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The Clinical Trials Network of the Society of Nuclear Medicine

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The Clinical Trials Network of the Society of Nuclear Medicine was formed to provide quality assurance of both imaging and radiopharmaceutical manufacturing in clinical trials. The intention is to register and qualify a large number (>200) of sites, both in the United States and internationally, to be able to do the positron emission tomography imaging part of clinical trials. Initially, the types of trials to be supported include evaluation of novel radiopharmaceuticals and trials that use approved or experimental radiopharmaceuticals for early assessment of tumor response to novel chemotherapy agents. The Clinical Trials Network is organized into 7 committees that provide overall oversight and strategic guidance, database management, site qualification and monitoring, scanner validation, clinical site orientation, technologist education, trial design, and a manufacturer's registry. At the end of the first year, more than 200 potential clinical trial sites and more than 125 manufacturing sites have expressed interest in participating. The qualification process is well underway. Funding is being provided by 3 large pharmaceutical companies. An investigational new drug application has been obtained for F-18 fluorothymidine that is held by Society of Nuclear Medicine to allow simplification of data management during multisite trials with F-18 fluorothymidine. A second investigational new drug application is in preparation for F-18 fluoromisonidazole. A supply of oncology chest phantoms has been manufactured and have been shipped to numerous sites for scanner validation. Educational materials are being developed for the physicians, technologists, and research coordinators at the sites. This is an important initiative that is likely to help significantly expand the role of molecular imaging and will help bring the right treatment to the right patient at the right time.
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There are 2 types of clinical trials that are of interest to the nuclear medicine/molecular imaging community: (1) trials of new radiopharmaceuticals to demonstrate safety and clinical efficacy that, if successful, will result in the approval of new agents that will expand our clinical imaging armamentarium; and (2) trials that use an existing approved agent or a novel molecular imaging technique, such as an investigational positron emission tomography (PET) metabolic agent or a radiolabeled receptor-imaging agent, to assess response to an investigational therapy. Molecular imaging often has the ability to provide an earlier indicator of response (or lack of response) to therapy than anatomic imaging or clinical endpoints.

Because increasing numbers of pharmaceutical companies are beginning to realize the potential value of molecular imaging as a way to determine response to therapy earlier in drug development, the leadership of the Society of Nuclear Medicine (SNM) realized the need to create a multicenter approach that could use key response markers, such as F-18 fluorothymidine (FLT) or F-18 fluoromisonidazole (FMISO). The Clinical Trials Network (CTN) of the SNM was formed to address the challenges and opportunities that exist in developing protocols, manufacturing the necessary investigational molecular imaging agents, and collaborating with pharmaceutical manufacturers to assure high-quality imaging at multiple research centers.

New Radiopharmaceuticals

There have been remarkably few new radiopharmaceuticals approved. The reason for this is multifactorial: (1) The projected market for new diagnostic and therapeutic radiopharmaceuticals is relatively small, especially compared with most therapeutic pharmaceuticals. Therefore, the return on investment is not as high. (2) Investigational new drug (IND) applications for radiopharmaceuticals are subject to the same

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regulatory requirements as for new drugs, which means they come under the same level of scrutiny as therapeutic drugs in clinical safety testing and manufacturing requirements. The expense of development can reach the level of a therapeutic drug without the potential return on investment. (3) Reimbursement for medical imaging procedures in general is decreasing and the payers, both government and private, are reluctant to reimburse for new procedures until strong efficacy evidence is available.

In addition, imaging agents developed in academic settings are often not patented, and therefore have no attached intellectual property. Often, the academic developer publishes their research without obtaining a patent, moving that knowledge into the public domain. These agents include FLT, FMISO, F-18 fluorodopa, and several others. Because a corporate entity cannot own the exclusive right to market these agents, no single company is likely to invest the time and funds that would be necessary to bring the agents through clinical trial and approval, because they recognize their competitors will benefit as much from such approval as they would.

Thus, in an effort to bring new agents to approval, there are 2 kinds of radiopharmaceutical efficacy clinical trials that need to be undertaken: (1) with new, proprietary agents that have been developed by a radiopharmaceutical developer/manufacturer; and (2) trials of the public domain agents (generic agents) to develop sufficient efficacy and toxicity data to be able to bring them to approval. Both types of clinical trials need to be carefully standardized.

There is a major problem in finding funding for the clinical trials necessary for the generic agents because most of the traditional funding agencies do not define these clinical trials as novel science. This is a "Catch-22," making it unlikely that the generic agents will ever be approved in the current academic and regulatory framework. An important goal of the CTN is to establish relationships with pharmaceutical manufacturers who are developing clinical trials for their drug products and would be interested in using the generic agents to acquire the necessary safety and efficacy data required for eventual approval of these agents.

Assessment of Response to Therapy

The use of novel imaging techniques can potentially provide sponsors of therapeutic trials an early measure of response, or lack of response, in phase 1 or phase 2 testing. The "go or no-go" decision to develop a new molecular entity for therapy is critically important for pharmaceutical companies because investment in later phase trials can cost millions of dollars to learn that a new therapy does not perform effectively. Making the decision to terminate development of a new drug early is as important to a drug company as early determination of effectiveness of the therapy.

Uptake of many metabolic imaging agents, such as FLT, is regarded as an early indicator of response to therapy in the setting of assessing efficacy of new cancer cytotoxic chemotherapy drugs. Several large pharmaceutical companies are now beginning to use FLT in early-phase clinical trials, particularly to be able to make accurate early decisions about the suitability of a new agent to proceed into large later phase trials. Because of this high economic incentive, and because there is an increasing recognition that molecular imaging is likely to become part of the personalized medicine approach to select the right specific therapeutic drug for an individual patient, the large pharmaceutical companies have increasing interest in using quantitative molecular imaging, usually with PET agents in their clinical trials.

Challenges With Molecular Imaging Trials

The pharmaceutical industry's initial experience in trials incorporating PET imaging has not been uniformly successful. The imaging part of the trials can be complex, needs to be scheduled in a consistent relationship to the therapy schedule, and needs to be performed in a consistent and standardized manner with adherence to the clinical trial protocol. Many of the companies and the associated Clinical Research Organizations (CROs) are not familiar with the requirements of PET imaging and the potential large variation in the quality of the imaging that can occur if it is not carefully standardized.

In addition, pharmaceutical companies encountered another significant problem as they began to use FLT PET imaging in multisite clinical trials: each of the sites produced the F-18 FLT under a different IND. Because there were subtle variations in the syntheses used at the different sites, it was difficult to assure that the FLT was identical at all sites, and therefore that the efficacy measurement was standardized.

In recognition of these challenges, the CTN was created. The goals of the CTN are to assure high-quality standardization of both the imaging methodology, including patient preparation, along with standardization of the manufacturing of the imaging agent. Initially FLT was deemed to be the most appropriate PET agent for the first centralized IND application held by SNM that all the manufacturing sites could access. This would assure the necessary and consistent manufacturing and quality of FLT across all trial sites. This should lead to more efficient clinical trials and a much higher acceptability of the resultant imaging data when it is ultimately presented to the FDA.

Recognition of the need for an organization, such as the CTN, did not occur suddenly, rather it evolved slowly over the years from 2006 to 2008. There were several meetings and discussions with both the Food and Drug Administration (FDA) and with some of the pharmaceutical companies that were beginning to use fluorodeoxyglucose and FLT in clinical trials. The FDA provided significant guidance on which approaches would be acceptable and reasonable from their point of view, and increased their understanding of the unique issues that are associated with clinical trials involving PET molecular imaging. The concept of the need for a single IND, to be held by SNM, was generated at these meetings

with the FDA. The acute need for high-quality standardization of the imaging component of clinical trials became apparent from discussions with the interested pharmaceutical companies, in that several have had significant problems in this area.

Once the decision was made to create the CTN, it started as a relatively simple committee. However it soon became apparent that there were specific areas that needed a concentrated leadership and workforce. The resultant current structure is the third or fourth re-structuring and it appears to now work reasonably effectively.

Because a major goal of the CTN is to provide high-quality support for pharmaceutical clinical trials, the leadership of the CTN went to several of the pharmaceutical companies to propose that they, the pharmaceutical companies, provide funding for the infrastructure for the CTN. There are significant ongoing tasks within the CTN that definitely need support, including organizing the registration, qualification, and scanner validation of the potential clinical trial sites and the potential manufacturing sites and developing and administering the educational materials for physicians, technologists, and research coordinators for each site. In addition there is a commitment to move forward with submission of additional INDs of the public domain agents. Currently, the CTN is preparing the second SNM-sponsored centralized IND for FMISO.

The CTN is not an imaging CRO or core laboratory. The CTN can play a key role in aiding both the CRO and sponsor in acquiring the highest-quality molecular imaging data for multisite clinical trials. The CTN does not intend to manage the trials, collect imaging data generated in a trial, or provide image analysis capability. However, because of concern that there might be significant overlap between the CTN and imaging core laboratories, the CTN hosted a meeting with representatives from 9 CROs at the SNM Mid-winter meeting in Albuquerque in February 2010 to discuss the likely relationship between the CTN and the CROs. It was definitely a useful discussion, with both groups coming away with a better understanding of the roles of the 2 types of organization. Such meetings will continue to be held annually because it is critical to the success of the CTN that a strong working relationship is developed with the relevant CROs while the CTN assists in the imaging quality assurance aspects of a multisite clinical trial. The current organizational structure of the CTN is shown in Fig. 1.

The Strategic Planning Committee comprises representatives from the founding pharmaceutical members, members of the Operations Committee and CTN leadership. This Committee meets at least twice per year and provides oversight and strategic guidance for the entire CTN effort. The Operations Committee oversees the management and coordination of activities undertaken by the 6 other CTN committees and provides continuing oversight of all CTN operations. It is composed of the CTN co-chairs and the 6 CTN committee chairs.

The Database Committee was organized to define the structure of the CTN database that houses all information related to both the imaging and manufacturers sites who wish

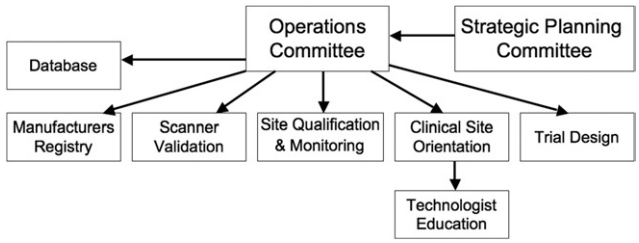

Figure 1 Organizational structure of the SNM clinical trials network.

to be included in industry-sponsored clinical trials. Imaging sites enter information on their imaging capabilities, experience of site personnel and the site's research infrastructure. Manufacturers, both private and academic, provide their production capabilities, types, and amounts of radiopharmaceuticals they produce and frequency of production. This information is protected and is only provided to industry once they join the CTN.

The Site Qualification and Monitoring Committee oversees the methods for, and status of, registered imaging sites. A site is considered "fully qualified" for conducting imaging studies after successfully completing the CTN scanner validation program and meets a minimum of required elements by completing online questionnaires (site qualification; Fig. 2). Such sites can then move on to qualify for participation in specific clinical trials at the individual sponsor's discretion. This committee will also provide ongoing monitoring of the site's ability to provide reproducible data and compliance to imaging protocols.

The Scanner Validation Committee, via the CTN phantom program, uses a clinical simulator (phantom) to evaluate each imaging site's equipment and their personnel's ability to detect lesions and provide reproducible data. A potential imaging site must successfully validate their scanner(s) before the scanner can be included in clinical trials. More than 1 scanner can be validated at a single site, and only validated scanners can be used in an industry-sponsored clinical trial.

The Clinical Site Orientation Committee provides the framework for educational opportunities in training personnel at imaging sites, including the investigators. The committee identifies local, regional, and international meetings where the CTN can promote the idea of the practice of clinical trials and, if successful, create a change in how imaging is performed in clinical trials. Other tasks include providing educational materials to potential trial sites in the registry, working with multicenter IND groups to educate the academic community on the requirements for INDs, and developing a group of rotating speakers to present at SNM chapter meetings and other meetings to promote better understanding of the CTN, as well as possible participation in the CTN.

The Technologist Education Group, a subcommittee of the Site Orientation Committee, was developed to help train nuclear medicine technologists who are interested in becoming more involved in clinical research. Currently, there are a series of courses approved for credit, with another 10 courses being written and planned for submission for approved credits. This group is a driving force in improving imaging at

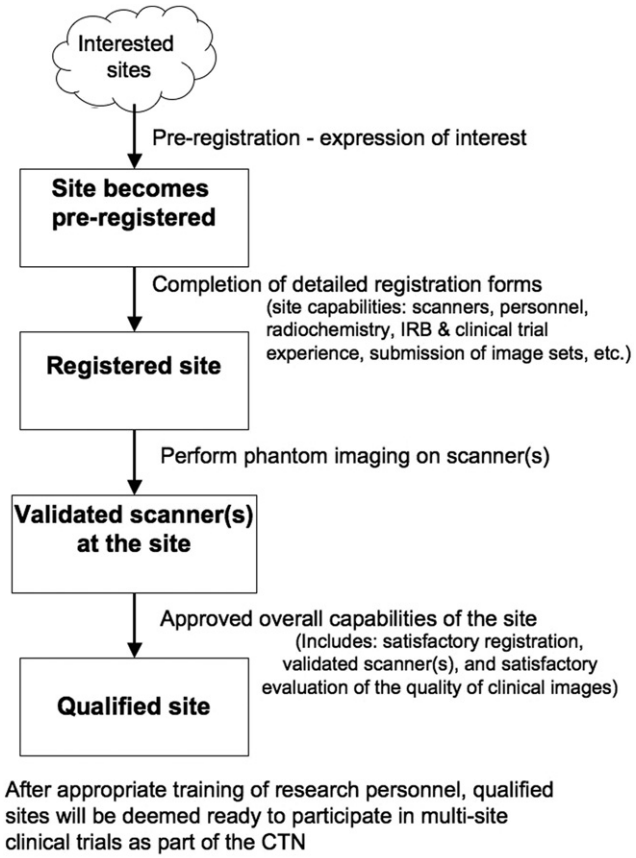

Figure 2 Process of registration, validation, and qualification for CTN imaging sites.

clinical sites and also provides the participating technologists with multiple opportunities for advancement and career growth.

The Trial Design Committee's key role is to assist in defining minimum standards for clinical trial protocols, create standard imaging clinical trial research forms and develop standard imaging protocols for FLT, FDG, and other International Conference on Harmonisation-compliant imaging protocols in general. Committee members will work with sponsors to ensure that sites selected for the registry are willing to modify their standard imaging protocols to match specific protocol requirements so that imaging can be standardized across sites.

The Manufacturers Registry Committee works with radiopharmaceutical manufacturers to encourage their participation in the CTN registry. It promotes site compliance with current PET current good manufacturing practice rules and is defining SNM PET manufacturing guidelines. Committee members promote engagement of manufacturing sites to provide feedback, as well as input into improving and expanding the role and responsibilities of the manufacturers in clinical imaging studies.

At the current time (early 2010), more than 240 clinical imaging sites and more than 200 manufacturing sites have expressed interest in participating in the CTN. Approximately 150 imaging sites have been registered and are completing the required questionnaires and subsequent scanner validation process. Eighteen sites have completed the scanner validation process to date, and 19 more are in various stages of the process. More than 40 sites are completing their questionnaires and 7 sites are now fully qualified. Manufacturing sites for FLT are being registered and their information evaluated. The overall process of registration, validation, and qualification of imaging sites is outlined in Fig. 2, and the process for registration of manufacturing sites is shown in Fig. 3.

Accomplishments

Some key accomplishments that have been achieved by the end of the first year of operations are the following:

- 3 pharmaceutical partners have now joined with the CTN and have agreed to provide financial support of the required infrastructure and processes;
- The CTN imaging site registry database is functional, and currently includes more than 240 sites worldwide who have expressed interest (more than 25% participation from outside the United States);
- the manufacturer's registry has been initiated, with more than 200 sites expressing interest in participating to date (early 2010);
- the CTN has obtained approval from FDA for the first SNM-centralized IND for an imaging biomarker, FLT;
- the initial FLT phantom demonstration project has been completed;
- FMISO has been selected as the next imaging agent for submission of an SNM-sponsored centralized IND;
- A supply of oncology chest phantoms to support ongoing site qualification process has been manufactured, and they have been shipped to numerous sites for scanner validation;
- design and initial manufacturing of a brain phantom prototype has been completed, with a cardiac phantom planned for midyear 2010;

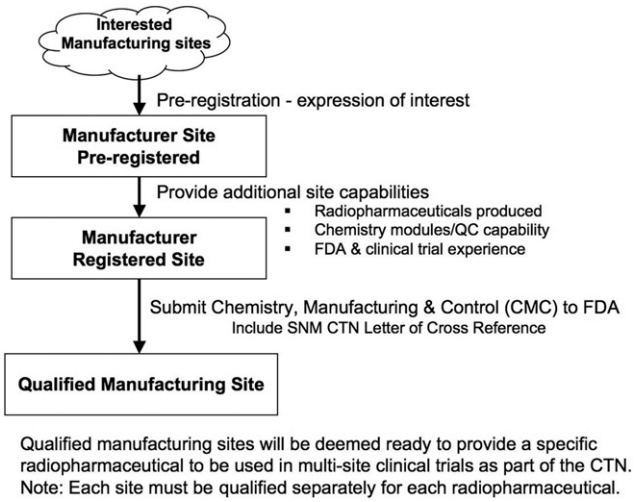

Figure 3 Process for registration, evaluation, and qualification of radiopharmaceutical manufacturing sites.

- 2 full-time staff members have been recruited who are experienced in pharmaceutical and academic clinical trials work; and
- multiple ongoing CTN-supported educational activities to advance awareness and understanding of the "Practice of Clinical Trials" have been assembled and are being used for training within the imaging community.

Plans

Our goal is to have at least 40 US and 20 non-US sites scanner validated and fully qualified by the end of 2010. The top 3 initiatives that are critical to successful implementation of the CTN, and are the short-term goals for 2010 are:

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 determined by an imaging measurement or assessment. Denials of new drug applications are often based on data rejection because of nonstandardization 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.

2: Create a Community of Trained and Certified Molecular Imaging Research Technologists

Increased 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.

3: Deliver High-Quality Programs and Services

As we approach each definitive phase of CTN planning, we are definitely aware of our available resources and in the strategic planning we are taking care to determine just which capabilities we can manage ourselves and what must be outsourced or not done at all.

It is anticipated that, as CTN-assisted trials are underway, and once the CTN has successfully demonstrated the value of careful imaging standardization and extensive education of site imaging personnel, it will become clear that this is an important and essential component in multisite clinical trials that have a significant molecular imaging component. This should lead to increasing support and thus the ability to provide these services at the highest level. We also anticipate that the CTN will be able to support NIH-funded multisite clinical trials to help develop the data to show the efficacy of new agents and approaches in the treatment of a wide spectrum of disease.

We are very enthusiastic about the progress the CTN initiative has made to date and the plans for 2010 and beyond. This is an important initiative that is likely to help significantly expand the role of molecular imaging and will help bring the right treatment to the right patient at the right time.

More information is available at the CTN Web site: www.snm.org/clinicaltrials.