

Pathways

THE CLINICAL TRIALS NETWORK NEWSLETTER

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CTN Provides “Academic CRO” Services

Satoshi Minoshima, MD, PhD

When SNMMI created the Clinical Trials Network (CTN) in October of 2008, its main goal was to address the widely recognized need for validated imaging biomarkers that could be used in streamlining the development and registration of investigational therapeutics. CTN leadership soon realized that scientific validation of imaging biomarkers itself was a complex and difficult task. As such, CTN updated its mission and goals to better address the changing needs of the community and patients as well as the evolving regulatory and economic landscape in the United States.

CTN has embraced its leadership role in advancing the use of radiopharmaceuticals and optimizing the use of molecular imaging in clinical trials and dissemination into clinical practice. In support of this vision, tools and resources exist to increase the availability and performance of molecular imaging radiopharmaceuticals in clinical trials through standardization, coordination and education. This includes establishing global collaborations with societies, manufacturers and other groups to expand access to more agents for use in trials, and working with regulatory bodies to simplify and streamline the process leading to increased approvals of PET imaging agents.

Years of experience supporting clinical trials have now put CTN in a unique position to offer these valuable resources and expertise to academic researchers as a specific set of services, similar to what a Contract Research Organization (CRO) offers industry, in support of investigator-initiated clinical studies. As an “Academic CRO,” CTN would work with researchers to identify needs based upon study objectives. If you are considering a trial that would benefit from adding additional institutions, CTN can coordinate multiple sites in a single trial. Infrastructure for image and clinical data storage in a central repository is available through CTN as well as the wide-range of services as described below.

TRIAL DESIGN AND DEVELOPMENT: *Expertise in incorporating molecular imaging in drug development trial design*

Co-chairs have a combined 60+ years of experience using investigational and approved PET imaging in research studies.

- Accuracy in trial design is key to successfully meeting study endpoints. Consultation by experts will
 - ▶ Identify the appropriate radiotracer to meet study objectives
 - ▶ Incorporate the appropriate imaging requirements and methods specific to the drug/disease being studied
 - ▶ Develop a precise, tracer-specific imaging manual to ensure images meet study endpoints
- Central image and data review and storage provides a secure location for monitoring study activity



Satoshi Minoshima, MD, PhD
SNMMI, Chair
Scientific Program Committee
Professor and Chair
Department of Radiology
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Message from the Co-Chairs: CTN Helps Move Promising Molecular Imaging Agents to Regulatory Approval



Michael Graham, PhD, MD



John M. Hoffman, MD

A key goal of the Clinical Trial Network (CTN) is to promote the use of investigational radiopharmaceuticals in clinical research and to facilitate their regulatory approval for use in the clinical setting. CTN has identified a number of molecular imaging agents that show promise for patients, and it has been working with investigators, stakeholders, and other groups to move them closer to approval in the United States.

It is well known that the U.S. lags behind other countries in obtaining regulatory approval for molecular imaging agents that will benefit patients. One representative example is the group of Ga-68-radiolabeled somatostatin receptor ligands that have been used clinically around the world for over a decade to image neuroendocrine tumors (NETs). In the United States, however, these agents remain investigational. Efforts to move these agents to approval prompted the formation of the Gallium Users Group by SNMMI, with CTN taking a leadership role in focusing the work already underway by a collaborative effort with other stakeholders. Development of template IND documents, which include imaging parameters and a chemistry, manufacturing, and control (CMC) section, are available on the CTN website and applicable for any of the DOTA agents. In

fact, the FDA referenced these documents to others. Most recently, Advanced Accelerator Applications (AAA) has consulted with CTN to help file their NDA for DOTATATE, which was submitted in September 2015 and accepted by the FDA for expedited review. CTN and the Gallium Users Group are now developing document templates for using Gallium-PSMA to image prostate cancer patients.

Another agent in which CTN has been involved is fluciclovine for imaging prostate cancer in patients with biochemical failure. Over the past two years, CTN has worked with Blue Earth Diagnostics (BED), the agent's sponsor, advance the development of the agent. In December, BED announced that the NDA for fluciclovine was accepted by FDA and granted priority review.

In CTN's ongoing interactions with the FDA, it is clear that the FDA is attempting to make the pathway for approving novel molecular imaging radiopharmaceuticals simpler and faster when presented with the appropriate data to support the approvals. CTN continues to work with the FDA as well as researchers, companies, and others to ensure that high-quality applications are submitted for regulatory review and eventual approval.

CTN 2016 Webinar Series

The CTN Education Committee is currently planning their 2016 Webinar Series. Beginning in February and occurring every other month, these six, one-hour webinars present timely topics of interest for the entire community and offer CE credit at a nominal fee. A few of the topics scheduled for live presentation in 2016 include

- PET QC: Optimizing Scanner Performance
- Using Fluciclovine in the Recurrent Prostate Cancer Patient
- Managing Neuroendocrine Tumor Patients with ⁶⁸Ga-DOTATATE
- The Language of Clinical Research

Check the [CTN website](#) for updates on the webinar topics and speakers for 2016, as well as other CTN educational offerings. If you are unable to attend the live webinars, recordings are available in the [SNMMI Learning Center](#).



Robert Flavell, MD, PhD

Focus on the Intern

2015-2017

Dr. Rob Flavell is the CTN intern for 2015–2017. He completed his residency in radiology at the University of California, San Francisco, where he is currently a fellow in nuclear medicine. Dr. Flavell's research interests include radiochemistry, PET radiopharmaceuticals, development and hyperpolarized C-13 MRI. He plans to spend his time with the CTN assisting the Gallium Users Group in creating a clinical trial protocol and accompanying documents for the development of Ga-68-PSMA, among other projects. We welcome Dr. Flavell to the CTN!



Ngoneh Jallow, PhD



Jonathon A. Nye, PhD

National Trends of CT Radiation Dose in Whole-body PET/CT

Ngoneh Jallow, PhD and Jonathon A. Nye, PhD

Computed tomography (CT) plays an essential role in hybrid nuclear medicine systems and has a strong presence in whole-body oncology studies as part of combined PET/CT systems. The CT systems are equivalent in power output to their stand-alone models and may be used for diagnostic purposes under appropriate CT technique. However, there is limited guidance on CT dosimetry metrics in the nuclear medicine practice standards literature, and many of these reports reference dedicated diagnostic CT practice standards, which may not be appropriate for PET/CT. Compared to dedicated CT exams that typically focus on a body section (chest, abdomen, pelvis), a CT for oncology PET commonly spans from head to mid-thigh. In addition, a PET/CT exam has potential for high patient dose from the combination of the X-rays used to acquire the CT image and the radiotracer administered into the patient to acquire the PET image. Therefore, it is essential to practice good CT dose stewardship and optimize the CT protocol to achieve desirable contrast at a minimum dose. A step in this direction is to establish diagnostic reference levels (DRL) of CT dose from oncology PET/CT that can assist sites in the optimization of their imaging protocols.

The SNMMI Clinical Trials Network (CTN) program has collected CT acquisition parameters from over 280 PET/CT sites since 2010 as part of its Scanner Validation Program. These data were used to calculate the body computed tomography dose index (CTDI), a measure of the average absorbed dose from the irradiation of contiguous slices in a standard phantom. From these data, a DRL may be established that is defined as the 75th percentile of the CTDI values. Figure 1 shows a histogram of CTDI acquired between years 2010 and 2014 (inclusive), and statistics from these plots including mean, median and DRL are reported in Table 1. Compared to dedicated diagnostic CT scanners performing chest (DRL = 30mGy), abdomen (DRL = 35mGy) and pelvic (DRL = 35mGy) exams[1], the CTDI values reported in Table 1 for oncology PET/CT are markedly lower. The difference between these CTDI values can be explained by the intent of the exam, where CT for oncology PET is rarely acquired with techniques that are intended for dedicated CT procedures. Instead, the purpose of CT for PET is to support the function data, and this permits a wider variety of technique including substantial reductions in radiation dose.

These national data provide a value to sites as mark-

ers of appropriate CTDI values when performing PET/CT exams. The 75th percentile for CTDI was approximately 9.8mGy averaged over all reporting years as noted in Table 1. Facilities operating above 9.8mGy should carefully review their protocols to check that appropriate CT techniques are being used. It is intended that these data will assist in the optimization of CT for oncology PET/CT and provide a benchmark for the installation of new scanners.

Reference:

1. Protection ICoR. Diagnostic Reference Levels in Medical Imaging: Review and Additional Advice [cited 2015 11/30/2015]. Available from: http://www.icrp.org/docs/DRL_for_web.pdf.

Year	Number of data sets	CTDI _{vol} (mGy)		
		Mean	Median	75th percentile
2010	35	6.9	6.2	9.8
2011	65	6.8	6.2	9.8
2012	76	7.0	5.7	10.2
2013	42	6.9	5.6	9.7
2014	14	7.5	4.9	9.7

Table 1. Mean, median and 75th percentile of CTDI_{vol} for years 2010 to 2014

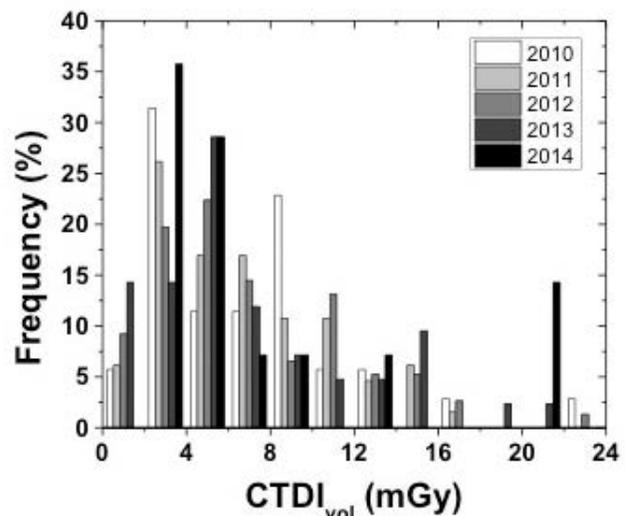


Figure 1. Histogram of CTDI_{vol} for years 2010 to 2014.

- ▶ Upload, review and store images and study data
- ▶ Development and online completion of study-specific eCRFs
- ▶ Standardize data input and review
- CTN Radiopharmaceutical Manufacturers Committee provides auditing services to ensure manufacturing sites maintain a high level of quality and compliance.
- General templates for IND applications, CRFs and imaging manuals on select agents are available on the CTN website for academic researchers.

EDUCATION AND TRAINING: Robust and dynamic curriculum on all aspects of clinical research

Training imaging personnel on research methods and practices promotes compliance to study protocols and GCPs.

- High-quality educational resources reach a wide audience having different areas of expertise and levels of experience.
- Over 30 basic, intermediate and advanced courses are currently available online for a nominal fee; all have AMA PRA and VOICE credit.
- Unique courses provide information to assist imagers in acquiring high-quality study scans to improve acceptability of data for drug approval.

PET IMAGE STANDARDIZATION: Data on more than 600 sets of unique PET scans

Our unique “clinical simulator” phantom obtains both qualitative and quantitative measurements.

- The CTN Scanner Validation Program experience includes validations on over 250 scanners located at over 170 sites in 24 countries.

- Analysis of recorded CTN scanner validation results helps establish image acquisition and reconstruction criteria for clinical research on a per scanner basis.
- Experts can also review study subject images across sites in a multicenter trial.

GLOBAL DATABASE: Information on over 400 PET clinical imaging and radiopharmaceutical sites

Collaborations with international groups provide a “real-time” picture of PET sites and radiopharmaceuticals worldwide.

- The CTN proprietary database collects and stores data on both clinical PET imaging sites and radiopharmaceutical manufacturers.
 - ▶ Research infrastructure and personnel experience
 - ▶ Site access to investigational agents
 - ▶ Imaging and production capabilities
 - ▶ Availability and regulatory information on investigational radiopharmaceuticals
- Information aids investigators in study site and tracer selection.

CTN recognizes that it is not a traditional imaging CRO and has no plans to act as such. It avails its expertise to academic researchers in areas where it excels and where its resources can make the most impact in moving investigational PET agents into the clinical arena. SNMMI and CTN leaders are excited to offer their expertise to academic investigators to provide their knowledge and experience to the community.

If you are interested in working with SNMMI CTN on your project, please contact ctnadmin@snmmi.org.

CTN Numbers At-a-Glance



6 FLT manufacturers under the SNMMI-CTN IND



7 investigational radiopharmaceuticals under study

24 countries represented in the CTN database



171 sites with validated PET/CT scanners

253 validated PET/CT scanners

435 sites registered in the CTN database

Special FEATURE

Ga-68 PSMA PET in the United States

Thomas A. Hope, MD and Andrei Iagaru, MD

Imaging patients with prostate cancer has seen a dramatic change outside the United States during the last year. Since the first patients were reported using Ga-68 (HBED-CC) PSMA in 2012 by researchers at the University of Heidelberg, there have been many published articles with data on more than 700 patients, with 13 publications in 2015 alone. Taking advantage of the wide adoption of Ga-68 DOTA-TOC and DOTA-TATE, which increased the availability of gallium generators and synthesis modules, Ga-68 PSMA has spread quickly to numerous sites around the world. In Australia, for example, Drs. Rodney Hicks and Louise Emmett report over 20 centers currently use Ga-68 PSMA, and over 1,000 patients have been imaged at Peter MacCallum Cancer Centre (East Melbourne) in the past year alone.

Given what appears to be a clear benefit over standard of care imaging as well as choline PET imaging, described in the Radiotracer Spotlight article by Drs. Hope and Flavell in this newsletter, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) created the Gallium Users Group and charged the Clinical Trials Network (CTN) to lead a task force focused on developing protocols for using Ga-68 PSMA. Two protocols are now underway: one for initial staging in intermediate- and high-risk pre-prostatectomy patients, and the second in patients with biochemical recurrence (Figure 1). Although CTN does not hold the IND for these initial studies, a collaborative effort across academic institutions in the United States has helped lead to the creation of protocol document templates that can be shared. Dr. Steve Cho, University of Wisconsin, is leading the development of the biochemical recurrence protocol and Dr. Hope, University of California, San Francisco, is leading the protocol for the pre-prostatectomy group. Although the focus initially lies with these two indications, there is also broad applicability of PSMA for use in evaluating response to therapies in castrate-resistant prostate cancer patients.

In an effort to promote the use of novel PET imaging agents in research, the FDA made available an investigational new drug (IND) authorization using a cost-recovery mechanism that allows institutions to bill private carriers for the direct costs associated with the imaging agent. Based upon the recent success of this method for DOTA-TOC and DOTA-TATE imaging studies, the University of California, San Francisco, has begun a Ga-68 PSMA imaging study using this IND cost-recovery mechanism. At Stanford University, initial studies using Ga-68 PSMA done under RDRC approval have been completed, and an IND has been submitted to allow further data accrual.

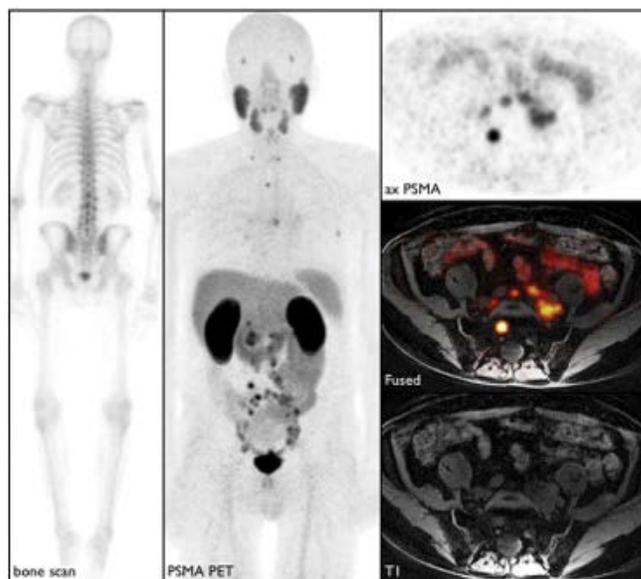


Figure 1. A 76-year-old man with biochemical recurrence after prostatectomy seen at UCSF. The MDP bone scan (left column) performed within two weeks of the PET/MRI demonstrates no evidence of osseous metastatic disease. The PSMA PET (center column) and MRI (right column, bottom image) demonstrates numerous retroperitoneal and pelvic nodal metastases as well as multiple osseous metastases. The top figure in the right column demonstrates a single osseous metastasis to S1 (SUVmax of 32), which is not appreciated on MDP bone scan.

Collaborative efforts between multiple academic centers under the SNMMI/CTN umbrella and similar protocols in place at other institutions should serve as the basis for collecting a considerable amount of high-quality data for submission to the FDA for eventual approval of Ga-68 PSMA. Hopefully, industry will also participate in this effort that has as its main goal to improve the care of prostate cancer patients in the U.S. and around the world.



Thomas A. Hope, MD



Andrei Iagaru, MD

Tech Talk

MENTORING: A KEY FOR SUCCESS

Lisa Dunwald, MPH



The value of a mentor in achieving professional and intellectual growth cannot be overstated. For trainees in the medical research setting, having a mentor can help to develop and improve your skills as a researcher. Mentors advise, guide, inform, encourage and support you in your career development.

In my professional journey as a researcher, I have been fortunate to have extraordinary mentors who have helped to guide and shape my career in Nuclear Medicine and Molecular Imaging. I have benefited from working for notable teaching institutions that encouraged managers and physicians to support career development, while emphasizing the responsible conduct of research.

Early in my career, I was presented with an opportunity to oversee the technical aspects of a pilot research project. With this responsibility came additional research activities that included creating databases, analyzing data, writing scientific abstracts and manuscripts and preparing posters and presentations. As a neophyte to research, I was eager to learn more about the technical nuances of successfully conducting research and presenting findings. Having a mentor I could approach with questions was critical to my success. In fact, these early research and mentoring experiences facilitated my desire to pursue a master's degree in public health, which has allowed me to contribute to research with a higher degree of responsibility—and success.

If you are contemplating becoming involved in clinical research, establishing a mentoring relationship could be key to your success. Mentoring relationships are respectful, with both parties learning from each other. Strive to identify whose knowledge and experience you respect and whose wisdom will foster your professional growth and advancement in clinical research.

“ IF I HAVE SEEN FURTHER, IT IS BY
STANDING ON THE SHOULDERS OF
GIANTS. ” – ISAAC NEWTON

Research Essentials: Avoiding Imaging Artifacts in Clinical Research

Image artifacts can be attributed to a single event or combination of causes at any point in the scan process. These can be related to the patient, imaging equipment, reconstruction and quantitation. Anything that affects the physics of imaging—positron range, detector size, non-colinearity, depth of interaction, partial volume effect—creates an artifact. The presence of an artifact could prevent an image from being accurately acquired, read and reported. In clinical practice, this is problematic. In clinical research, however, it could potentially provide incorrect data that may keep a promising therapy from reaching the patient.

TYPES OF ARTIFACTS

Patient: These are fairly common, but the easiest to avoid through appropriate patient screening and preparation. Patient motion, positioning and presence of metal/other implants are common problems in both CT and PET. With PET/CT, both the PET camera and CT scanner must be correctly aligned to avoid attenuation correction artifacts. Also, PET agents present their own unique patient-related problems.

- Agent-related limitations (e.g., FDG and glucose)
- Appropriate tracer distribution—concentration dilutes with time so the timing of imaging is crucial
- Distinguishing inflammation vs. active disease
- Irregularities in uptake due to room temp, brown fat, or muscle

Machine: Following an appropriate QC schedule will help keep the equipment in optimal condition and minimize this type of artifact.

- CT: rings, timing (contrast), partial volume, parameters
- PET: randoms, scatter, dead time, partial volume, bed positions

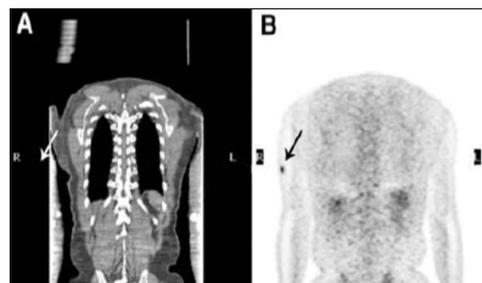
Reconstruction and Quantitation: Avoid noise and streaks from motion to improve image reconstruction. Keep the processing workstation in good condition, and follow the manufacturer's suggested levels for brightness and contrast, alignment values and use of the color tables. Perform accurate SUV measurements.

Operator errors account for most artifacts and poor image quality!

In most cases, artifacts can be avoided by being diligent in following precise protocol guidelines, performing appropriate QC and understanding the physics of scanning. Knowledgeable technologists can minimize artifacts in both clinical practice and clinical research, and produce better-quality PET/CT images.

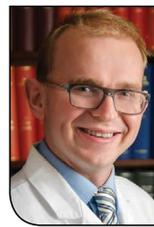
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Field of view truncation artifact. Sureshbabu and Mawlawi. *J Nucl Med Technol*: 33:156-161:2005

RADIOTRACER SPOTLIGHT



Robert R. Flavell, MD, PhD



Thomas A. Hope, MD

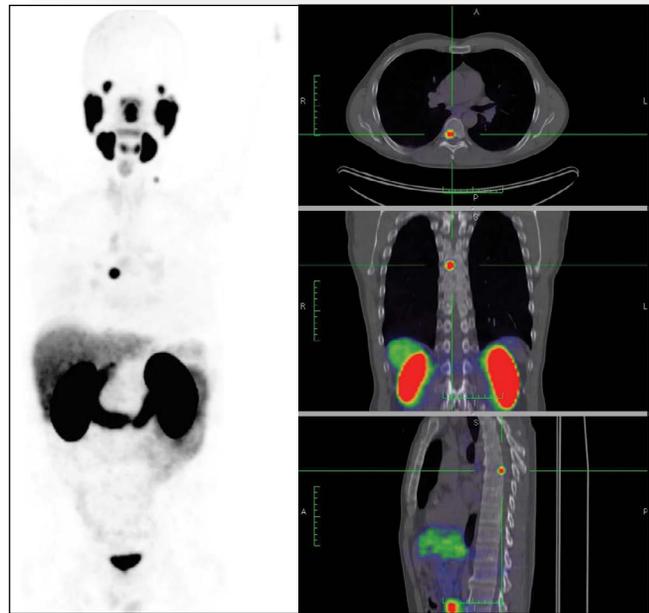
➤ ⁶⁸Ga-PSMA FOR IMAGING PROSTATE CANCER

Robert R. Flavell, MD, PhD and Thomas A. Hope, MD

Prostate cancer presents with a broad clinical spectrum, ranging from indolent to highly aggressive disease. Patients who present with high-grade disease or who develop rising prostate specific antigen (PSA) following definitive treatment (biochemical recurrence) are staged with CT or MRI and bone scan using either F-18-NaF or Tc-99m-bisphosphonate agents. C-11-choline (used under NDA at Mayo Clinic) and F-18-fluoromethylcholine have also shown promise. More recently, prostate specific membrane antigen (PSMA)-targeting agents have demonstrated promise for staging patients with high-risk disease or biochemical recurrence[1]. PSMA is a membrane-bound enzyme, which is highly expressed on prostate cancer in comparison to normal tissue. Therefore, PSMA-targeted imaging has promise for high target to background ratio imaging.

Since its initial evaluation in 2013[2], Ga-68-PSMA has rapidly emerged as a promising new tracer for detecting biochemical recurrence and use in high-risk initial staging (see figure), although small metastatic lymph nodes can be missed[3]. Ga-68-PSMA is produced using a Ge-68/Ga-68 generator with a simple one-step radiolabeling procedure[4]. This holds potential advantages, as the synthesis does not require an on-site cyclotron. Other promising PSMA targeting F-18-labeled agents have also been reported[5,6].

Trials evaluating the clinical performance of Ga-68-PSMA have been conducted in Europe and in Australia. In a recent trial, Eiber et al. found an 89.5% sensitivity for the detection of recurrent disease in patients with biochemical recurrence[7]. Two other studies found that Ga-68-PSMA had superior sensitivity when compared with F-18-fluoromethylcholine for the detection of metastases in patients with biochemical recurrence, particularly for patients with PSA < 0.5 [8,9]. According to Dr. Uwe Haberkorn of the University of Heidelberg, he “expects that PSMA ligand-based diagnostics and therapy will have its place in the clinical routine for follow up and treatment of patients with prostate cancer.”



Patient with biochemical recurrence, PSA 0.7, with maximum intensity projection (top) and PET/CT fusion images (bottom) demonstrating a thoracic spine bone metastasis.

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Tech Tip: IMAGING FOR CLINICAL TRIALS – Matt McDonald, BS, CNMT

- ALWAYS check if the scan is part of a clinical trial before imaging.
- ALWAYS follow the research protocol. Some studies require images that aren't typically performed as standard of care.
- ALWAYS de-identify images and submit DICOM-compatible “raw” data. ALWAYS document the following:
 - ▶ Scanner details: manufacturer and model number
 - ▶ Image acquisition details: time/counts per image, matrix and views obtained
 - ▶ Radiopharmaceutical details: time of injection and acquisition, uptake time and radiopharmaceutical agent and dose. (Note: some trials require a post-administration syringe count as well.)



CTN Offers Services for Academic Clinical Research

The Clinical Trials Network offers a variety of services to assist academic investigators with their clinical research.

- Coordinate activities for a trial involving multiple academic institutions
- Trial design using PET imaging
- Protocol and study document development
- Scanner validation and QC troubleshooting
- Central repository for image and clinical data
- Access to information on investigational PET agents for use in clinical trials

Contact CTN for more information at ctnadmin@snmmi.org.

Save the Dates

SNMMI 2016 Mid-Winter Meeting

January 28–31, 2016 • Orlando, FL

AACR Annual Meeting 2016

April 16–20, 2016 • New Orleans, LA

2016 ASCO Annual Meeting

June 3–7, 2016 • Chicago, IL

SNMMI 2016 Annual Meeting

June 11–15, 2016 • San Diego, CA

DIA 2016 52nd Annual Meeting

June 26–30, 2016 • Philadelphia, PA

WMIC 2016

September 7–10, 2016 • New York, NY

EANM - 29th Annual Congress

October 15–19, 2016 • Barcelona, Spain

4th Theranostics World Congress 2016

November 7–9, 2016 • Melbourne, Australia



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