SNMMI Clinical Trials Network Research Series for Technologists: Introduction

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The field of nuclear medicine and molecular imaging has grown tremendously over the past several years with the approval of new imaging agents, diagnostic radiopharmaceuticals, and radiopharmaceutical therapies. Clinical research continues to expand within nuclear medicine and molecular imaging departments. Working as a nuclear medicine technologist on a clinical trial or with investigational radiopharmaceuticals can be quite different from working in an approved-drug setting in the clinic. Nuclear medicine technologists involved in clinical trials can be at the front line of following rigorous trial requirements and ensuring good-quality data. The details of working in clinical research are often not taught in nuclear medicine technologist programs. As such, there is an emerging need for education about clinical research for both experienced and new nuclear medicine technologists, particularly for those working with investigational radiopharmaceuticals. This article is an introduction to the SNMMI Clinical Trials Network Research Series for Technologists. This series of articles aims to provide education on working in the context of a clinical trial within the nuclear medicine department. The following 7 topics will be addressed in the series: ethical issues in clinical research, application of good clinical practice to clinical research in medical imaging, contract research organizations with application in clinical imaging, a clinical research primer on the regulatory process for how and when radiopharmaceuticals can be used and the role of the institutional review board, use of imaging agents in therapeutic drug development and approval, imaging agent trials, and imaging agents with radiopharmaceutical therapies in clinical trials. Other topics may be added over the course of the development of the series.

Key Words: clinical research; FDA; good clinical practice; protocol; clinical trial

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An important goal for this series of articles is to provide clinical research education to nuclear medicine technologists and information to those in our community interested in the use of molecular imaging as a biomarker and in the development, regulatory, and approval process for new, investigational molecular imaging diagnostic and therapeutic radiopharmaceuticals. Various sources of information are available and valuable to review (*1–4*). The Society of Nuclear Medicine and Molecular Imaging (SNMMI) created the Clinical Trials Network (CTN) in 2008 to advance the use of molecular imaging and therapeutic radiopharmaceuticals in clinical trials. Through the work of its committees (a database committee, a committee that validates scanners and qualifies sites, an education committee, a gallium users group/committee for access to nonproprietary radiopharmaceuticals, and a radiopharmaceutical manufacturers committee), the CTN fulfills its mission of facilitating the effective use of diagnostic and therapeutic molecular imaging and radiopharmaceuticals in clinical trials in many ways. One way is by maintaining a searchable database of molecular imaging and radiopharmaceutical production sites to assist clinical trial sponsors with site selection for their studies. Another is by validating PET/CT scanners with the CTN proprietary chest oncology phantom to ensure that the scanners are producing accurate quantitative data, as well as providing harmonized reconstruction parameters across multiple centers. In addition, the CTN characterizes and calibrates SPECT/CT scanners to ensure that they are producing accurate quantitative data, to assist with dosimetry measurements for radiopharmaceutical therapy dose determinations. The CTN also audits investigational radiopharmaceuticals produced for clinical trials under investigational-new-drug applications to help ensure the safety, consistency, and purity of the drugs being administered to study patients, as well as assisting with trial design and protocol development for molecular imaging and radiopharmaceutical therapy clinical trials. Finally, the CTN develops

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educational programs for live meetings, webinars, and online courses, including imaging interpretation training sessions that help nuclear medicine professionals learn about working in clinical research and about translating clinical trial experience into the clinical implementation of new tracers and radiopharmaceutical therapies after approval (*5*).

The nuclear medicine field has experienced a decade of growth in Food and Drug Administration (FDA) approvals from 2011 to 2021 (Table 1), with 2 SPECT imaging agents, 8 PET oncology imaging agents, 5 PET brain imaging agents, and 3 radiopharmaceutical therapy agents approved (*6*,*7*). These approved radiopharmaceuticals are being used as biomarkers in clinical trials of therapeutic drugs to assess response.

Because of the growth in radiopharmaceutical approvals (*6*), there is also more interest in, and a greater need for, education about clinical research, the process and challenges for approvals, and implementation of new imaging agents and radiopharmaceutical therapies into the clinic. With recent approvals and anticipated future approvals of radiopharmaceutical therapies, the SNMMI CTN therapy toolkit was created to provide educational tools, including a therapy implementation checklist, and to help sites establish a successful radiopharmaceutical therapy program (*8*). Working in a clinical trial context can create a set of challenges different from those in an approved-drug setting. Nuclear medicine technologists must learn new terms and acronyms that are common language in clinical trials, understand the complexities of a protocol, and be able to follow rigorous clinical trial requirements to provide quality data. Since most nuclear medicine technology programs do not address these details, the CTN has provided this series of articles to help meet the educational needs of nuclear medicine technologists working in clinical research. This introductory article begins with an overview of some basic terms and concepts included in clinical trials and then summarizes the subsequent set of articles in the series.

OVERVIEW OF BASIC TERMS, CONCEPTS, AND PHASES OF CLINICAL TRIALS

There are many terms, acronyms, and concepts involved in clinical trials that may be new to nuclear medicine technologists. Learning the language of clinical trials is important for nuclear medicine technologists to be able to understand instructions within a protocol, provide high-quality data, and communicate with the sponsor and research team. The CTN currently has a couple of courses in the SNMMI Learning Center that provide an overview of research team members, study documents, phases of clinical trials, and common terms and acronyms used in clinical research: "CTN Course 102: The Language of Clinical Trials" (*9*) and "CTN Course 116: Imaging in Clinical Research—Elements for Success" (*10*). Definitions are given below for many of the common terms (in alphabetical order):

- Adverse drug reaction: An unintended reaction to a drug taken at normal doses (*11*).
- Adverse event: Any untoward medical occurrence in a study subject who has been administered a pharmaceutical product; it does not necessarily need to have a causal relationship with this treatment (*11*).
- Blinding (masking): The process thorough which study subjects, the investigator, or other involved parties in a clinical trial are kept unaware of the treatment assignments of study subjects (*11*).
- Case history: The investigator's subject source documents and case report forms for a trial (*11*).
- Case report form: A record of pertinent information collected on each subject based on the protocol during a clinical trial (*11*).
- Clinical research associate (monitor): A sponsor monitor who visits sites periodically during a study to monitor data and assess study progress (*11*).
- Clinical research coordinator (study coordinator, research coordinator): A person at the investigational site who manages the daily operations of a clinical investigation and reports to the investigator (*11*). An individual can become a certified clinical research coordinator by having 2 or more years of experience and passing an exam (*11*).
- Clinical trial (clinical study, clinical investigation): Any experiment that involves a test article (drug, device, biologic) and one or more human subjects (*11*).
- *Code of Federal Regulations*: Organization of rules published by the U.S. federal government departments and agencies; divided into 50 titles (*12*).
- Contract: A written, dated, and signed agreement between 2 or more parties that lays out any arrangements or delegation and distribution of tasks and obligations, including, if appropriate, on financial matters (*11*).
- Contract research organization (CRO): A person or organization with which the sponsor contracts to perform one or more of the sponsor's trial-related duties and functions (*11*).
- Control group: A group of subjects who are not treated with the investigational product; this group is compared with the treatment group (*11*).
- Data management: The process of handling the data generated and collected during a clinical trial, usually including data entry and data management (*11*).
- Double-blind: The design of a study in which neither the investigator nor the subjects know which treatment the subject is receiving (*11*).
- Drug: An article (other than food) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals (*11*).
- Essential documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (*11*).
- FDA form 1572: A legally binding, signed agreement between the principal investigator and the FDA that the former will conduct the study in accordance with the protocol (*10*).
- Good clinical practice (GCP): The regulations and guidelines that specify the responsibilities of sponsors, investigators, monitors, and institutional review boards (IRBs) involved in clinical

TABLE 1
FDA-Approved Molecular Imaging and Therapeutic Radiopharmaceuticals from 2011 to 2021 (*6,7*)

Year of approval	Drug	Indication	Modality
2011	^{123}I-ioflupane (DaTscan; GE Healthcare)	Parkinson disease	Single-photon imaging
2012	^{18}F-florbetapir (Amyvid; Eli Lilly)	Alzheimer disease	PET brain imaging
2012	^{11}C-choline (Mayo Clinic)	Prostate CANCER	PET oncology
2013	^{123}I-MIBG iobenguane (Progenics)	Pheochromocytoma, paraganglioma	Single-photon imaging
2013	^{223}Ra-dichloride (Xofigo; Bayer Healthcare)	Prostate cancer	Radiopharmaceutical therapy
2013	^{18}F-flutemetamol (Vizamyl; GE Healthcare)	Alzheimer disease	PET brain imaging
2014	^{18}F-florbetaben (Neuraceq; Piramal)	Alzheimer disease	PET brain imaging
2016	^{18}F-fluciclovine (Axumin; Blue Earth)	Prostate cancer	PET oncology
2016	^{68}Ga-DOTATATE (Netspot; AAA/Novartis)	Neuroendocrine cancer	PET oncology
2018	^{177}Lu-DOTATATE (Lutathera; AAA/Novartis)	Neuroendocrine cancer	Radiopharmaceutical therapy
2018	^{131}I-MIBG iobenguane (Azedra; Progenics)	Pheochromocytoma, paraganglioma	Radiopharmaceutical therapy
2019	^{68}Ga-DOTATOC (University of Iowa)	Neuroendocrine cancer	PET oncology
2019	^{18}F-fluorodopa (Feinstein Institute)	Parkinson disease	PET brain imaging
2020	^{18}F-fluoroestradiol (Cerianna; Zionexa)	Breast cancer	PET oncology
2020	^{18}F-flortaucipir (Tauvid; Lilly)	Alzheimer disease	PET brain imaging
2020	^{64}Cu-DOTATATE (Detectnet; RadioMedix-Curium)	Neuroendocrine cancer	PET oncology
2020	^{68}Ga PSMA-11 (UCSF–UCLA)	Prostate cancer	PET oncology
2021	^{18}F-DCFPyL or ^{18}F-piflufolastat (Pylarify; Lantheus)	Prostate cancer	PET oncology

trials. They are meant to protect the safety, rights, and welfare of subjects while ensuring the accuracy of data collected (*11*).

- Human subject (study subject, study participant): An individual who participates in research, either as a recipient of the test article or as a control (*11*).
- Imaging manual: A document that contains detailed information on the scanning requirements for a clinical trial, such as patient preparation, dose, uptake time, acquisition and reconstruction parameters, deidentification, and image transmittal requirements (*10*).
- Inclusion and exclusion criteria: The characteristics that must be present (inclusion) or absent (exclusion) for a subject to qualify for a clinical trial, as per the protocol for the trial (*11*).
- Informed consent: The process by which a subject, after reviewing the clinical trial procedures, voluntarily provides a signature to confirm willingness to participate (*11*).
- IRB: Any board, committee, or group formally designated to review biomedical research involving human subjects, approve the initiation of such research, and periodically review it (*11*).
- IRB approval: The determination of an IRB that a clinical investigation may be conducted within the constraints set by the IRB and applicable regulations (*11*).
- International Conference on Harmonization: A conference that promotes public health safety through international harmonization (*13*).
- Investigational-new-drug application: The application submitted to the FDA per regulations within title 21, part 312, of the *Code of Federal Regulations* to start clinical testing of a new drug or biologic in humans (*11*).
- Investigator (clinical investigator, principal investigator): An individual who conducts a clinical investigation—that is, under whose immediate direction the test article is dispensed or, in the case of an investigation conducted by a team of individuals, who is the responsible team leader (*11*).
- Investigator brochure: A compilation of all information known to date about the test product, including chemistry and formulation information and preclinical and clinical data. It is updated at least annually. Once the product is marketed, it is replaced by the package insert for the product (*11*).
- Legally authorized representative: An individual, a judicial body, or another body authorized under applicable law to consent on behalf of a potential subject to the subject's participation in research (*11*).
- Minimal risk: A term indicating that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or routine medical care (*11*).
- New-drug application: The marketing application for a new drug submitted to the FDA under the requirements of title 21, part 314, of the *Code of Federal Regulations*. The new-drug application contains all nonclinical, clinical, pharmacologic, pharmacokinetic, and stability data required by the FDA (*11*).
- Placebo: An inactive substance designed to resemble the drug being tested (*11*).
- Quality assurance: Systems and procedures designed to ensure that a study is being performed in accordance with GCP guidelines and that the data being generated are accurate (*11*).
- Radioactive drug research committee: A committee that reviews research protocols that include the use of radioactive drugs and approves those protocols once a certain list of requirements is met (*14*).
- Randomization: A method by which study subjects are randomly assigned to treatment groups. It helps to reduce bias in a trial by ensuring that there is no pattern in the way subjects are assigned to treatment groups (*11*).
- Regulatory coordinator: A member of the research team who is responsible for submitting protocol documents to the IRB and maintaining regulatory files (*9*).

- Scientific review committee: A committee that reviews research protocols for scientific merit to determine whether involvement of human subjects is justified (*10*).
- Serious adverse event: After administration of any dose of a drug, any untoward medical occurrence that results in death, is life-threatening, requires hospitalization, or results in persistent or significant disability or incapacity; a serious adverse event can also be a congenital anomaly or birth defect (*11*).
- Source document: Original documents and records including, but not limited to, hospital records, clinical and office notes, laboratory notes, subjects' diaries or evaluation checklists, pharmacy records, copies of transcripts, images, and subject files (*11*).
- Sponsor: A person or entity who initiates a clinical investigation but does not actually conduct the investigation (*11*).
- Standard operating procedures: Official written instructions for the management and conduct of clinical trial processes, ensuring that they are performed consistently and efficiently (*11*).
- Study protocol: The formal plan for carrying out a clinical investigation.
- Study protocol amendment: Planned changes to the protocol that must be approved by the review boards before being applied to the participants.
- Study protocol deviations: Any change, divergence, or departure from the study design or procedures defined in the protocol (*15*).
- Study protocol exception (planned protocol deviation): A temporary protocol deviation that is preapproved by the funding agency.
- Study protocol violation (important protocol deviation): A change, divergence, or departure from the study requirements, whether by the subject or the investigator, that resulted in a subject's withdrawal from study participation (*15*).
- Subinvestigator (coinvestigator): An individual who performs critical clinical trial–related procedures or makes important decisions and is supervised by the investigator (*9*).
- Unanticipated event: A problem involving risks to human subjects or others participating in a clinical research study. These events need to be collected and reported (*11*).

Clinical trials involve active participation of people to test the safety and efficacy of new medical treatments (*16*). Clinical trials are divided into phases (Table 2); the different phase numbers serve as markers or milestones in the drug development process and are not necessarily distinct consecutive periods (*16*). The regulatory aspects of a clinical trial for an approved agent being studied in a therapeutic drug trial can differ from those for a new diagnostic radiopharmaceutical being studied for eventual approval. The drug development process can be further complicated by the fact that the approved agent may still be carefully monitored, particularly if the trial is a response assessment. Having a knowledge of the basic terms described above will increase one's understanding of the topics that will be discussed in the series.

SERIES TOPIC 1: ETHICAL ISSUES IN CLINICAL RESEARCH

To understand what it means to conduct ethical medical studies and work in clinical research, it is important to be familiar with the historical context of why current enforceable policies exist in clinical practice and in clinical trial regulations. This first topic in the series will review several agencies, mostly in the United States, that oversee both clinical and research policies in medical practice. Some of the agencies and their responsibilities discussed in this article include the FDA (which ensures the safety, efficacy, and security of human and veterinary drugs, biologic products, and medical devices (*17*)), the Nuclear Regulatory Commission (which ensures that radioactive materials are used safely (*18*)), the Joint Commission (which encourages excellence and quality while evaluating health-care organizations (*19*)), the Office for Human Research Protection (which provided leadership for protecting human subjects in research (*20*)), and the World Health Organization (which helps ensure healthy lives and the well-being of all peoples (*21*)).

This article moves into a discussion of the ethical requirements for humans involved in clinical research. It explores the historical examples of medical mistreatment in research and the main regulations developed to guide current researchers in informed research studies. Some of these ethical principles and laws that have shaped clinical research practices include the U.S. *Code of Federal Regulations,* the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. These all work together to help manage the applicable ethical and scientific quality standards included in GCP, which outlines the responsibilities of the investigator, sponsor, and institution involved in human subject research, as well as the design of clinical trials (*22*).

SERIES TOPIC 2: APPLICATION OF GCP TO CLINICAL RESEARCH IN MEDICAL IMAGING

After understanding the context of the development of current clinical trial regulations, it is important to know the meaning of those regulations, the language used in clinical trials, and how the regulations and language all apply toward GCP. The objective of this second topic in the series includes the importance of GCP and the relationship between GCP and federal regulations that govern human subject research in the United States. The article will describe good documentation practices for collection and recording of raw and processed data; define source material, source documents, and the differences between them; characterize the critical role of technologists in mitigating key risks to data standardization in trials that rely on imaging endpoints; and describe how to read and follow a sponsored research protocol while relying on key supplemental documents such as an imaging charter.

The article also provides other material useful for readers, including the use of documentation tools such as a delegation log and drug accountability log; definitions and descriptions of adverse event; the role of the medical imaging provider in reporting adverse events to the sponsor; and the need to work together with the sponsor, investigator,

TABLE 2
Phases of Clinical Trials (*16*)

Phase	Primary purpose	Study participants
Preclinical	Collect data to determine basic physical, chemical, and biologic characteristics of new compound	Cell studies and animal studies
I	Safety in humans	Healthy volunteers or people with the disease or condition (usually 20–100 participants)
II	Efficacy in target/disease condition; determination of dose	People with the disease or condition (usually a few hundred participants)
III	Efficacy and monitoring of adverse events; comparison to current standard treatment	People with the disease or condition (often thousands of participants)
IV	Safety and efficacy over time, usually after FDA approval	People with the disease or condition (usually thousands of participants)

and study coordinator to produce high-quality, reproducible, and audit-ready data.

SERIES TOPIC 3: CROS WITH APPLICATIONS IN CLINICAL IMAGING

CROs can play a major role in ensuring safe and ethical clinical trials, which help in the development of new drugs and medical devices that benefit millions of patients worldwide (*23*). Sponsors contract with imaging CROs, which assume the responsibility of performing services or managing the imaging portion of the trial. These aspects often include writing imaging manuals, reviewing image charters, qualifying and training sites, collecting and performing quality control of study images, and performing image analysis. Clinical research conducted by CROs increased 40% from 2008 to 2014 and is expected to reach over $45 billion a year by 2022 (*23*). This third topic of the CTN series will discuss, in detail, clinical trial management and tasks performed by an imaging CRO, common primary and secondary endpoints tied to imaging in clinical trials, centralized image review with response assessment criteria, potential safety assessments measured during clinical trials, and the use of nuclear medicine and molecular imaging in drug development.

Finally, the article will discuss how an imaging CRO can serve as a gateway to a research-focused career for nuclear medicine technologists.

SERIES TOPIC 4: CLINICAL RESEARCH PRIMER—REGULATORY PROCESSES, PARTS I AND II (HOW AND WHEN RADIOPHARMACEUTICALS CAN BE USED AND THE ROLE OF THE IRB)

Regulatory processes are developed to ensure patient safety, patient privacy, and data integrity while conducting effective research. This fourth topic in the series will familiarize the reader with the regulatory process for clinical research involving radiopharmaceuticals by providing a basic understanding of how and when radiopharmaceuticals can be used. This focus will identify and explain the role of the IRB or ethics committee in protecting human subjects. It will continue to define terms, exemptions, and processes that are specific to the clinical research environment. This topic will describe the importance of a clinical trial and how the protocol needs to be written and interpreted to comply with the objectives of the research being performed.

SERIES TOPICS 5–7: USE OF IMAGING AGENTS IN THERAPEUTIC DRUG DEVELOPMENT AND APPROVAL, IMAGING AGENT TRIALS, AND IMAGING AGENTS WITH RADIOPHARMACEUTICAL THERAPIES IN CLINICAL TRIALS

Molecular imaging agents used as a biomarker in clinical trials can provide sponsors of therapeutic agents, such as a chemotherapy for cancer, with valuable information to determine eligibility, efficacy, and response. This can be done by showing either the presence or lack of disease, by confirming whether the drug would bind to a particular target, and by predicting or showing a patient's response to therapy. The last 3 topics in this series will review the use of imaging in clinical trials and discuss many aspects of clinical research, including inclusion and exclusion criteria, biomarkers, surrogate endpoints, test–retest variability, radiolabeling of a drug, biodistribution, monitoring and audit processes, clinical and research lab assessments, dosimetry, tumor response assessments, protocol deviations and violations, adverse event reporting, common documents in clinical trials, administration techniques, and attention to details in following the imaging parameters in the protocol.

Each topic will further examine the types of studies, namely phase 1 through phase 4. The fifth topic will focus on the use of an imaging agent in a study designed to help develop and approve a nonradioactive therapeutic drug. The sixth topic will examine clinical research on an imaging agent. The seventh topic will review the use of an imaging agent along with a radiopharmaceutical therapy in a clinical trial, such as a theranostic study. This last topic will also discuss use of positive scan findings to qualify a patient for therapy, the administration of concomitant medications, and posttherapy imaging.

CONCLUSION

The radiopharmaceutical market is expected to grow from $5.9 billion in 2021 to over $10.5 billion in 2026,

nearly doubling in 5 y (*24*). This expansion represents the lives of actual patients who are impacted because of a diagnosis or therapy that nuclear medicine can provide (*24*). The phases of drug development, the investigational-new-drug application requirements, and the clinical research process can be difficult to navigate in the clinical setting. Recent advances in β-amyloid therapies in Alzheimer disease, immune modulation therapy for cancer, and radiopharmaceutical therapies have increased the demand for highly trained research personnel with nuclear medicine expertise to assist in the design, conduct, and analysis of clinical trial data and results. The SNMMI CTN recognized the need to develop a committee to ensure the advancement and development of new radiopharmaceuticals and clinical trials. The CTN has a variety of resources to assist the nuclear medicine community involved in research, including scanner validation programs, educational opportunities, a therapy toolkit, a database of molecular imaging and radiopharmaceutical production sites to assist clinical trial sponsors with site selection, and assistance with trial design and protocol development. Clinical trial education will help advance not only the career of a nuclear medicine technologist but also the entire field of medicine.

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