997 (1997 FDAMA), USP’s role in the regulation of PET RP took on added importance. FDAMA required a new approval path and separate Current Good Manufacturing Practices (cGMPs) for PET, different from cGMPs for traditional drugs, be established. Additionally, FDAMA declared that PET RP would be considered “adulterated” if not prepared in compliance with the USP Chapter <823>, “Radiopharmaceuticals for Positron Emission Tomography—Compounding,” and appropriate monographs, if they were available. This rule would exist until there was a final cGMP for PET rule in place.

Many in the PET community are only now becoming familiar with the central role the USP plays in PET RP production. The USP Chapter <823> contains the current requirements for production of all PET drugs, including investigational and research PET drugs, and supersedes USP Chapter <797>, “Pharmaceutical Compounding—Sterile Preparations” for PET RP compounding. On December 10, 2009, the FDA published the final rule for cGMP for PET (21 CFR Part 212). Part 212 will apply to all FDA-approved PET drugs which currently are F-18 Fluorodeoxyglucose (FDG), F-18 Fluoride and N-13 Ammonia. It requires that a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) be filed by the effective date of December 12, 2011 for any facility producing any approved PET drug. Part 212 also allows for investigational PET drugs, produced under an Investigational New Drug (IND) application or with the approval of a Radioactive Drug Research Committee (RDRC), to meet cGMP by complying with either USP Chapter <823>, or the regulations in Part 212.

Reference (JNM 45:1, Jan 2004, 13N-16N)
Save the Dates

FDA, SNM, and RSNA Joint Workshop on Imaging and PET Manufacturing
April 13 - April 14, 2010
Natcher Conference Center, National Institutes of Health, Bethesda, MD

The Clinical Trials Network Workshop
2010 SNM Annual Meeting
Saturday, June 5, 2010
SNM Annual Meeting, Salt Lake City, Utah

Advancing the Practice of Clinical Trials

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