The CTN Oncology Phantom Program: Evaluating 6 Years of Scanner Performance Data

Since 2008, the Clinical Trials Network (CTN) under SNMMI has operated an active PET/CT phantom imaging program using their oncology clinical simulator chest phantom designed to validate scanners for participation in oncology clinical trials. Since its inception, the program has collected nearly 500 phantom data sets from nearly 200 imaging sites sampling the spectrum of commercially available PET/CT systems. The combined and collated phantom data describe a global profile of quantitative performance and variability of PET/CT data used in both clinical practice and clinical trials. Most importantly, analysis of the data is leading to a further understanding of both the magnitude and root causes of variiances in quantitative PET/CT imaging in the multicenter clinical trial environment. These results, combined with the experiences of other international scanner validation programs, are pointing to the necessity for better standardization of methodologies when quantitative PET/CT measurements are used either in clinical practice or, more importantly, in multicenter clinical trials.

The CTN oncology clinical simulator phantom is an anthropomorphic chest phantom, with lung fields and six spherical objects with inner-diameters ranging from 7–20 mm, reproducibly secured at specific locations within the phantom (Fig. 1). This phantom (A) has a single 7-mm sphere located in the mediastinum (B), two 10 mm spheres placed in the lung fields (C), a third 10 mm sphere in an area corresponding to an axillary lymph node (D), a 15 mm sphere in the left shoulder (E), and a 20 mm sphere in the right lung (F). Radionuclide concentrations for the phantom fill were chosen to simulate clinical FDG-scan statistics and generate a 4:1 lesion background concentration ratio to present a challenging imaging scenario. Quantitative imaging results (SUVs of the spherical lesions and background concentrations) show that the CTN phantom can provide meaningful data for validating PET/CT systems in a multicenter clinical trial environment.

Figure 1. CTN oncology phantom: lesion sizes and locations
regions) from this large, well-curated collection of phantom data are entered into CTN's database and have provided the opportunity to perform an analysis not only of the variability of quantitative scanner behavior over the universe of all PET/CT scanners but also of scanner make and model and reconstruction-specific quantitative performance.

Analysis of the CTN oncology phantom has elucidated several important issues associated with quantitative scanner performance. First, quantitative performance of PET/CT scanners as defined by their “recovery coefficients” (PET-measured activity concentration divided by actual activity concentration) for different-sized spheres varies considerably not only between scanner models but also within the very same model using different reconstructions. The magnitude of the variability was illuminating, and there was wide variability, most dependent on the post-reconstruction smoothing filter width and less so upon the iteration/subset choice. Figure 2, a histogram plot of the 15 mm sphere from more than 400 phantom scans (theoretical SUV\textsubscript{max} = 4.0) demonstrates two clear findings: first, it shows enhanced quantitative performance of newer model time-of-flight–enabled PET scanners over their non–time-of-flight counterparts; second, clear overestimation of the SUV\textsubscript{max} can be seen in sites that use the advanced point response function–enabled reconstructions currently available on some systems. Overall, the plot represents potential for an alarming spread of quantitative SUV\textsubscript{max} values for similar objects, depending upon the scanner model and chosen reconstruction. In an uncontrolled clinical trial environment, this generates a large variance in quantitative data. It also has implications in the clinical use of PET/CT when absolute SUV\textsubscript{max} cutoffs are used for clinical decision making.

The second and, perhaps, the most surprising result from the CTN scanner validation phantom datasets is the diversity of reconstruction parameter sets that are being used clinically. In a sub-analysis of phantom data sets from 207 different PET/CT scanners (9 different models), 117 discrete reconstruction parameter sets are represented, with each demonstrating different lesion-size–dependent quantitative properties (recovery coefficients). Manufacturers understandably provide both the means and the opportunity for each site to optimize reconstructions to their own physician preferences; however, this creates an environment where substantial quantitative variability will be inevitable in any multicenter trial. This situation suggests that perhaps a conversation should begin to either narrow the universe of available reconstructions or consider standardizing reconstructions in the CTN.

**Figure 2.** SUV\textsubscript{max} histogram distribution for the 15 mm left shoulder spherical lesion. More recent model time-of-flight–enabled scanners demonstrated higher SUV\textsubscript{max} values, in general, than non–time-of-flight machines. Point response function reconstructions generate anomalously high quantitative values.

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**Message from the Co-Chairs:**

**Standardization: Keeping Pace with Technology**

The mission of the Clinical Trials Network (CTN) within SNMMI is to advance the use of molecular imaging biomarkers in clinical trials through standardization of radiochemistry and imaging methodology. The Scanner Validation Program has been one of the major accomplishments since our inception in 2008. To date, well over 500 sets of images have been reviewed and more than 240 PET/CT scanners have been validated. This effort has resulted in a recent publication by Sunderland and Christian (J Nucl Med 2015;56:145–152). This issue of Pathways, John Sunderland provides a synopsis of the results.

The scanner validation process has been integral in identifying issues with scanners that can potentially affect the integrity of data used in multicenter clinical trials utilizing PET/CT imaging. In a number of cases, sites were unaware that their scanner needed calibration or that the dose calibrator was not functioning properly. By working with the Scanner Validation Committee and its reviewers, sites have been able to correct problems and improve image acquisition and standardization both for clinical trials and in their clinical patients.

As we move forward with the program, two key findings need to be further studied.

- The newer time-of-flight (ToF) scanners, even without enhanced point-response-function reconstructions, have quantitative performance characteristics that are significantly different than those of earlier generation scanners. As a result, quantitative metrics generated in multicenter clinical trials—such as the SUV\textsubscript{mean} and SUV\textsubscript{max}—will affect the quantitative endpoints of a trial when both old and new ToF scanners are used. This will potentially increase the statistical variance of the results.

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Continued on page 4. See Message from Co-Chairs.
IDEAS Study Approved by CMS

Excerpt from a press release by the Alzheimer’s Association (April 16, 2015), “MAJOR NEW RESEARCH STUDY TO DEMONSTRATE VALUE OF PET SCANS IN ALZHEIMER’S DISEASE DIAGNOSIS”

A new four-year research study—The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study—recently received approval with requirements by the Centers for Medicare & Medicaid Services (CMS) to determine the clinical usefulness and value in diagnosing Alzheimer’s and other dementias in certain situations of a brain positron emission tomography (PET) scan that detects a core feature of Alzheimer’s disease.

The IDEAS Study will address two specific aims:
- **Aim 1:** Assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria1.
- **Aim 2:** Assess the impact of amyloid PET over 12 months on major medical outcomes such as hospital admissions and emergency room visits in patients enrolled in the study compared to matched patients not in the study.

IDEAS plans to enroll a total of 18,488 Medicare beneficiaries age 65 and older meeting the appropriate use criteria (AUC) for brain amyloid PET scans. Subjects will be enrolled over 24 months at roughly 200 sites throughout the United States and be recruited into one of two sub-groups: (1) progressive, unexplained MCI, and (2) dementia of uncertain cause. All referrals to the study and for amyloid PET will come from dementia specialists, defined by the Alzheimer’s Association and SNMMI as “physicians trained and board-certified in neurology, psychiatry, or geriatric medicine who devote a substantial proportion of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia, including probable or suspected Alzheimer’s disease.”

IDEAS is led by the Alzheimer’s Association and will be managed by the American College of Radiology Imaging Network (ACRIN). Participating providers will be reimbursed for the PET scans under the CMS Coverage with Evidence Development (CED) policy2 that requires research study participation as a condition of Medicare payment.

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clinical reconstructions or to at least limit reconstructions in a clinical trial scenario to a limited number of well-characterized reconstructions. In a best-case scenario, at least for clinical trial purposes, reconstructions should be fully harmonized.

A third discussion point speaks to the debate concerning the value of a clinical simulation phantom (such as the CTN's oncology phantom) versus the geometric phantoms more typically used by other validation organizations. One surprising finding from the CTN phantom data was that for several PET/CT scanner models, background SUV average values (nominally = 1.0) differed in a statistically significant way in different regions of the same phantom. Results such as this suggest that the asymmetric geometry and non-uniform makeup of the CTN oncology phantom has the potential to uncover subtle but important quantitative nuances related to scatter or attenuation issues that are invisible to the largely geometrically symmetric phantoms more commonly in use.

The current quantitation situation surrounding PET/CT scanners presents a conundrum for organizations, like CTN, that validate scanners for clinical trials. Should criteria for scanner validation be based upon a scanner’s demonstrated ability to quantitatively perform the same (to within tolerances) as other scanners of the same make and model, thereby demonstrating that it is performing the way it “should”? Or, does it make more sense to demand more enforced quantitative conformance to a more general standard (the harmonization approach), whereby sites would be required to reconstruct using prescribed, model-specific reconstruction parameter sets designed to optimize harmonized quantitative performance rather than using their standard clinical reconstruction parameters? The nature and magnitude of the situation is illustrated in Figure 3, which shows (A) SUV_max values for a non-time-of-flight scanner versus (B) a time-of-flight–enabled scanner.

The CTN Scanner Validation Committee is currently wrestling with this question, as the answer is not obvious and may very well be trial dependent. Regardless, it is clearly an area where open discussion between academia, contract research organizations, pharmaceutical companies (trial sponsors) and FDA should occur.

Reference:

Message from Co-Chairs
Currently, vendors allow clinical sites to choose their own iterative reconstruction parameters that are set to generate images that have been tuned and optimized to the local reading physicians’ preference. This non-standardized approach is generating a chaotic quantitative environment with greater variability in the SUV assessments that are used as endpoints in the clinical trial. This subsequently creates a challenging situation within the context of multicenter studies.

When PET/CT is used in multicenter trials as a quantitative assessment of tumor response, it must be a reliable tool with well-understood performance characteristics that can provide both accurate and reproducible measurements. The technology of PET/CT imaging is ever changing, and CTN will continue its efforts to keep pace with it—to identify issues that affect the ability to provide the quantitative information required to promote and increase the use of novel radio tracers in clinical trials and help facilitate drug development.
The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Johns Hopkins University convened to cosponsor the Third Theranostics World Congress on Gallium-68 and PRRT, held March 12–14, 2015, at the Johns Hopkins Medical Campus in Baltimore, Md. Innovative applications and new research results were presented for 68Ga-labeled PET radiopharmaceuticals, including PSMA and CXCR4 targeted imaging and applying the same peptides labeled with beta emitters like 177Lu or 90Y to peptide radioligand therapy (PRLT) of prostate, small cell lung cancer, lymphoma and other malignancies. Although widely used in Europe for more than a decade, 68Ga and 177Lu, as well as 90Y labeled somatostatin receptor ligands, have only been used in the U.S. in trials under Investigational New Drug (IND) applications (e.g., 68Ga DOTATOC or DOTATATE or DOTANOC) or in clinical trials (177Lu DOTATATE). Efforts to obtain approval of these ligands in the U.S. have increased significantly over the past two years, and the potential of having an approved agent available in the U.S. in the near future is promising.

The Congress attracted more than 200 attendees comprising investigators, clinicians, radiochemists, physicists and other scientists from 16 countries representing five continents. Meeting days were separated into subspecialty fields that included chemistry/generators, pre-clinical, and clinical topics. Included in the 11 scientific sessions were two plenary lectures, 23 invited and 26 oral abstract presentations, and one panel discussion on the approval status of Ga-labeled somatostatin receptor imaging agents in the United States. The Thursday plenary speaker was Dr. Jean Claude Reubi from Bern, Switzerland, author of more than 500 scientific articles, holder of a dozen of patents, and patent applications and recognized internationally for his research. He presented “Peptide Membrane Receptors as Targets in Cancer.” On Friday, Dr. Ralph Hruban, Professor of Pathology and Oncology at the Johns Hopkins University School of Medicine, presented “Genetic Alterations in NETs.” Dr. Hruban has written more than 600 scientific papers and five books and has received numerous awards. He is an Institute for Scientific Information highly cited researcher and is recognized by Essential Science Indicators as the most highly cited pancreatic cancer scientist.

Over 71 accepted posters were on display throughout the meeting, and authors were available for discussion of their work during designated times. Thursday’s posters were primarily chemistry in nature, while Friday represented

Continued on page 8. See Special Feature.
Professional growth is frequently associated with overcoming tribulations. As a “test of one’s courage or perseverance,” it is often not easy to see the benefit of taking on new tasks and doing extra procedures, such as those required in clinical trials, when they may just bring unwanted aggravations to an already hectic day. However, those who relish the opportunity to grow, and provide high-quality patient care through clinical research, see things differently.

Twenty-three years ago, I began a career in nuclear medicine, starting in a department that performed only the “bread and butter” procedures of nuclear medicine imaging. Thirteen years ago, PET was in its infancy and, at our current institution, FDG-18 was driven in from more than four hours away. Industry-sponsored PET protocols were all over the board for qualifying scanners and doing research procedures. Each study often requested that up to three different phantoms be scanned for quality control purposes, and imaging technologists, like me, were overwhelmed. Many key research players soon recognized that a more organized approach was necessary if we hope to standardize PET imaging in multicenter trials, and efforts have been underway since then to accomplish that goal.

Today, 13 years after the introduction of PET, there is a cyclotron only blocks away from my institution, and we are able to perform a multitude of trials with different agents (i.e., FMISO, NaF, Amyvid™, and others). The increased number of clinical trials at our facility has enabled us to offer our patients additional options in managing their care.

Assisting nuclear medicine technologists and scientists in overcoming the challenges encountered in clinical trials is a key goal for the Clinical Trials Network and its many volunteers, who truly believe that dealing with tribulations only improves patient care and helps technologists expand their base knowledge to reach new horizons. So, “with [clinical] trials, there may be tribulations”—but the positive outcomes gained from overcoming them is what moves us all to face them head on and share the positive results with others.

Research Essentials: Improving Image Standardization in Multicenter Trials

In molecular imaging, standardization represents the assurance that a PET image (or any medical image) acquired at one site is essentially the same as those from another. Because research primarily uses quantitative measurements, standardized imaging means that a change in a calculated measurement, such as an SUV, has the same relative meaning for all study images. In March 2015, the FDA issued a guidance document for comment entitled “Clinical Trial Imaging Endpoint Process Standards.” Its purpose is to “assist sponsors in optimizing the quality of imaging data obtained in clinical trials intended to support approval of drugs and biological products (medical imaging agents).” The guidance focuses on important elements—acquisition, display, archiving, and interpretation—that must be taken into consideration when imaging is used to assess a trial’s primary endpoint or a component of the endpoint.

Here are some practical tips to help improve standardization at your site:

- Identify research patients **before** they show up for imaging so subject data are not excluded.
- Keep PET equipment in calibration and perform routine QC.
- Follow the study-specific imaging parameters even if they differ from your standard clinical procedure; contact the sponsor if the protocol does not provide enough detail.
- Train ALL technologists on study protocols and hold “refresher” sessions to eliminate variability in image acquisition and measurements.

What is an acceptable, diagnostic and useable medical image for standard patient care may not be acceptable for quantitative research analysis. When image standardization improves, there is a greater likelihood of achieving harmonization in clinical research.

Reference: L. Trembath. Central Chapter Newsletter, Summer 2010
What’s Happening

New Education Subcommittee Forming

The current CTN “100-level” curriculum offers a comprehensive selection of research-related courses on topics that cover both basic and intermediate information to support clinical research activities in the imaging arena. During 2014, however, CTN realized that a gap existed in readily available and inexpensive higher-level clinical research education for study investigators, scientists and members of industry on advanced topics such as research methodology, incorporating investigational imaging agents in trial design, and translating pre-clinical results to clinical application. Although the majority of the 100-level courses were developed by volunteers—both nuclear medicine technologists and researchers with expertise in the topics—we recognized that a different approach would need to be taken with preparing this higher-level curriculum.

To that end, CTN is moving forward with establishing the “Advanced Curriculum Sub-Committee” under the CTN Site Education Committee to facilitate development of a more advanced “200” level courses as well as a “300” level designed for study personnel who do not have a nuclear medicine background or are not directly part of a molecular imaging research program.

Operations Committee met to identify gaps and proposed the following topics:

- Review of cancer therapeutics/mechanisms of action
- Statistics for imaging scientists
- Phases of drug development for investigators and researchers
- Phases of drug development for researchers
- Monitoring PET imaging trials for non-nuclear medicine-trained CRAs

CTN has offered webinars in the past that covered a number of advanced-level topics, but they were not officially set up as courses. This subcommittee plans to approach past speakers and ask them to record their talks as courses, which will then be available in the SNMMI Learning Center.

The next, and very critical, step for CTN is to identify a chair for the subcommittee who has knowledge and interest in this area and can help guide all involved in this project. The CTN Operations Committee is currently reviewing candidates but is accepting additional names as well. Our goal is to launch the first of these courses at the SNMMI 2016 Annual Meeting. If you are interested in joining this subcommittee in any capacity, please contact CTN staff at ctnadmin@snmmi.org.

Tech Tip

Britney Beardmore, BS, CNMT, PET, RT(CT)

- **Continuous Learning:** Be aware of educational opportunities. The process of acquiring new skills and gathering information increases mental acuity and excitement to tackle technological advances. Improve your understanding of research ethics and increase overall compliance with Good Clinical Practice.

- **Advancement Opportunities:** Look within your own organization for career growth and development. Communicate to supervisors and physicians your desire to take on new projects and mentor new employees/students. Ask to become involved in imaging research.

- **Develop Social Awareness:** Be a team player and empathetic to those around you, including patients and colleagues.

- **Stay Positive:** Positivity is powerful and can achieve astounding results. Collect every piece of research data with the understanding that it has the potential to impact patient care.

- **Take a Vacation:** GET AWAY; healthy work/life balance is essential to preventing burnout.

CTN Numbers At-a-Glance

- 6 FLT manufacturers under the SNMMI-CTN IND
- 7 investigational radiopharmaceuticals under study
- 20 recorded courses with CME credit
- 24 countries represented in the CTN database
- 163 sites with validated PET/CT scanners
- 241 PET/CT scanners validated
- 411 registered sites in the CTN database
work on pre-clinical and clinical research. Six abstracts were selected to receive recognition awards: first, second, and third place for oral presentations and first, second, and third place for poster presentations. The winners were announced at the closing ceremony and presented with a certificate. A JNM Supplement containing all accepted abstracts will be available in May 2015.

View all of the video recordings, free of charge, from the entire three-day Congress at https://vimeo.com/channels/3wtc.

We look forward to the 4th Theranostics World Congress being held in Melbourne, Australia, November 6-8, 2016. Check http://wcga68.org/ for updates.

**Clinical Trials Network**

**2015 WEBINAR SERIES**

There are four excellent webinars remaining in 2015. All CTN webinars are presented at 3:00 pm Eastern time. If you cannot attend the live sessions, recordings of the webinars are offered for sale in the SNMMI Learning Center two weeks after the presentation date. [Register today!](#)

**JUNE 25**

Paul Galette: CT Basics for PET/CT in Clinical Research

**AUGUST 20**

Kellie Bodeker: Good Clinical Practice (GCP) Review for Imaging and Radiation Trials

**OCTOBER 15**

John Sunderland: CTN Scanner Validation Data: What Does it Mean?

**DECEMBER 10**

Ruth Tesar and Sue Halliday: Coding and Billing for PET Imaging Agents in Clinical Trials

If you are unable to attend the live webinars, recordings are made available in the [SNMMI Learning Center](#).

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**Save the Dates**

**DIA 2015 51st Annual Meeting**
June 14–18, 2015 • Washington, DC

**World Molecular Imaging Congress**
September 2–5, 2015 • Honolulu, HI

**28th Annual Congress of the European Association of Nuclear Medicine**
October 10–14, 2015 • Hamburg, Germany

**NANETS 8th Annual NET Conference**
October 16–17, 2015 • Austin, TX

**55th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine**
November 5-7, 2015 • Tokyo, Japan

**RSNA 2015 101st Scientific Assembly and Annual Meeting**
November 29–December 4, 2015 • Chicago, IL

**SNMMI 2016 Mid-Winter Meeting**
January 28–31, 2016 • Orlando, FL