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Clinical Trials in Molecular Imaging: The Importance of Following the Protocol*

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Nuclear medicine technologists and investigators who perform imaging procedures in clinical trials often have not received training on clinical research regulations, such as Title 21, part 312, of the *Code of Federal Regulations* or Good Clinical Practices. These regulations directly affect implementation of the therapeutic or imaging protocol. Lack of understanding of the regulatory expectations in clinical research can lead to unintended errors or omissions in critical data that are needed for development of a new drug. One common error is not following the protocol exactly as written, or modifying the imaging parameters in some way as to make the data nonstandard from site to site. These errors and omissions are a source of delay in the development of new imaging and therapeutic products. Although not following the protocol does not result in criminal penalties per se, errors and omissions can lead to regulatory consequences such as warning letters to the investigator or sponsor, which if not resolved can lead to barring a site or investigator from participation in any future research trials. Pharmaceutical sponsors, device sponsors, and federal granting agencies such as the National Cancer Institute enter into contracts with imaging sites under the expectation that the investigator and all research staff know and understand clinical research regulations. This article is intended to teach imaging personnel what any sponsor (pharmaceutical, device, or federal agency) is expecting from research imaging and how lack of understanding of Good Clinical Practices and federal regulations can impede the optimal success of a research study. After reading this article, nuclear medicine technologists should be able to understand the importance of following the clinical trial protocol to exact specifications, create a list of questions that should be answered by the sponsor or trial organizers before patient enrollment, describe Form FDA 1572, and describe the terms *protocol, protocol deviation, protocol violation,* and *protocol exception.*

Key Words: protocol; protocol deviation; protocol violation; Form FDA 1572; protocol exception

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Molecular imaging techniques such as PET and SPECT can used by sponsors of clinical research to test the therapeutic effectiveness of a new drug or regimen for cancer, neurologic conditions, heart disease, or any other number of clinical conditions. In conditions such as cancer or heart disease, waiting for a hard outcome such as recurrence of disease or heart attack in order to measure the effectiveness of therapy means that clinical trials lasting months or years are needed to measure whether a treatment is effective compared with a gold standard. Using molecular imaging, it is possible to see whether a therapy is having a result much sooner, such as a change in the glucose use of a tumor (e.g., ^{18}F-FDG) or a decrease in ischemic areas of the heart (e.g., PET cardiac techniques). Sponsors of clinical research can use these techniques in early phases of drug development to see whether there is a physiologic response to a therapy and make decisions about whether research should continue. The result is a faster go/no-go decision on development of a particular compound, decreasing the investment of time and money for compounds that are not likely to be successful and increasing the investment into potentially successful treatments. For patients with cancer, heart disease, Parkinson disease, and other disorders, this translates into development of successful therapies in a shorter time.

The challenge for imaging researchers in multicenter-sponsored trials is producing data that can be used in quantitative analysis of data from all sites, not just any individual site. This requires using the same patient preparation, acquisition, and processing parameters at all sites, so that a quantitative measurement such as change in standardized uptake value after therapy can be measured in a large group of patients across multiple institutions. The process of producing data that are quantitatively the same from site to site is referred to as standardization. To produce standardized data, sites must follow the protocol precisely as intended and not alter it in any way that would affect multisite analysis. The consequences of nonstandard data are significant: the data from a patient or an entire site can be considered nonevaluable and removed from the analysis, resulting in the need to add patients to the study. This

immediately increases the time and cost of the study and complicates the measurement of treatment impact. Additionally, the investigator and sponsor may come under regulatory scrutiny for not following the protocol, as the federal regulations clearly state that the protocol is the description of all procedures that will be performed. Most poignant, however, is the wasted time and effort of patients who volunteer to endure additional risk and discomfort in the hope of contributing to the advancement of medical science.

TYPES OF SPONSORED STUDIES

Sponsored studies in molecular imaging come in several forms: those in which the radiopharmaceutical is the investigational product under study, those in which imaging using an approved agent measures the therapeutic efficacy of the investigational product, and those in which both the imaging agent and the therapeutic agent are investigational.

The first type of study, that in which the radiopharmaceutical is the investigational drug, is typically conducted by companies that have a primary interest in imaging or radioisotope therapy. The sponsor may have at least some in-house experience with imaging and may be familiar with the regulations and procedures involved in handling radioactive material. For this type of study, the imaging or therapy procedure is often described in detail in the clinical protocol. Often, a nuclear medicine physician is the principal investigator for these trials. Nuclear medicine technologists and investigators are familiar with this process, which has resulted in many of the radiopharmaceuticals that we use in clinical nuclear medicine today: Cardiolite (^{99m}Tc-sestamibi; Lantheus Medical Imaging), Myoview (^{99m}Tc-tetrofosmin; GE Healthcare), ProstaScint (capromab pendetide; EUSA Pharma), and OctreoScan (^{111}In-pentetreotide; Covidien) to name a few. All Food and Drug Administration (FDA) regulations that apply to any investigational drug apply to an investigational radiopharmaceutical, even if it is being developed for diagnostic purposes (i.e., scanning).

The second type of sponsored protocol in imaging is that in which an imaging procedure is part of evaluating an investigational therapeutic product or procedure. An example of this is seen in cardiology when myocardial perfusion imaging with approved radiopharmaceuticals is used to test the efficacy of new cardiac medications. Another example is when ^{18}F-FDG PET is used in oncology to measure response to an investigational chemotherapy. The nuclear medicine physician is often a subinvestigator in this type of trial, and the principal investigator is a therapeutic expert, such as a cardiologist, neurologist, or oncologist. Imaging is only one part of the clinical investigation in these examples; however, that does not minimize its importance to the study.

The third scenario—one in which both the radiopharmaceutical and the therapeutic intervention are investigational—is becoming more common in molecular imaging with the development of new PET biomarkers. For example, the effectiveness of an investigational cancer therapy may be tested by pre- and posttherapy 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) PET images. (^{18}F-FLT is a marker of cell proliferation, and a decrease in ^{18}F-FLT uptake after treatment may indicate early effectiveness of therapy.) Both the cancer therapy and ^{18}F-FLT are investigational in this example and are covered under the same federal regulations and guidelines. The investigator is subject to the same regulations about drug accountability for ^{18}F-FLT as for the investigational chemotherapy agent.

DEFINITION OF A PROTOCOL

No matter the type of clinical trial in which imaging is involved, the same expectations of the sponsor and regulatory agencies exist: the imager must follow the protocol as described and produce data that are standardized in order to facilitate analysis across multiple sites. Health care professionals use the term *protocol* in daily work; however, this term can have several meanings depending on context. In clinical trials, the term has a specific meaning.

A protocol is a document that describes the objectives, design, methodology, statistical considerations, and organization of the trial (*1*). Title 21, part 312, of the *Code of Federal Regulations* describes what a protocol document must contain:

- A statement of the objectives and purpose of the study, and the observations and measurements to be made to fulfill the objectives of the study.
- The name and address and a statement of the qualifications of each investigator and the name of each subinvestigator working under the supervision of the investigator, the name and address of the research facilities to be used, and the name and address of each reviewing Institutional Review Board (IRB) (in practice, this information is often not included in the protocol document per se but is part of Form FDA 1572, Statement of Investigator).
- The criteria for patient inclusion and exclusion and an estimate of the number of patients to be studied.
- A description of the design of the study, including the kind of control group to be used, if any.
- A description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
- The method for determining the doses to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.
- A description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

There are a couple of important details that should be emphasized. First, the protocol is a document, meaning that it is written. In practice, this means that a protocol has a version number and effective date and is submitted to the

regulatory authority (e.g., FDA or National Cancer Institute) and the IRB. Sites should make sure that all protocol instructions from a sponsor are part of a written document, that only the currently approved version is being used, and that there is IRB approval for any procedures to be performed on human patients.

Second, the protocol must contain the method for determining the doses to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug. If the radiopharmaceutical is investigational, such as with ^{18}F-FLT or other PET research drugs, the protocol must define the dose that each patient will receive. The nuclear medicine technologist or investigator cannot alter any individual patient's dose without approval from the sponsor.

Third, the protocol definition includes a description of the observations and measurements to be made to fulfill the objectives of the study. If PET or SPECT is one of the measurements being made to fulfill protocol objectives, a description of the procedure should be included in the protocol. For practical purposes, sponsors often write a general description of the PET or SPECT procedure in the protocol (such as when and how often it should be performed and the dose of radiopharmaceutical to be used) and then include technical details in a separate manual. This allows the sponsor the flexibility to alter imaging parameters, if necessary, or to include site-specific instrumentation requirements, without requiring IRB approval such as with a protocol amendment.

FORM FDA 1572

Once a protocol is approved by the IRB, the investigator cannot make changes except by first notifying the sponsor, unless the changes are necessary to protect patient safety. Investigators agree to this condition when they sign Form FDA 1572. This form is a binding agreement with the FDA that the investigator will follow the protocol set up by the sponsor. The form states that subjects' right of refusal to participate in the study, right to receive treatment, and safety and welfare must be protected. The form also states that all investigational drugs must be used solely for the investigation and in accordance with the procedural protocol. Critical for medical imaging investigators is the agreement they make with the FDA and sponsor to conduct the studies in accordance with the relevant, current protocol and to make changes in the protocol only after notifying the sponsor, except when necessary to protect the safety, right, or welfare of the subject (*2*). In strong terms, this agreement with the FDA says that the site personnel will not change the protocol, including imaging parameters, unless the sponsor has been notified. The safety caveat allows a nuclear medicine department to change a protocol when the safety of the patient is paramount, such as an intervention due to an adverse event.

Form FDA 1572 is signed by the principal investigator and contains the following information (*2*): the name and address of the investigator; name and code number (if any) of the protocol in the Investigational New Drug application identifying the study to be conducted by the investigator; name and address of any medical school, hospital, or other research facility where the clinical investigation will be conducted; name and address of any clinical laboratory facilities to be used in the study; name and address of the IRB that is responsible for review and approval of the study; and names of subinvestigators (e.g., research fellows or residents) who will be assisting the investigator in the investigation.

Form FDA 1572 also includes a commitment that the investigator will conduct the study in accordance with the relevant, current protocols and will make changes in a protocol only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects; will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements; will personally conduct or supervise the described investigations; will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to informed consent (Title 21, part 50, of the *Code of Federal Regulations*) and IRB approval (Title 21, part 56, of the *Code of Federal Regulations*) are being met; will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with part 312.64; has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in helping the investigator meet the above commitments.

In addition, for an investigation that is subject to institutional review requirement under part 56, Form FDA 1572 includes a commitment by the investigator that an IRB that complies with the requirements of part 56 will be responsible for the initial and continuing review and approval of the clinical investigation, that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that the investigator will not make any changes in the research without IRB approval, except when necessary to eliminate apparent immediate hazards to human subjects.

All nuclear medicine physicians who participate in the trial by reading images, administering investigational product, or analyzing data should be listed on Form FDA 1572 as subinvestigators. Because nuclear medicine technologists can be such an integral part of collecting research data, some sponsors require that any technologist who will participate in the study be listed on Form FDA 1572 and that documentation of training and licensure be collected and submitted to the sponsor for regulatory filing. Some sponsors or institutions require listing of research nurses or physician assistants who conduct the informed consent

process or perform procedures on research patients. However, the most common practice is the inclusion of only physicians and scientists on Form FDA 1572.

PROTOCOL AMENDMENTS

Protocols can be changed through a formal process called an amendment. A protocol amendment is a written description of a change to or formal clarification of a protocol (*1*). Amendments are intentional prospective changes to a protocol. A sponsor may amend a protocol for new scientific data that have come in, or because the practical implementation of data collection requires the protocol to be altered. (For this reason, it is not uncommon to see protocol amendments after the first 1 or 2 patients are enrolled.) According to federal regulations, a sponsor must submit amendments describing any change that affects the safety of subjects in a phase I trial or that affect the safety, scope, or quality of the study in a phase II or III trial. Some examples of changes in a protocol that require amendments are, first, an increase of drug dose or change in duration of exposure of any individual subject to the drug; second, any significant increase in the number of subjects under study; and third, any significant change in the design of the protocol. In addition, an amendment is required for the addition of a new test or procedure that is intended to monitor safety, or the dropping of a test intended to monitor safety (*3*). From a practical level, a research protocol will be amended formally when there is any change to it.

A protocol amendment must be formally reviewed and approved by the IRB before the change can be implemented with patients. If the amendment is administrative or clerical, such as correction of typographic errors, approval by the IRB is not required; however, notification must be on file. Sometimes enrollment in a study can continue while the amendment is under review by the IRB; sometimes the amendment is of such importance that accrual to the study is halted until the amendment is approved. If the amendment includes any changes to procedures that a patient will undergo as part of the study, a change in the consent form will be included as well. Nuclear medicine technologists and investigators should confirm that the patient has signed the currently approved consent form and that the imaging procedure is in accordance with the currently approved protocol and amendments. A failure to perform the study under the most current version of the protocol, including approved amendments, is a serious infraction of clinical trial regulations.

REGULATORY REQUIREMENTS

Control of the investigational drug, whether it be the imaging tracer or the therapeutic agent, is a key focus of the FDA regulations. If an investigational radiopharmaceutical is being used in the trial, following protocol and adhering to the Form FDA 1572 agreement includes maintaining strict control of the investigational drug. Section 312.61 of the *Code of Federal Regulations* states that the drug will be administered only under the investigator's or a subinvestigator's personal supervision and that the investigator will not supply the investigational drug to anyone not authorized to receive it. In practice, that means that only those who are eligible for the clinical protocol and who have provided informed consent should receive the investigational product. If there is extra radiopharmaceutical in a production run, it cannot be used for nonresearch subjects or for any purpose other than what is stated in the protocol.

The investigator is required to keep drug accountability documentation. Most sponsors will provide drug accountability logs to be filled in by the radiopharmacy. These logs require entries for when the drug is received at the clinical site, how much is received, how much is dispensed, to whom and on what date it is dispensed, and what is done with the remaining product. (Sometimes these logs are created by a pharmacist for a traditional type of drug and need to be revised somewhat for a radiopharmaceutical.) Keeping a drug accountability log for an investigational radiopharmaceutical is in addition to all the record keeping that must be done for radioactive materials—simply keeping the dosing logs as per Nuclear Regulatory Commission or state requirements is not sufficient. At the completion of the trial or if the investigation is terminated for any reason, the investigational product has to be returned to the sponsor or destroyed. For radiopharmaceuticals, the typical disposition consists of allowing decay to background, discarding or destroying the nonradioactive vial, and documenting that disposal.

The sponsor of a clinical trial also has regulatory requirements with regard to the protocol. The sponsor is responsible for selecting only qualified investigators by way of education, training, and experience. Choosing investigators to conduct a clinical trial is done carefully by screening many names and institutions to find the most appropriate people and sites to be involved. To document this due diligence, a sponsor collects and reviews the curriculum vitae and medical license of every investigator and subinvestigator on the trial.

PROTOCOL DEVIATIONS AND VIOLATIONS

Deviations

Even when a site makes every attempt to follow a protocol exactly as prescribed, things can happen over which the site has no control (such as a blood sample being missed due to clotting of an intravenous line), and deviations can occur. A protocol deviation is defined as a variation from the processes or procedures defined in a protocol (*1*). The FDA inspection manual describes a deviation as "an unplanned excursion from the protocol that is not implemented or intended as a systemic change. . .[or] any other, unplanned instance(s) of protocol noncompliance" (*4*). Protocol deviations are usually described after an event occurs, such as if vital signs are missed or taken outside the window prescribed in the protocol. As the term is commonly used, a protocol deviation does not make all the patient's data ineligible for analysis and does not affect the safety of the human subject (as opposed to a more

serious deviation, referred to as a violation.) Sometimes an investigator will ask a sponsor before the event for permission to alter the protocol in a minor way because of logistic factors. A protocol deviation that has prior approval from the sponsor is sometimes referred to as a protocol exception or waiver. Just like a deviation, a protocol exception usually does not make the subject unevaluable and does not affect the safety of the subject. If a site requests a protocol exception or waiver, the site must receive permission in writing in order for the waiver to be considered granted.

One example of a protocol deviation is as follows: A research protocol requires that a patient's platelet count must be at least 150,000/mm^3 for the patient to be eligible for enrollment. An otherwise eligible subject presents with a platelet count of 149,000/mm^3, and no clinical issues result from the lower platelet count. The investigator, sponsor, and medical monitor agree that the laboratory values do not constitute a clinical risk to the patient, nor do they pose a risk to data integrity. The investigator can request a protocol exception and the drug company can grant the exception to enroll the patient in the study. This patient's data will still be evaluable because the medical monitor has determined that there is no additional risk to the patient's safety and well-being.

Here is a second example: The protocol requires that vital signs be taken every 15 ± 2 min after injection of the investigational radiopharmaceutical. At the 45-min time period, the patient is returning to the department after using the restroom, and the vital signs are taken at 50 min. The nuclear medicine technologist documents in writing the deviation that occurred and why it happened. The sponsor determines that the patient's data are still eligible for analysis and that the patient was not put in jeopardy by having the vital signs measured outside the prescribed window.

In general, it is important that clinical trial sites keep the number of protocol deviations as low as possible. Deviations are acceptable to the sponsor and from a regulatory standpoint when the clinical or technical situation is beyond the technologist's control. Whether protocol deviations must be reported to the IRB varies from institution to institution. Many IRBs require reporting of only those protocol deviations that affect safety measurements. For example, if a patient is supposed to have blood tests done to monitor the effects of the investigational drug and does not show up for the appointment, this may be a protocol deviation that is reportable to the IRB. Each site should carefully review its institution's requirements for reporting protocol deviations.

Protocol deviations should never be used by a nuclear medicine technologist or investigator to make the protocol easier, to conform to routine departmental procedures and therefore be easier to implement, or even to get better images, such as to theoretically improve resolution. Changes of this sort risk not only image standardization but also the reputation of the investigator and site with the sponsor.

Violations

Federal regulations do not distinguish between a protocol deviation and a violation, but the industry standard is to use the terms to differentiate between minor and serious protocol deviations. The term *protocol violation* is used to describe a significant departure from the processes outlined in the protocol or regulations. Protocol violations put data at risk for noninclusion into the study or potentially put the institution at risk for not following appropriate safety precautions. For the sponsor, a protocol violation represents a loss of data, time, and money. When protocol violations occur, the sponsor has a regulatory responsibility to investigate and provide additional training to site personnel so the violation is not repeated.

One example of a protocol violation is as follows: A technologist changes the technical parameters of the acquisition in an effort to improve image resolution but in doing so makes the data nonstandard with other sites. The data cannot be used in the study analysis, and to meet the statistical requirements of the study, patients must be added to the study.

Here is a second example: Study procedures are performed on a patient without patient consent. For example, a research ^{18}F-FDG PET scan is done on one day, and the consent form is signed a day later. This discrepancy in dates may result in this patient's data not being eligible for the trial. The informed consent process is the foundation for ethical research practices, and a practice of performing research on patients who are not properly given the opportunity to provide consent is a serious problem in the eyes of the IRB and the FDA.

When a deviation occurs, or if any imaging data are missing or inconsistent, a query or data clarification request or form may be sent by the sponsor or the sponsor's representative (e.g., core laboratory or contract research organization). A query or data clarification form does not necessarily indicate a deviation or violation; it may simply be a request for further information. If the query uncovers a deviation or violation, however, a protocol deviation form is usually sent to the site. Site personnel are then required to document why the deviation or violation occurred. Some sponsors require that the investigator sign all protocol deviation forms; some allow signature by the investigator's designee. Typically, however, when there is a protocol violation, the investigator will need to review and sign all documentation. A common example of a query in an imaging study is when the date of birth in an image header does not match other documentation such as in the case report form. A query allows the sponsor to confirm which date of birth is correct.

Avoiding Deviations and Violations

Avoiding protocol deviations and violations is a crucial part of being a good research site. Here are some methods that research sites have successfully used to keep deviations and violations to a minimum:

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- Have the imaging department provide education and written information to all imaging technologists in the department, even those who will not routinely be participating in the scanning of research patients. The clinical trial protocol may be different from the site's standard-of-care protocol. If a technologist is brought in to cover for a research technologist's lunch, illness, or vacation, the covering technologist will have to been alerted to the study requirements. It is advantageous for a site to have multiple imaging technologists trained on the protocols to follow for patients in clinical trials.
- Keep a copy of all source documents in the department records. The sponsor will often supply source documentation worksheets that are standardized from patient to patient and from site to site.
- Keep a copy of the protocol and technical manual within the department, in addition to providing one to each technologist.
- Take the opportunity, at routine staff meetings, to reinforce the importance of image standardization in clinical trials and the consequences of nonstandard image data.
- Create a procedure flow sheet or checklist that includes all pertinent protocol information to help keep all imaging staff organized, if the sponsor does not provide such an aid.
- Remind the staff to review all study documentation at least 1 d before the patient's arrival. There may be months between individual patients on a study if the patient population has a rare condition or if the study entry criteria are strict. Technologists should not rely on memory for details of the protocol.
- Have imaging staff identify all research patients even if the study protocol is just the standard of care (i.e., the parameters for imaging are the same as what is done for daily clinical patients.) Identification of study patients will ensure that study-related worksheets and forms are completed.
- Ensure that the front desk staff or scheduling staff is aware of the protocol, the patients who are scheduled for research, any special patient preparation instructions, any additional time constraints due to the research, and any relevant information about specimen collection and handling.
- Have the imaging department design a procedure to notify the technologists when a trial participant is scheduled to have a scan. The technologist will then have time to perform any mandatory quality control before the scan. The procedure should also include a way of identifying the participant upon arrival on the day of the scan.
- Establish good communication between the imaging department and the clinical department staff, especially if the principal investigator is not a nuclear medicine physician but instead is an oncologist, cardiologist, or other specialist. Develop a routine channel of communication for research-related information, such as setting up routine clinical meetings or inviting representatives of the clinical department to imaging staff meetings. Improvements in routine communication will also improve protocol-related communication.
- Schedule a radiation safety training session for clinical staff who are unused to working with imaging protocols but are interested in learning how to handle radioactive specimens or are in contact with study participants who have been injected with an isotope.
- Teach nonnuclear research staff about imaging procedures to help them better describe those procedures to potential patients and therefore improve patient compliance with the study.

Minimizing protocol deviations is crucial once a study has begun; however, before the study is even open for enrollment, working with the sponsor can help nuclear medicine personnel prepare for optimal performance. Here are some things that successful imaging research sites have learned:

- Meet with the sponsor before agreeing to participate as a site in the trial. Determine whether you have the equipment to meet the protocol specifications and the staff to perform all the study-related duties. If the preliminary protocol documentation does not provide enough information for you to make a decision, ask detailed questions to get the information you need.
- If the sponsor (or a contract research organization hired by the sponsor) asks you to complete a protocol-specific application regarding site personnel and equipment, complete and return the application as soon as possible in order to quickly resolve any questions.
- Ask about any special phantoms or quality control procedures that may be involved in the study. Such extra procedures may be time consuming and should be part of your decision about whether to participate.
- Determine whether the nuclear medicine department will be responsible for procedures such as performing electrocardiograms, checking vital signs, taking blood samples, and performing physical examinations. If so, determine whether you have sufficient staff, expertise, and resources to perform these tasks.
- Ask whether there are scanner qualification requirements for participation in a study. To avoid potential duplication of efforts, make sure the sponsor is aware if you are a member of the Clinical Trials Network, are accredited by the Intersocietal Commission on Accreditation of Nuclear Laboratories or the American College of Radiology, or have participated in studies sponsored by the American College of Radiology Imaging Network.
- Determine whether you have access to the investigational radiopharmaceutical that is being studied and whether you are capable of performing any additional radiopharmacy duties that may be required on site, such as preparing a unit dose or performing quality control.

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- If urine or blood collections are required, determine who will be responsible for handling the specimens. If nuclear medicine staff will be responsible, make sure you have space for storage of materials, expertise in handling, and proper equipment for analysis. Does radiation safety need to be involved if radioactive urine or blood samples are being stored?
- Ask about image data transfer. Will the sponsor require secure file transfer protocols over the Internet, and does your institution allow passage of patient data through its firewall? Will information technology personnel or hospital administration need to be involved in order to grant permission for data transfer? If data are to be collected onto a compact disk, does your imaging equipment allow for transfer and storage onto a compact disk?
- Ask about protected health information. Will the nuclear medicine department be required to mask all data as to patient identity before transfer, or can masking be done at a core laboratory or contract research organization?
- Ask about how quickly data will need to be transmitted. If the sponsor requires data to be submitted within 24 h of imaging, will your site be able to reasonably accomplish that?
- Ask about what data need to be submitted. Attenuation-corrected and noncorrected? Raw data and processed data? Do the data have to be labeled in a specific way?
- Ask to review the source document worksheets or case report forms before the study begins so that the staff can be trained on what information is required for each patient. Data that may be required on a case report form can include scan date, dose assay time (before and after injection), net administered activity (possibly decay-corrected), time of injection, and scan start and end times. The accuracy of this information is vital and will be part of the sponsor's quality control process.

CONCLUSION

As has been illustrated in this article, "following the protocol" is not a simple instruction. Nuclear medicine technologists and investigators should be aware of regulations involving clinical trials and sponsors' expectation of compliance. Protocol deviations and violations should be minimized in order to produce standardized image data and honor the investigator's commitment as stated on FDA 1572. The consequence of not following protocol specifications on any given trial is increased cost and increased time to completion. The general consequence of not following protocol specifications in molecular imaging trials is a lack of confidence in PET for measurement of therapeutic efficacy. By using the suggestions in this article, and seeking education and training on clinical trial regulations, nuclear medicine technologists and investigators can produce high-quality standardized research data. These standardized data will lead to reliable information about the efficacy of therapeutic interventions. Ultimately, patients will be served by more and better therapies for cancer, heart disease, Parkinson disease, and many other illnesses.

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