Since 2009, the Clinical Trials Network (CTN) has been validating PET/CT scanners used in clinical trials. This successful program was one of the first developed by CTN and it continues today. Since its inception, CTN has completed more than 600 validations on 269 scanners in more than 15 countries around the world. Some sites have validated their scanners every year for 8 years. This cache of imaging data allows the CTN to assess how a scanner performed quantitatively—on a lesion-by-lesion basis—relative to other scanners of the same scanner model. The feedback on the program has been overwhelmingly positive and affects not only clinical trial patients but all patients scanned on a validated scanner.

So, in 2015 when The Joint Commission published new “Diagnostic Imaging Requirements” that mandated phantom-based PET/CT scanner performance evaluations by diagnostic medical physicists, the CTN stepped in to assist. Image uniformity, high contrast resolution/system spatial resolution, low contrast resolution or detectability, and artifact evaluation are the newly required components. No guidance is given as to which phantoms or criteria are to be used in these assessments. Since most PET/CT scanners in the United States are hospital-based, and 82% of hospitals are currently Joint Commission accredited, these new required evaluations impact the majority of PET/CT scanners in the United States. To help the PET/CT imaging community come into compliance with these new requirements while also providing meaningful and actionable scanner performance information, CTN has developed and is currently launching a phantom-based PET/CT scanner evaluation program designed specifically to address this new compliance need.

The proposed phantom program requires sites to perform two phantom scans. The first scan is of a standard uniform 20 cm diameter cylinder phantom filled with aqueous [18F]FDG. Data from this scan are used to meet mandated image uniformity and spatial resolution measurements. The second phantom scan uses a new version of the CTN anthropomorphic oncology phantom with 12 spheres (Figures 1A and 1B) ranging in size from 7-37mm imaged at a 4:1 sphere-to-background ratio. The phantom data are acquired using the site’s standard oncology protocol, including time per bed position and reconstruction parameters (advanced reconstructions allowed). Image data yield a contrast recovery coefficient curve, clinically relevant noise assessment and assessment of low-contrast lesion detectability. The site simply needs to upload the DICOM datasets to the CTN server using a Dropbox-type system,
Clinical Trials Network Launching PET Phantom

Continued from page 1.

The Power of Partnerships

The Clinical Trials Network (CTN) has partnered with the National Cancer Institute (NCI) and academic sites to apply to the Food and Drug Administration (FDA) for a New Drug Application (NDA) for the use of the PET tracer $^{18}$F-FDOPA (3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine) in congenital hyperinsulinism, a rare but very serious disease in infants. Excessive secretion of insulin leads to low blood sugar levels that can cause seizures, brain damage and even death. In some infants, a focal lesion in the pancreas is responsible for the hyperinsulinism, and this form is typically cured with surgical resection while maintaining normal pancreatic function. $^{18}$F-FDOPA can help localize these focal lesions and guide the surgeon to selectively remove the culprit lesion. Because of this resection, investigators have the best reference standard for imaging studies—pathologic tissue confirmation of the imaging finding. Being able to report a tissue reference standard makes the published data uncharacteristically strong. In fact, the literature forms the basis of this NDA. In a pre-NDA meeting, the FDA has agreed to this pathway in principle. The CTN has obtained an Orphan Drug Designation for $^{18}$F-FDOPA-PET in congenital hyperinsulinism, and if the NDA is approved, exclusivity will be waived to make this tracer widely available. The planned submission date is second quarter 2018.

This progress toward approval of $^{18}$F-FDOPA for congenital hyperinsulinism demonstrates how partnerships between the SNMMI, the federal government, and academic institutions can help make molecular imaging agents more widely available. Academic partners in this endeavor include Children’s Hospital of Philadelphia, Washington University in St. Louis, and Cook Children’s Medical Center in Fort Worth. This kind of cooperative approach is best suited to non-proprietary tracers and may serve as a model for seeking approval of other radiopharmaceuticals.

Another exciting aspect of this initiative is the versatility of $^{18}$F-FDOPA as an imaging agent. $^{18}$F-FDOPA has long been used in research studies to measure changes in dopamine synthesis and synaptic packaging in Parkinson’s disease and other movement disorders. Structurally, $^{18}$F-FDOPA is an aromatic amino acid that targets system L amino acid transporters in gliomas, neuroendocrine tumors, neuroblastoma and medullary thyroid cancers. $^{18}$F-FDOPA is a substrate for the enzyme DOPA decarboxylase (DCC), which may lead to trapping of its radiolabeled metabolites in some hormonally active tumors. Although the current NDA effort is focused on congenital hyperinsulinism, FDA approval would make it easier to gain approval to use $^{18}$F-FDOPA for one or more of these other applications.

The CTN is very excited to help make this important, imaging agent available to infants, their families and the doctors who care for them. For more information, a webinar by Lisa States, MD, is available for a small fee at https://www.snmmilearningcenter.org/Activity/5768241/disclaimerspopup.aspx.
With many exciting recent developments in the field of nuclear medicine therapy, such as Lu-177-dotatate and Ra-223-dichloride therapy, another new therapeutic radiopharmaceutical will hopefully be available in the coming months—high-specific-activity I-131 meta-iodobenzylguanidine (HSA-I-131-MIBG)—which will be marketed by Progenics Pharmaceuticals as “AZEDRA®.” Progenics is seeking FDA approval for AZEDRA as a therapeutic agent in patients with malignant (metastatic) or recurrent or unresectable pheochromocytoma and paraganglioma (PPGL). AZEDRA is currently under consideration for approval via the FDA Priority Review mechanism, with the expected action date for an FDA decision July 30, 2018. AZEDRA had previously received a fast-track designation (2006), Orphan Drug status (2006) and breakthrough therapy designation (2015) from the FDA. In addition, the European Medicines Agency granted AZEDRA Orphan Drug status (2008) in neuroblastoma.

A phase 1 dose escalation trial1 showed that HSA-I-131-MIBG is well tolerated with 84% of adverse events categorized as mild or moderate in severity. Maximum tolerated dose was determined to be 296 MBq/kg (8 mCi/kg). Most patients showed at least partial biochemical response as judged by decrease in serum chromogranin A and total metanephrines, and overall survival was 86% at 1 year and 62% at 2 years post-treatment.

A multi-center, open-label, pivotal phase II study investigated the efficacy and safety of HSA-I-131-MIBG in patients with malignant (metastatic) or recurrent or unresectable PPGL.2 MIBG-avid PPGL patients ineligible for curative surgery or chemotherapy and on a stable antihypertensive regimen for tumor-related hypertension were enrolled. Patients received up to two therapeutic doses of HSA-I-131-MIBG, each 296 MBq/kg to a maximum of 18.5 GBq (500 mCi), approximately three months apart. The primary endpoint was clinical benefit as defined by the proportion of patients with at least 50% reduction of all antihypertensive medication(s) lasting ≥6 months. Secondary endpoints included objective tumor response by RECIST and overall survival. Sixty-eight patients received at least one therapeutic dose (full analysis; FA), and 50 patients received two therapeutic doses (per protocol; PP). Most patients had multiple sites of metastatic disease, and 50% (32/64) had lung and/or liver metastasis. The primary endpoint was met by 25% of FA patients, and 32% of PP patients; 23% and 30% of evaluable FA and PP patients achieved a best confirmed tumor response of partial response. The most common (≥50%) treatment-emergent adverse events were myelosuppression, nausea and fatigue. Results from this study suggest that HSA-I-131-MIBG is an efficacious and safe treatment for an ultra-orphan disease with no approved therapies in the United States and offers a meaningful benefit to patients with MIBG-avid, advanced PPGL.

This patient population has few therapeutic alternatives; there are currently no approved pharmacological treatments in the United States for recurrent and/or metastatic PPGL. “We took a proven target for neuroendocrine tumors and developed a novel molecule with high specific activity, then demonstrated robust efficacy and safety in the largest prospective study to date in malignant pheo/para patients,” said Vivien Wong, Executive Vice President, R&D, Progenics Pharmaceuticals, Inc. “If approved, AZEDRA will provide a treatment option that could reduce tumor burden and control symptoms to address the unmet medical need in these patients.”

References:
2. Jimenez C, et al. AZEDRA® (iobenguane I 131) in Patients with Metastatic or Recurrent or Unresectable Pheochromocytoma or Paraganglioma: Biochemical Tumor Marker Results of a Multicenter, Open-label Pivotal Phase 2 Study. Presented at Endocrine Society Annual Meeting, Chicago, March 2018.

Figure 1A. Bone scan from 9/2007 showing multiple bony metastases.
Figure 1B. Anterior MIBG scan from 9/2007 showing multiple MIBG-avid bony metastases and primary right adrenal pheochromocytoma.
Figure 1C. Bone scan from 9/2010 showing near complete and durable resolution of bone metastases.
The Oncology Center of Excellence (OCE) was developed to coordinate activities among Food and Drug Administration (FDA) Centers applicable to oncology, including coordination of staff, streamlining of review activities, promotion of scientific programs, staff recruitment and development, enhancement of interactions, and facilitation of collaborative relationships within the Department of Health and Human Services. On March 15, 2018, FDA held a public listening session that brought together members of the medical community, such as the advocacy community and oncology professional societies, to provide recommendations to the FDA regarding the OCE. Specifically, the OCE wanted to hear comments regarding what stakeholders want in terms of structure, function, regulatory purview and activity. CTN co-chair Jonathan McConathy, MD, PhD, spoke on behalf of the Society of Nuclear Medicine and Molecular Imaging.

In his comments, Dr. McConathy noted that currently, the United States lags behind its international colleagues, particularly in Europe, in the availability of cutting-edge radiopharmaceuticals for our patients. The Oncologic Center of Excellence can assist us in catching up with our international peers and provide state-of-the-art nuclear medicine in the United States. Increased coordination within and between federal agencies that regulate the development and reimbursement of these technologies could greatly impact research and patient care using nuclear medicine techniques.

The FDA approval process for theranostic agents, which can be used for both imaging and therapy, would benefit from a single, well-defined regulatory pathway that combines expertise in medical imaging and therapeutics. Recently, a new class of agents has emerged using small molecules that target specific receptors on cancer cells. The first approved theranostic pair in this class is Ga-68-DOTATATE (NETSPOT) and Lu-177-DOTATATE (Lutathera). These agents target neuroendocrine tumors, such as carcinoid, and were approved separately in June 2016 and January 2018, respectively. If Ga-68-DOTATATE images show high uptake in the tumor, then treatment with Lu-177-DOTATATE is appropriate and usually leads to marked decrease in the size of tumors and lessening of patient symptoms, along with significant improvement in survival.

The next theranostic pair will almost certainly be directed against the PSMA receptor, which is highly upregulated in prostate cancer. Preliminary results from thousands of patients in Europe and Australia have shown remarkable efficacy, and clinical trials are currently getting underway in the United States. The overall impact of being able to effectively treat metastatic prostate cancer patients in the same “pairing” manner used with NETSPOT/Lutatera has the potential to entirely change how prostate cancer is managed and treated. There are several other potential theranostic pairs targeting melanoma, myeloma, lung cancer and other tumors that are in pre-clinical and phase 1 development. These agents will also be coming up for approval in the next few years.

The success shown to date from active coordination between Center for Drug Evaluation and Research (CDER) imaging and therapeutic divisions within the FDA must be continued; it is critical to generating clear guidance and efficient review in the approval process of medical imaging radiotracers and therapeutics.
We were very fortunate to have trained and practiced at two large, renowned medical institutions before joining the SNMMI Clinical Trials Network Team. We had the opportunity to be involved in not only everyday imaging studies but also special projects and research opportunities.

- Tessa participated in research that changed the standard operating protocols for her department; some are still in place today. She was also able to take what she learned in the field to teach a class at a local college.
- Shyanne was involved in her first research project as a student when there was a cholecystokinin (CCK) shortage for hepato-biliary scans. The doctors were forced to find an alternative for the CCK and decided to use milk. Results showed the results were the same as with CCK. The data were later published in an abstract at the SNMMI Annual Meeting in 2015.

Changing roles from technologists to Clinical Trials Network staff has been seamless and rewarding. The work that we performed as technologists prepared us to be better all-around CTN staff members, bringing a different perspective to projects. Instead of working hands-on with patients or in PET research, we are now involved in the “back end” of various projects, with some focusing on developing new radiopharmaceuticals or finding new ways to use older ones. We were lucky to have seen two new radiopharmaceuticals approved by the Food and Drug Administration in the past two years—a wonderful advancement for the field! As technologists, we use our background to complete daily quality control measurements and our experiences in the field to develop new tools and educational programs that technologists can use for career advancement. Being familiar with nuclear medicine imaging processes and software from our clinical days allows us to actively participate and contribute to the CTN scanner validation program.

Regardless of the side—research or clinical—the goal is the same: It’s all for the patients. So don’t be afraid to change your current role for another one, maybe even one in research!

In the NEWS

Parallel Review of Drugs: FDA Update

Michael Graham, PhD, MD

The 39th annual High Country Nuclear Medicine Conference was held in Sun Valley, ID, this year from March 3 to 7. There were many notable offerings, one of which was “Parallel rather than sequential review of new imaging drug applications for FDA approval and CMS coverage,” presented in a session on Regulatory and Legislative Developments on March 5 by Dr. Lou Marzella from the Division of Medical Imaging Products at the FDA, and co-authored by Alex Hofling, a colleague of Dr. Marzella’s.

The goal of the collaboration between the Coverage and Analysis Group at CMS and the Division of Medical Imaging Products at FDA is not to create new standards but rather to implement parallel review and a compression of product development and regulatory review timelines. The major points presented in the talk were:

- Engage multiple stakeholders and develop evidence to support approval and reimbursement from several sites in an organized, consistent way.
- Trial design should include impact on clinical care and outcome (when possible) along with more conventional measures of safety and efficacy.
- Accelerated approval of new drugs and new indications for older drugs are possible using the cost recovery mechanism.
- CMS coverage decisions are currently made locally for most agents, usually within weeks. Non-oncologic PET agents go through a National Coverage Decision process, which takes much longer. One example is amyloid PET agents, which were first FDA-approved in 2012. CMS issued a non-coverage decision in 2013 but has accepted the concept of new trial, i.e., the IDEAS trial, which is now underway. If all goes well, CMS expects to reconsider its decision in 2020/2021.
- FDA and CMS are committed to exploring collaborative new processes for evidence development, particularly important for the emerging concept of precision medicine.
- CMS and FDA are working together to develop a program for parallel review of drugs, similar to the medical devices parallel review plan that was implemented in October 2016.
Preparing Literature Searches for Clinical Research

While working in a clinical environment, situations often arise where information or data need to be referenced to answer a specific question. In today’s technological age, where data is literally right at our fingertips on our personal devices, the tendency is to open an internet browser and use a search engine to find information. The risk is that literature generated by a search engine might not have a sound research methodology or come from a peer-reviewed source. Information from the literature needs to be accessed and analyzed in such a way that the scientific validity of the information can be analyzed.

Comprehensive literature searches are typically the first step in a process to uncover evidence related to a clinical research question. Multiple techniques for conducting literature searches and reviews are available from researchers like Creswell (2009), Booth, Sutton and Papaioannou (2016) and Fink (2014). Even though different researchers have different nuances in their search protocols, several basic steps are inherent in each approach.

The first step is to choose an appropriate database from which to query information. The most common databases for clinical research include EBSCO, Medline, Primo, ERIC and ProQuest. Typically these databases require institutional subscriptions, and your institutional librarian or research assistant can help you gain access.

Once a database is selected, the next step is to generate search terms to retrieve information related to your topic. It is recommended to use multiple synonyms of the key words to ensure adequate data retrieval. For example, if your search term is “bone scan,” likely subsequent search terms would be “bone scintigraphy; bone imaging; skeletal imaging.” Performing multiple iterations of the same search with different terms will ultimately lead to data saturation, where your searches are not generating any new information. When data saturation occurs, the process of synthesizing the literature occurs. This includes reviewing each article to determine the overall quality of the research and whether the information is relevant in answering the original question that prompted the literature search.

The ability to conduct literature searches to answer clinical research questions is a valuable skill for everyone who works in a clinical practice. Anyone who wishes to improve or enhance their literature search skills should find the method best suited to their skill set and take advantage of resources available through their institutional library or research assistant.

References:
- Fink A. Conducting research literature reviews: From the internet to paper. 2014; Sage Publishing.

Tech Tip
Reasoning Shortcuts to Avoid in Human Subject Research

When working with human research subjects, it’s important to be aware of one’s own reasoning shortcuts and implicit bias that might otherwise skew data or make our data incomplete. A strong, well-thought-out research protocol with enough blinding can help avoid common reasoning shortcuts and enable us to obtain all pertinent information from the patient accurately and completely. Some examples of potential reasoning shortcuts and bias to avoid include:

- **Availability Heuristic**—you overestimate the likelihood of a certain result because it’s fresh in your memory from a previous occurrence.
- **Fundamental Attribution Error**—you believe the subject’s behavior is due to their personality while your behavior is due to the situation.
- **Confirmation/Verification Bias**—you focus on and search for information that fits your beliefs.
CTN Highlights at the SNMMI 2018 Annual Meeting

Please join us for the latest information on new PET imaging agents and radiotherapies and how they impact patient care. CTN is offering a number of continuing education courses, including two that are co-sponsored with other SNMMI centers. Two additional non-CE sessions provide updates on timely topics. Include all of these offerings in your schedule so you don’t miss the current news. To view the entire educational program and develop your personalized schedule, visit snmmi.org/AM.

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<th>Course</th>
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<tr>
<td>CE04</td>
<td>Using Lutetium LU 177 DOTATATE – Nuts and Bolts Experience</td>
<td>Saturday, June 23</td>
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<tr>
<td>CE22</td>
<td>Theraonotics of Neuroendocrine Tumors- PRRT Co-sponsored with SNMMI Therapy Center of Excellence</td>
<td>Sunday, June 24</td>
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<td>CE39</td>
<td>TBI, CTE, and Molecular Imaging: What We Know Today</td>
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<td>CE87</td>
<td>US Regulatory Pathways for Radiopharmaceutical Research Co-sponsored with SNMMI Center for Molecular Imaging Innovation and Translation</td>
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<td>CTN Gallium Information Session</td>
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<td>N/A</td>
<td>Emerging Technologies Session Co-sponsored with SNMMI Center for Molecular Imaging Innovation and Translation</td>
<td>Monday, June 25</td>
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<tr>
<td>TS11</td>
<td>The Expanding Role of the Nuclear Medicine Technologist</td>
<td>Tuesday, June 26</td>
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<tr>
<td>CE81</td>
<td>Teaching an Old Dog New Tricks: F-DOPA</td>
<td>Tuesday, June 26</td>
<td>12:30 – 2:00 pm</td>
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Connect The Pieces and Initiate Your Site’s Compliance Strategy

Are Your PET/CT Scanners Joint Commission Compliant?
The Joint Commission recently updated the diagnostic imaging requirements for the hospital and ambulatory care programs.

SNMMI will analyze your images and send you back a report signed by a qualified physicist documenting compliance with the new Joint Commission diagnostic imaging requirements.

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To Learn More: ctnadmin@snmmi.org

Save the Dates

SNMMI 2018 Annual Meeting
June 23–26, 2018 • Philadelphia, PA

54th DIA Annual Meeting 2018
June 24–28, 2018 • Boston, MA

WMIC 2018 – World Molecular Imaging Congress
September 12–15, 2018 • Seattle, WA

NANETS Annual Multidisciplinary NET Disease Symposium
October 4–6, 2018 • Seattle, WA

European Association of Nuclear Medicine (EANM18)
October 12–17, 2018 • Dusseldorf, Germany

RSNA 104th Scientific Assembly and Annual Meeting
November 25–30, 2018 • Chicago, IL

FDA Oncology Center of Excellence (OCE) 2nd Annual Educational Workshop
November 27, 2018 • Silver Spring, MD

SNMMI 2019 Mid-Winter Meeting
January 17–28, 2019 • Palm Springs, CA

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