SNMMI Clinical Trials Network Research Series for Technologists: An Introduction to Conducting Theranostic Clinical Trials

Freddy Gonzalez[1], Peter J.H. Scott[2], Charlotte Denise Jeffers[3], and S. Cheenu Kappadath[4]

[1]*Department of Diagnostic Imaging, M.D. Anderson Cancer Center, Houston, Texas;* [2]*Department of Radiology, University of Michigan, Ann Arbor, Michigan;* [3]*Department of Radiology, University of Alabama at Birmingham, Birmingham, Alabama; and* [4]*Department of Imaging Physics, M.D. Anderson Cancer Center, Houston, Texas*

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This article is intended to introduce nuclear medicine technologists (NMTs) to the nuances of radiopharmaceutical therapy clinical trials. Here, we outline the potential roles and responsibilities of the NMT in clinical trials and provide context on different aspects of radionuclide therapy. The regulatory process involving investigational therapeutic radiopharmaceuticals is seldom taught to NMT students, nor is it included in the entry-level nuclear medicine certification examinations. Often, NMTs must spend significant time preparing for therapeutic clinical trials on their own, using multiple academic sources, seeking advice from various health care professionals, and reviewing numerous trial-specific manuals to recognize the detailed requirements. The emergence of theranostics has spurred an increase in the development of therapeutic radiopharmaceuticals. Investigators with a robust nuclear medicine background are required to help develop successful therapeutic clinical trials, and well-informed NMTs are crucial to the success of such trials. This article follows a series of previous publications from the Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network research series for technologists and is intended to guide the investigational radiopharmaceutical landscape.

Key Words: theranostics; infusion; dosimetry; technologist

J Nucl Med Technol 2024; 52:184–191
DOI: 10.2967/jnmt.123.266588

Theranostics is a paradigm that allows for the imaging and treating of neoplastic lesions using a pair of designed radiopharmaceuticals that localize to the same specific cellular target, with one of them being labeled with a dedicated radionuclide for therapy and the other with a dedicated radionuclide for diagnostic imaging. Theranostics provides oncologists unique insight by being able to "see what we treat and treat what we see" (*1*). One of the advantages of the oncology theranostic model is the ability to use the diagnostic radiopharmaceutical to confirm target expression, based on targeted tumor or receptor type, and thus predict which patients may benefit from radiopharmaceuticals. Theranostics can provide oncologists with noninvasive quantification of disease avidity, indicating whether patients are good candidates for radiopharmaceutical therapy. Dozens of companies have entered the theranostic space, and there are currently numerous ongoing theranostic clinical trials, as indicated in Table 1. However, nuclear medicine technologists (NMTs) are typically not trained or tested on how to support a theranostic clinical trial.

Didactic materials in nuclear medicine programs aid in preparing future NMTs with the knowledge of how to use Food and Drug Administration (FDA)–approved diagnostic and therapeutic radiopharmaceuticals safely and effectively. These FDA-approved radiopharmaceuticals have been rigorously tested and used for years, with extensive data available on application and associated risks. However, while working in nuclear medicine clinics, NMTs are increasingly asked to aid with clinical trials for investigational radiopharmaceuticals (*2*). Often, imaging and treatment of clinical trial patients occur during the busy regular clinical workflow but may involve protocols and procedures different from those routinely applied. This delicate balance requires the expertise and detailed dedication of a well-informed NMT to help support a successful theranostic clinical trial while also managing routine clinical operations.

REVIEW OF PROTOCOL MANUALS

Clinical trials must undergo FDA-mandated phases to ensure that investigational radiopharmaceuticals are safe

Received Sep. 1, 2023; revision accepted Nov. 14, 2023.
For correspondence or reprints, contact Freddy Gonzalez (jagonzalez1@mdanderson.org).
Published online Jan. 9, 2024.

TABLE 1
Investigational Theranostic Clinical Trials List

Diagnostic radiopharmaceutical	Therapeutic radiopharmaceutical and clinical trial name	Sponsor	Indication	Clinicaltrials.gov identifier
^{68}Ga-DOTATATE	^{177}Lu-DOTATATE (NETTER-2)	Novartis Pharmaceuticals	Somatostatin tumors	NCT03972488
^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE	^{225}Ac-RYZ101 (ACTION-1)	RayzeBio	Somatostatin tumors	NCT05477576
^{68}Ga-DOTATATE	^{177}Lu-edotreotide (COMPOSE)	ITM Solucin GmbH	Somatostatin tumors	NCT04919226
^{64}Cu-sartate	^{67}Cu-sartate	Clarity Pharmaceuticals Ltd.	Neuroblastoma	NCT04023331
^{68}Ga-PSMA-11	^{177}Lu-PSMA-617 (PSMAfore)	Novartis Pharmaceuticals	Prostate cancer	NCT04689828
^{68}Ga-PSMA-11	^{177}Lu-PSMA-617 (PSMAddition)	Novartis Pharmaceuticals	Prostate cancer	NCT04720157
PSMA agent	^{177}Lu-PSMA-I&T (ECLIPSE)	Curium US LLC	Prostate cancer	NCT05204927
^{68}Ga-PSMA-11	^{177}Lu-DOTA-rosopatamab (PROSTACT)	Telix International Pty Ltd.	Prostate cancer	NCT04876651
PSMA agent	^{177}Lu-rhPSMA-10.1	Blue Earth Therapeutics Ltd.	Prostate cancer	NCT05413850
^{68}Ga-PSMA-11	^{225}Ac-PSMA-617	Telix International Pty Ltd.	Prostate cancer	NCT04597411
^{64}Cu-SAR-BBN	^{67}Cu-SAR-BBN (COMBAT)	Clarity Pharmaceuticals Ltd.	Prostate cancer	NCT05633160
^{68}Ga-NeoB	^{177}Lu-NeoB (NeoRay)	Advanced Accelerator Applications	Solid tumors	NCT03872778
^{68}Ga-DOTATATE	^{177}Lu-DOTATATE	Novartis Pharmaceuticals	Glioblastoma	NCT05109728
^{68}Ga-FAP-2286	^{177}Lu-FAP-2286 (LuMIERE)	Novartis Pharmaceuticals	Solid tumors	NCT04939610
^{68}Ga-DOTA-FAPI	^{177}Lu-DOTA-FAPI	First Affiliated Hospital of Xiamen University	Various cancers	NCT04849247
^{89}Zr-girentuximab	^{177}Lu-girentuximab	Memorial Sloan Kettering Cancer Center	Renal cancer	NCT05239533
^{111}In-FPI-1547	^{225}Ac-FPI-1434	Fusion Pharmaceuticals Inc.	Solid tumors	NCT03746431

and effective and comply with all the required rules and regulations (*3*). Additionally, clinical trials approved by an institutional review board or the equivalent are conducted with the trial participants' written informed consent. Each clinical trial has specific requirements, outlined in the primary protocol, and may include additional manuals such as the technical operations manual, imaging manual, and pharmacy manual. Clinical trials may require the use of FDA-approved radiopharmaceuticals for a nonapproved indication, such as using ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE for patients with newly diagnosed and recurrent glioblastoma (*4*). The NMT should review the appropriate trial manuals and identify the specific imaging parameters for the radiopharmaceutical—parameters that may differ from the clinical parameters. NMTs are encouraged to review the relevant sections of all provided manuals from a technical perspective and prepare to adhere to those requirements. Once all the manuals are reviewed, NMTs should advise the principal investigator regarding all preparations needed to conduct the protocol locally. If any potential barriers are identified, the NMT should support the primary investigator in communicating them to the multidisciplinary team and, if necessary, to the protocol sponsor to ensure that they are addressed and that a given study is feasible. Manuals should be reviewed and preparations completed before the site initiation visit and preparations confirmed before the first patient is enrolled. This proactive approach is critical to understanding the protocol requirements and developing a good local process.

Reviewing, comprehending, and correctly applying several manuals' worth of protocol-specific information and detailed applications require adequate time and focus while developing local logistics with a multidisciplinary team for the clinical trial. Understanding the intricate complexities of a clinical trial is essential, but it can be challenging to recall multiple manuals' worth of detailed information (*5*). One approach is to condense the technical requirements of the protocols into a local, site-specific day-of-infusion or day-of-imaging document. This document is not intended to replace sponsor-required documents or manuals but serves as a quick reference for the essential items of which an NMT needs to be aware. This local document may include such items as the subject identification number, cohort or phase the patient is enrolled in, number of therapeutic cycles, dosage amount (weight-based or fixed), administered and residual measurements, radiopharmaceutical-specific dose calibrator dial setting, duration of infusion, infusion timing, biologic sampling protocols (including any testing or storage requirements), requirements for scintigraphic imaging, and postinfusion radiation safety precautions.

The local document may also include contact information for pertinent staff, such as authorized users, medical physicists, electrocardiography staff, phlebotomists, radiation safety specialists, nurses, the primary investigator, referring physicians, study coordinators, statisticians, social workers, blood draw personnel (e.g., arterial lines increasingly need to be placed by interventional radiologists), and nuclear

pharmacists or radiochemists at the radiopharmacy or production site.

These items and personnel (*6*) will vary with the clinical trial requirements and the clinical sites' needs. As the clinical trial progresses, the data acquired may influence changes to the initial version of the protocol. Therefore, the NMT should be aware of any protocol addendums, memos, or protocol revisions to ensure compliance with the updated trial.

EQUIPMENT QUALIFICATIONS

Nuclear medicine instrumentation, both imaging and nonimaging, is an essential tool in the execution of a radiopharmaceutical clinical trial (*7*). Nuclear medicine imaging uses devices such as γ-cameras, hybrid PET scanners combined with either a CT scanner (PET/CT) or an MRI scanner (PET/MRI), and hybrid SPECT scanners combined with a CT scanner (SPECT/CT) to produce biodistribution images of the diagnostic radiopharmaceuticals in the body's internal organs and tissues (*8*). Diagnostic imaging in a theranostic clinical trial helps with the selection of appropriate patients through confirmation of target expression on an initial scan and verification of radiopharmaceutical treatment response on follow-up scans. Nonimaging nuclear medicine instrumentation, such as dose calibrators, well counters, and ionization survey meters, is essential in supporting a theranostic radiopharmaceutical clinical trial. Nonimaging equipment should be calibrated for each clinical trial. For example, dose calibrators are essential for determining the activity administered to the patient, and well counters are essential for radiation safety and biologic sample counting. After therapeutic administration, ionization meters are routinely used to determine patient exposure rates for determination of and compliance with patient-release criteria.

The success of these therapies largely depends on accurate calibration and configuration of the instrumentation and adherence to the recommended quality control procedures. In radiopharmaceutical clinical trials, equipment qualification is essential to confirm that the results obtained are accurate and reliable. Clinical trials involve testing novel investigational drugs or therapies, and the data obtained from these trials are used to evaluate the safety and efficacy of the treatment. Any variability in the imaging results or dosing can lead to incorrect conclusions regarding the safety and efficacy of the treatment. Therefore, it is essential to qualify equipment as part of the clinical trial process.

Quality Control Procedures

Quality control procedures are necessary to ensure that the instruments function correctly and that the information provided by the clinical trial meets the minimum quality standards. Quality control procedures also help to detect any problems that may arise during the therapy, potentially compromising the quality of the information collected. A good program for quality control would be comprehensive yet practical and straightforward to implement. Clinical trials are often conducted over several centers (multisite) and hence collect clinical data from various new and vintage equipment models. A robust quality control program is meant to ensure consistency in performance across a wide variety of systems over the frequently multiyear duration of the trial.

Dose Calibrators

Dose calibrators measure the amount of radioactive material present in a sample, typically a syringe or vial, meant for patient administration. Dose calibrators are essential in preparing radiopharmaceuticals and measuring residual radioactivity after patient administration (*9*). The accuracy of the dose calibrator is critical in determining the correct dosage to be administered. It is therefore essential to calibrate dose calibrators regularly and ensure they function correctly over a wide range of activities. Most often, the dose calibrator's calibration factor will need to be set by individual sites for the specific radionuclide administered and its specific form factor. Trial sponsors will typically provide a manufactured or, ideally, a National Institute of Standards and Technology (NIST)–certified calibrated activity against which the calibration factors for the dose calibrator used may be established.

Calibration and Configuration

Appropriate calibration of PET and SPECT scanners ensures quantitative accuracy in the resultant patient images of in vivo radiopharmaceutical biodistribution (*7*). The accuracy of these images also depends on items related to the appropriate data acquisition and reconstruction strategies (configuration) described in the imaging manual that should be provided as part of a theranostic trial.

PET/CT and SPECT/CT

In the context of clinical trials, equipment qualification is essential to ensure that the data obtained are accurate and reliable and adhere to regulatory requirements. A theranostic clinical trial may use any of a wide variety of nuclear medicine imaging modalities, such as whole-body planar imaging, dynamic imaging, PET/CT, and SPECT/CT, to select appropriate patients (e.g., the inclusion criteria with disease-expressing targeted receptors) and verify therapy (e.g., the adequacy of disease targeting after treatment for correlation with the outcome). After radiopharmaceutical administration, serial imaging plays a central role in assessing patient biodistribution, radiopharmaceutical kinetics, and patient-specific organ and tumor dosimetry. This theranostic imaging paradigm is particularly relevant in phase I trials, in which radiopharmaceutical safety and determination of organ doses are of primary concern.

The quality control procedures for PET and SPECT imaging devices, in addition to the mandated annual and periodic testing by federal, state, or accreditation regulations, may include regular phantom scans with a trial-specific radionuclide and protocol to assess performance quantitatively and qualitatively (*10*). Uniform cylindric water phantoms or fillable sphere phantoms with known activity are often scanned to calibrate the scanner for the radionuclide of interest (*11,12*). Scanners may need to

be configured with the energy windows, half-lives, and branching ratios specific to the radionuclide of interest, to ensure tighter control of the quantitative performance of the scanner and increase confidence in subtle changes in patient uptake. For the same reason, staying close to the recommended uptake time before patient imaging and using manufacturer-recommended acquisition and reconstruction protocols are essential. Equipment qualification involves a set of procedures to ensure that the equipment is operating correctly and consistently within acceptable parameters (*13*). Typically, the site may use only qualified equipment to collect and analyze patient data related to the clinical trial. By adhering to strict and consistent standards, we can ensure that radiopharmaceutical therapies are safe and effective, allowing patients to receive optimal care.

Well Counters and Ionization Survey Meters

For clinical trials, well counters can be used to determine the activity in samples of blood, urine, or cerebrospinal fluid. The ionization survey meter is often used to determine the exposure rate of the patient after administration of the therapeutic radiopharmaceutical. This measurement features prominently in the dose calculations to the most exposed person, such as those living with the patient, and guides the drafting of radioactive patient instructions after release. Although trial-specific settings or calibrations are not typically needed for well counters and ionization survey meters, calibrated equipment must still be used to confirm the veracity of the data used in managing patients enrolled in the clinical trial.

MULTIDISCIPLINARY TEAM LOGISTICS

Establishing clear roles and responsibilities among a multidisciplinary team is central to a successful clinical trial. Multidisciplinary teams may include a primary investigator, multiple coinvestigators, clinical and data coordinators, NMTs, nurses, advanced practitioners, data specialists, medical physicists or dosimetrists, sponsor-appointed delegates, social workers, radiation safety personnel, statisticians, and authorized users (*14*). The NMT has unique insight into the technical aspects of radiopharmaceutical imaging and administration that can help bridge knowledge gaps across the multidisciplinary team. Before the first patient is enrolled, it is essential to meet with all multidisciplinary team members and identify which member is responsible for which portions or tasks within the protocol. Effective communication and accounting for these items will help alleviate any uncertainty around each staff member's responsibility. These established roles and responsibilities must be documented on a protocol-specific delegation log for future reference and clinical trial compliance.

CLINICAL TRIAL ROAD MAP

Developing a locally created protocol-specific road map that outlines critical time points for complex clinical trials helps provide a concise, visual document that allows all members of the team and the patient to see what the protocol requires over time. Clinical road maps should be specific for each protocol and can be segmented to provide a general daily or weekly summary (*15*). The road map helps team members unfamiliar with nuclear medicine trials to better visualize the sequence of events and the specific protocol timelines. This clear understanding will help ensure that all members account for protocol-required criteria, avoid unnecessary delays, and collect good-quality data.

Therapeutic radiopharmaceuticals tend to be tolerated well by patients compared with systemic chemotherapy, and patients often experience moderately less severe and frequent side effects (*16*). Although there is always a potential for a reaction during or after infusion of the investigational radiopharmaceutical, identifying investigational product–induced reactions can be difficult because of the limited data available. There needs to be dedicated staff available to monitor the patient and to notify the primary investigator or the authorized user should any reactions occur. A clear and concise plan, for each protocol, details how to counteract minor or severe adverse reactions and is crucial for adequate patient care.

PROTOCOL PLANNING

Before the patient's scheduled day of investigational radiopharmaceutical infusion, it is recommended that the NMT walk through the patient's path related to the protocol and ensure that all required aspects of the trial are accounted for. The NMT should take this time to identify that all protocol-qualified equipment is in good operational order and ready for patient use. Performing protocol dry runs with as many front-line team members as possible will help identify areas or items that can be adjusted to simplify or improve workflow processes. Figure 1 provides a general overview for the NMT of the multiple clinical trial aspects to consider when performing a dry run. When paired with the local road map of the clinical trial, dry runs can aid in streamlining detailed tasks and help bring to light any unforeseen circumstances or identify an ambiguous responsibility. With the technical aspects of the protocol accounted for in the dry run, front-line staff can focus on collecting good-quality data while providing optimal patient care.

DRUG PREPARATION AND DOSAGE MEASUREMENT

The processes for production, delivery, and dispensing of investigational radiopharmaceuticals are subject to a variety of regulations and standards set forth by federal and state agencies and standard-setting organizations including the FDA, the U.S. Nuclear Regulatory Commission, the Department of Transportation, and the U.S. Pharmacopeia (USP). These drugs may be prepared in a variety of ways, including onsite at a cyclotron facility or radiopharmacy or offsite commercially. Although radiopharmaceutical production regulations are beyond the scope of this article, a review of

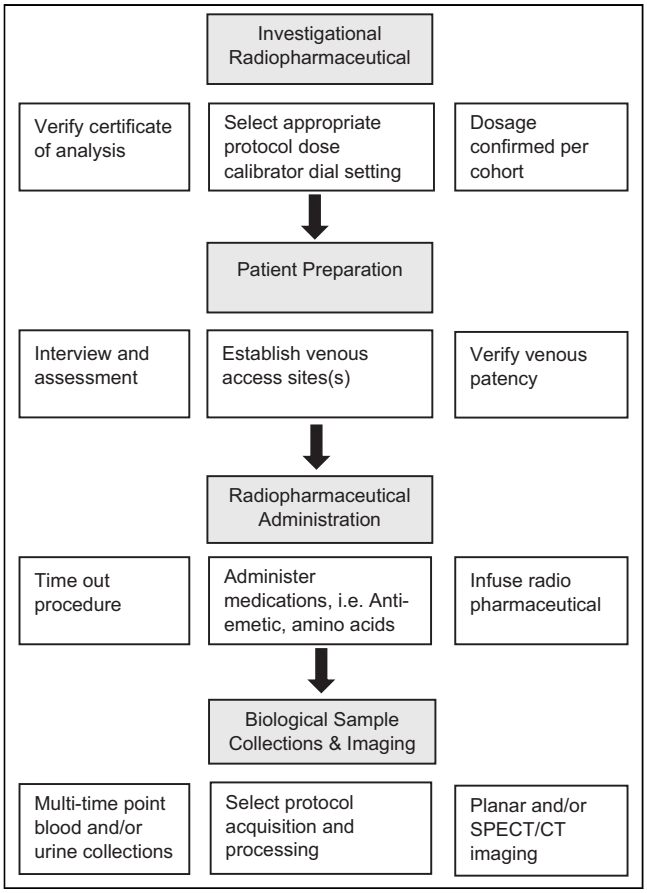

FIGURE 1. Streamlined depiction of common theranostic trial aspects.

the quality control certificate of analysis and dispensing of the final drug product is pertinent.

On release of the radiopharmaceutical to the clinical site, the production site may send a certificate of analysis outlining the quality control acceptance attributes such as appearance, purity, pH, and bacterial endotoxin results. Other information listed on the certificate of analysis may include drug expiration time, drug activity at calibration time, drug volume, and drug storage requirements. The authorized user and NMT should review all these data on receipt of the radiopharmaceutical and immediately communicate any issues to the trial sponsor or production site. Failure to identify and report drug product issues can lead to patient safety concerns, alteration of the biodistribution of the radiopharmaceutical, or other clinical trial complications.

The radiopharmaceutical may be released to a clinical site in a pharmacy bulk package (vial) or in a patient-specific syringe. According to USP chapter <825>, all manipulations necessary to transfer the drug to the final container (e.g., syringe or vial) for administration to the clinical trial participant are considered to be dispensing and must follow all applicable criteria outlined in the chapter (*17*). A thorough understanding of USP chapter <825> is required for dispensing radiopharmaceuticals, especially those that require further manipulation (i.e., transfer of the drug product from the original container to another container for dispensing to the participant). On review of the chapter, each site should identify appropriate spaces and equipment and, when necessary, should train personnel. If the site cannot meet the dispensing requirements to comply with USP chapter <825>, it may desire to partner with an onsite or commercial radiopharmacy to help prepare the radiopharmaceutical for dispensing.

INTRAVENOUS ADMINISTRATION METHODS

The administering NMT and authorized user should carefully choose an infusion method that abides with the needs of the clinical trial, is safe for patient use, adheres to the as-low-as-reasonably-achievable radiation safety principle, and accurately identifies the start and end of a continuous therapeutic infusion. Good-quality theranostic data start with a safe, accurate, and precisely timed intravenous radiopharmaceutical infusion.

Syringe Pump

If a syringe pump is to be used for the clinical trial and the NMT or authorized user decides to withdraw the therapeutic radiopharmaceutical from a vial into an appropriate-volume syringe, several factors must be considered. The team needs to account for the potential geometry effect on the radioactivity measurement, adhere with current USP guidelines, and avoid spillage of the radiopharmaceutical. The NMT needs to consider the utilization of syringe shields for large-volume syringes or injection pump shields that house the entire syringe pump along with the syringe. Once the syringe is loaded into the syringe pump, the NMT can use a 3-way stopcock connected to a saline flush. This setup is then connected to the patient's intravenous catheter with extension tubing. The syringe pump will mechanically compress the syringe at a programmed rate, infusing the radiopharmaceutical. When the pump has completely compressed the syringe plunger, the NMT will need to manually flush the syringe and extension tubing with 0.9% saline to ensure minimal residual activity in the infusion tubing.

Gravity Method

If the gravity method is to be used for the clinical trial, one common setup is to apply a sterile 0.9% saline bag with extension tubing connected to a short needle. This short needle is inserted into the septum of the vial that houses the radiopharmaceutical, ensuring that the short needle is above the volume of the radiopharmaceutical. Additionally, a long needle is inserted into the vial's septum and secured to the base of the vial. The long needle is connected to the extension tubing leading to the patient's intravenous catheter. The saline drip rate determines the radiopharmaceutical infusion duration. During the radiopharmaceutical infusion, NMTs have noted that the vial septum may weaken, and this weak point is a potential site for the radiopharmaceutical to leak because of the positive saline pressure in the vial

(*18*). The NMT must be vigilant about this possibility to avoid spillage. Another approach is to use a digital ion chamber to measure exposure from the vial or extension tubing to help determine the end of infusion based on the exposure fluctuations. However, this approach is an approximation at best and is not ideal when collecting biologic sample data at specific intervals during and after the radiopharmaceutical infusion.

Peristaltic Pump

A peristaltic pump delivers intravenous medications via a closed tubing system. Most peristaltic pumps come equipped with software that indicates low battery power, occlusion, faults, and air in the infusion line and alerts staff when the total volume has been infused. If a peristaltic pump is to be used for the clinical trial, the NMT can program the radiopharmaceutical infusion rate on the basis of the specified duration of administration and volume of the radiopharmaceutical to be infused. Once the pump is programmed, the NMT can observe the pump from a distance and observe the radiopharmaceutical volume being infused from the peristaltic pump control screen (*19*). The peristaltic pump can be used for single or multiple vials as needed.

IMAGING DOSIMETRY FOR THE NMT

Imaging and biologic sample–based dosimetry can aid with identifying the critical components of theranostic trials, such as radiopharmaceutical localization, targeted lesion residence time, rate of excretion, and estimation of absorbed dose to critical organs (*20*). Determining the absorbed dose to targeted lesions and the critical organs can be achieved using radiopharmaceuticals that have a designated target for therapy and the ability to be imaged via SPECT/CT or PET/CT. Radionuclides with long physical half-lives, such as ^{177}Lu,^{131}I, and ^{67}Cu, emit β-particles, which produce an intended therapeutic effect on the neoplastic lesion, but also emit γ-photons suitable for scintigraphic imaging. When linked to a bioconjugate, these radionuclides permit researchers to acquire multiple–time-point scintigraphic images and collect biologic samples over several hours or days after treatment. The NMT is key for acquiring these complex multiday acquisitions that provide valuable quantitative data (*21*). Through quantitative SPECT/CT or PET/CT acquisitions and pharmacokinetic mapping, medical physicists can analyze the dosimetry data to identify the optimal tumor-to-background ratio and the therapeutic radiopharmaceutical dosage that can safely be administered without causing toxicity to the patient. The ability to perform internal patient dosimetry and estimate the absorbed dose to critical organs is a distinctive attribute of theranostic radiopharmaceuticals (*22*). Control of the absorbed radiation dose to critical organs, especially bone marrow and kidneys, is vital for the safe and effective use of theranostic radiopharmaceuticals. Imaging and biologic sample collection–based dosimetry can be performed prospectively or retrospectively depending on the clinical trial application.

Before investigational radiopharmaceutical treatment, imaging dosimetry can be performed by administering a diagnostic amount of the therapeutic radiopharmaceutical or a surrogate diagnostic radiopharmaceutical that emits positrons or γ-photons. For example, positron-emitting ^{89}Zr nuclide and γ-emitting ^{111}In nuclide are often used as diagnostic radioactive elements because of their long physical half-lives of 78.4 and 67.2 h, respectively. The physical half-life of the diagnostic imaging tracer is typically paired with that of the therapeutic radionuclide to provide researchers with the opportunity for multiday dosimetry imaging in pretherapy analysis (*23*). Determining whether the investigational diagnostic radiopharmaceutical has a high affinity, low affinity, or no binding affinity to the targeted disease provides oncologists with detailed, noninvasive data on biologic distribution. Pretherapy dosimetry imaging provides an overview of the biologic distribution and excretion of the investigational radiopharmaceutical. Pretherapy imaging aids in determining the optimal therapeutic dosage to be administered and can help researchers predict the absorbed dose to the biologic target and critical organs. Finally, exposure-rate measurements of patient or pretherapy dosimetry can be used to estimate the patient-specific effective half-life that can be used in determination of patient-release considerations.

Retrospective dosimetry, which is performed after the patient has received a therapeutic amount of radiopharmaceutical, also has clinical value because it can inform the clinical provider about expected organ doses in subsequent cycles of treatment. For example, performing internal dosimetry after the first of a 4-cycle ^{177}Lu-DOTATATE regimen can inform on the dose contributions from cycles 2–4. Theranostic radiopharmaceuticals are unique in that the treatment can be imaged, providing a good scintigraphic representation of the biologic distribution and localization of the radiopharmaceutical.

Whether dosimetry is performed before or after therapeutic administration will be protocol-specific. The NMT needs to allocate sufficient time to identify the detailed requirements of each approach. Investigational radiopharmaceuticals should be measured using the protocol-approved dose calibrator with the established dial setting. Accurate measuring and recording of the total administered radioactivity are crucial to calculating the absorbed organ and tumor dose. Patients should be imaged using the protocol-approved PET/CT or SPECT/CT scanner and using the approved protocol imaging parameters. If multiple–time-point images are a protocol requirement, the NMT needs to acquire the patient images similarly at each time point. Imaging the patient in the same manner at each time point will help reduce any variability in count rate statistics. The NMT is a crucial contributor to collecting dosimetry data, and all efforts to reduce imaging inconsistencies should be made.

RADIATION SAFETY PRECAUTIONS

Regulations are set to limit the amount of radiation to which an individual member of the public can annually be exposed, including exposure from medical procedures. Properly monitoring and managing radiation exposure from patients who have undergone radiopharmaceutical therapies are essential to ensuring the health and safety of patients, caregivers, and health care professionals.

The release of a patient after therapeutic administration involving radioactive materials requires adherence to federal and state regulations, such as proposed revision 2 of Nuclear Regulatory Commission Regulatory Guide 8.39, "Release of Patients Administered Radioactive Material" (*24*). This guideline outlines the specific procedures that must be followed to ensure the safe release of patients. These procedures include monitoring radiation levels in the patient, documenting the patient's exposure, and ensuring that the patient's exposure levels do not exceed regulatory limits.

Per the guideline, licensees are authorized to release individuals who have been administered radiopharmaceuticals if the total effective dose-equivalent to any other individual from exposure to the released individual is not likely to increase by 5 mSv (500 mrem). It requires licensees to provide the discharged radioactive patient with instructions on recommended actions if the total effective dose-equivalent to any other individual is likely to exceed 1 mSv (100 mrem). Furthermore, it may also require the licensees to maintain a record (for 3 y after the date of release, depending on the release conditions and justifications used) of the basis for authorizing the release of an individual.

Calculation of the activities at which patients can be released was based on the method described in report 37 of the National Council on Radiation Protection and Measurements, "Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides" (*25*). The assumptions and conditions for the calculations, such as the occupancy factor, are described. The various options to release a radioactive patient generally fall into 3 categories: release based on administered activity, release based on measured dose rate, and release based on patient-specific dose calculations. The guideline (*24*) provides tabulated values of activity and dose rates, at 1 m from the patient, below which patients can be released without receiving specific instructions. The guideline offers half-lives and exposure rate constants for a comprehensive list of radionuclides that the licensee can use for patient-specific calculations. Example calculations are also provided.

It is likely that many of the newer radiopharmaceuticals, especially α-therapy, are not yet listed in the precalculated tables. In these scenarios, the formalism described to compute patient-specific calculations would need to be used. Also, there are some limitations present, in that the issues related to fractionated radiopharmaceutical therapy are not considered. For example, DOTATATE standard therapy involves 4 cycles of ^{177}Lu-DOTATATE and is based on the assumption that the total effective dose-equivalent to any individual is not likely to increase by 5 mSv or 1.25 (=5/4) mSv per cycle. There are no straightforward answers, and there is an opportunity to contribute to the body of knowledge needed to treat patients with radiopharmaceuticals.

β- and α-particles are 2 ionizing radiation types that pose challenges in radiation safety practices. β-particles are high-energy electrons that can penetrate the skin and damage cells. α-particles, conversely, are helium nuclei and are more massive than β-particles. They have low penetration power and can travel only a few centimeters in air and a few microns in human tissue. However, they are highly ionizing and can cause significant damage to cells if they enter the body through inhalation, ingestion, absorption, or open wounds. The management of β- and α-particles in health care settings requires specific safety measures. For example, use of appropriate protective equipment, such as gloves and masks, can prevent inhalation or ingestion of α-particles. Additionally, proper disposal of radioactive waste is critical in preventing the spread of contamination.

Radiation safety practices are crucial in health care, particularly in releasing patients who have undergone therapeutic administrations involving radioactive materials. The as-low-as-reasonably-achievable principle and Nuclear Regulatory Commission Regulatory Guide 8.39 provide guidance on maintaining exposure levels as low as reasonably achievable and ensuring the safe release of patients. By adhering to these safety practices, health care professionals can protect the health and safety of patients and themselves.

CONCLUSION

Nuclear medicine has entered a new age of theranostics. FDA-approved agents are transforming clinical care in oncology, and considerable investment in the field is simultaneously spurring development of innovative theranostic agents for other cancers. A well-informed NMT bridges knowledge gaps among the multidisciplinary team responsible for conducting theranostic clinical trials and is a crucial member of the team.

DISCLOSURE

S. Cheenu Kappadath has received research support from Sirtex Medical, Boston Scientific, and ABK Biomedical and has served as a consultant for Boston Scientific and Terumo Medical. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Amanda Abbot, Lance Burrell, and Dr. Homer A. Macapinlac for their valuable insight and review of this article.

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