SNMMI Clinical Trial Network Research Series for Technologists: Application of Good Clinical Practice to Clinical Research in Medical Imaging

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This article is part of a series developed by the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging to offer training and information for molecular imaging technologists and researchers about various aspects of clinical research. This article covers the topic of good clinical practice and how that relates to those portions of the *Code of Federal Regulations* that govern clinical research in the United States, such as title 21, part 312, and the Common Rule. The purpose of this article is to inform technologists and researchers about standard roles, documents, guidance, and processes that are elemental to the conduct of clinical trials and to offer additional resources for learning about these processes.

Key Words: good clinical practice; ICH E6; clinical research

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Participating in sponsored research trials is an exciting part of being a nuclear medicine or PET imaging technologist today. As described in an earlier article in this series, by Jeffers et al. (*1*), molecular imaging is a key part of the new-drug discovery paradigm that uses biomarkers and radiopharmaceutical products to answer critical questions on the pathway to development and approval of a new therapeutic drug. Nuclear medicine and PET technologists play a critical role in collecting research data in the form of patient scans, as well as safety data such as vital signs or pharmacokinetic data with blood sampling. This article will highlight aspects of good clinical practice (GCP) and federal research regulations that molecular imaging researchers and technologists should be aware of when planning and conducting research involving human subjects. The paper's focus is on drug development and use of molecular imaging as biomarkers, although the principles discussed are applicable to any clinical trial setting.

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GCP

GCP refers to a prescribed set of quality and ethical standards for how to plan, conduct, and document research involving human subjects. Compliance with the standards described in the GCP framework ensures that the rights, safety, and well-being of human subjects involved in research are protected and that the resulting research data are rigorous and have reliability and integrity.

A document on GCP is published by an organization called the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH publishes standards that cover topics in the categories of quality, safety, and efficacy in clinical trials. The collection of guidelines in the efficacy category contains 20 subjects, including topics such as pharmacovigilance, clinical study reports, dose–response studies, statistical principles, and GCP. The GCP publication, coded as E6 (an abbreviation for the sixth report in the efficacy section) in the ICH guidelines, was revised in 2016 and is officially entitled "Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice—E6(R2)." At the time of this writing, the ICH has drafted version R3, which is targeted for adoption in August 2023. The GCP publication and other ICH publications are easily found online with an internet search and are recommended reading for anyone interested in learning more about clinical research (*2*).

The ICH is an international consensus organization in which the U.S. Food and Drug Administration (FDA), European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, and other drug regulatory authorities

such as the Departments of Health of Australia, Brazil, China, Taipei, India, Russia, Singapore, and South Korea all have permanent representatives (*3*).

In addition to the international GCP standard, there are several sections in the *Code of Federal Regulations* (CFR) that govern human subject research in the United States and are aligned with GCP (*4*). The testing of investigational new drugs on human subjects is governed by title 21 of the CFR, part 312 (referred to as 21CFR§312) (*5*). Radiopharmaceuticals can also be used without an investigational-new-drug application in certain cases, such as when they meet the provisions for use under approval of an institutional radioactive drug research committee as defined in 21CFR§361 (*6*). Regulations for testing medical devices on human subjects are found in 21CFR§812 (*7*). Other types of research that do not involve an investigational drug or device, such as behavioral research or clinical trials with U.S. military personnel, are governed by 45CFR§46 under the Department of Health and Human Services (*8*). Protection of human subjects by the creation of institutional review boards (IRBs) and the informed consent process is found in 21CFR§50 and §56, respectively (*9,10*). An overview of the investigational-new-drug process and regulations can be found in a previous paper in this series (*11*).

GCP and federal regulations governing clinical research are applicable to all human subject research, including studies that use investigational radiopharmaceuticals for diagnosis or treatment, or approved radiopharmaceuticals used for screening, for monitoring therapy, or as biomarkers of a disease process. More information about various types of studies that use radiopharmaceuticals can be found in a previous paper in this series (*1*). Data resulting from the use of a molecular imaging biomarker in a study to investigate a new therapeutic are subject to levels of scrutiny similar to those for any other clinical trial data. GCP and federal research regulations are designed not only to protect patient privacy and safety but also to ensure that data are collected, documented, and reported with scientific rigor and quality.

COMMON RULE

Human subject research that is not for registration of a new drug or device is regulated by federal policy 45CFR§46, subpart A, which is known as the Common Rule (*12*). Subpart B of the federal policy includes additional protections for pregnant women, human fetuses, and neonates; additional protections are included in subpart C for prisoners and subpart D for children, both of whom are considered vulnerable populations (*13,14*).

More than 15 separate federal agencies have linked 45CFR§46 to their regulations, binding any of their research efforts in humans to the same regulatory statute. For all participating departments and agencies, the Common Rule outlines the basic provisions for IRBs, informed consent, and assurances of compliance (*15*).

The Department of Health and Human Services website provides educational videos, frequently asked questions, and other information about how recent changes in the Common Rule, effective in 2019, impact academic research centers (*16*). As with 21CFR§312, GCP is aligned with the Common Rule, and regulators expect researchers and staff to be compliant with both the current regulations and GCP principles.

KEY ROLES IN CLINICAL RESEARCH

Drug development research that uses molecular imaging for screening, diagnosis, monitoring of therapy, or as a biomarker is subject to the rules found in both 21CFR§312 and the GCP framework, as are the key roles and responsibilities.

Sponsor

The sponsor of a clinical trial is the person or entity that holds regulatory accountability for conduct of the trial. This is often, but not always, the same entity as the one that financially supports the research (e.g., a pharmaceutical company). Sponsors can be an individual person, pharmaceutical company, academic institution, government agency, or other organization. A sponsor initiates and is responsible for a clinical investigation but does not conduct trial activities unless the sponsor is a sponsor–investigator. Pharmaceutical sponsors typically contract with investigators (medical experts on the disease or condition under study) to conduct the trial. Sponsors have clearly defined responsibilities cited in GCP and 21CFR312§50. These responsibilities include selecting qualified investigators and providing them with all the information they need to conduct the investigation safely and properly; ensuring that the investigation is properly monitored; ensuring that the investigation is conducted in accordance with the investigational plan in the investigational-new-drug application, as well as with all protocols therein; maintaining an effective investigational-new-drug application with respect to all clinical trials; and promptly informing the FDA and all participating investigators of significant new adverse effects or risks (*17,18*).

Contract Research Organization (CRO)

A CRO is an entity that can be hired by the sponsor to conduct various aspects of the trial on the sponsor's behalf (*17*). A sponsor is allowed to transfer, in writing, any or all obligations described in 21CFR§312. Once the CRO assumes these obligations, the CRO is subject to the same regulatory oversight and action as the sponsor (*19*). In molecular imaging trials, it is common for a sponsor to engage an imaging CRO to work with nuclear medicine departments to obtain protocol-required scan data. An imaging CRO has personnel with specialized experience and knowledge in medical imaging, as well as in how to obtain, transfer, analyze, and archive image data used in clinical trials. CROs exist that can perform many functions in a clinical trial, such as laboratory testing, safety monitoring, statistics, cardiac monitoring, protocol development, and study monitoring.

Investigator

An investigator is an individual who conducts the clinical trial, or under whose direct supervision the trial activities are performed, and who is qualified by training and experience to perform the protocol procedures and ensure the safety of subjects. The investigator, often referred to as the principal investigator (PI), is the responsible team leader in a group of people who are conducting a trial. The PI is most commonly a medical doctor, but can also be a PhD, dentist, psychologist, osteopath, or another licensed professional such as a radiochemist or medical physicist, who is qualified by training and experience to conduct the research (*17*). Other individuals who work on the clinical trial team are referred to as subinvestigators per 21CFR§312.3 (*20*).

Although the sponsor holds responsibility for choosing qualified and trained investigators, the PI is responsible for ensuring that the clinical trial is conducted according to the protocol. The PI is also responsible for protecting the rights, safety, and welfare of patients in the trial; for obtaining informed consent from each person who receives the investigational drug; and for ensuring that any protected health information is handled in a compliant fashion. The PI is responsible for control of the investigational drug by keeping adequate records and by administering the investigational product only to subjects who are under the PI's personal supervision (or under the supervision of a subinvestigator) and who have consented to participate in the study (*17,21*). When a nuclear medicine technologist is responsible for injecting an investigational radiopharmaceutical, the technologist's name should be listed on the delegation-of-authority log, which is described later in this paper.

Investigators are responsible for preparing and maintaining accurate case histories (*17,22*) for all subjects in a clinical trial, whether the subject is receiving the investigational drug or serving as a control subject. This case history includes case report forms (CRFs) (often provided by the sponsor), hospital and progress notes, source documents, follow-up reports, and other records. The case history for every individual in the trial must document that informed consent had been obtained before any research procedures were performed, including but not limited to scans or lab tests. If molecular imaging is being used as a screening procedure for a trial involving an investigational drug, it is imperative that the informed consent be signed and on file before injection of any radiopharmaceutical (*17,23*).

Study Coordinator

The study coordinator, or clinical research coordinator, works under the direct supervision of the PI at the investigational site. This role is sometimes referred to as a clinical coordinator or as a study nurse when applicable. The study coordinator must be knowledgeable about GCP and research regulations and typically has some form of health-care training such as in nursing, radiology, or medical assistance. The study coordinator can assist with a myriad of administrative, clinical, regulatory, and documentation duties (*24*).

There are 2 major professional organizations that support, educate, and certify clinical research coordinators: the Association of Clinical Research Professionals (https://acrpnet.org/) and the Society of Clinical Research Associates (https://www.socra.org/). Certification by 1 of these 2 organizations indicates to an investigator and potential sponsor that an individual is trained in GCP and research regulations and has experience in the conduct of clinical trials.

Clinical Research Associate

A clinical research associate, or monitor, is hired by the sponsor or CRO to ensure that a clinical study is conducted according to the protocol and that the PI fulfills all responsibilities to the IRB, trial, and patients. Clinical research associates perform the work of monitoring, but they also may be involved in protocol writing, site selection, recruitment strategies, medical writing, and more. To monitor a clinical trial means to work directly with a research site and PI to oversee the conduct of the trial, ensuring that protocols are followed and that subjects' safety and privacy rights are protected. Monitors compare case report forms against source documents, ensure that written informed consent is documented for each subject before any study procedures take place, enquires about discrepant data points, and reviews the drug accountability log for omissions or errors, as well as performing other tasks. Monitors also conduct the study-initiation and close-out visits; provide protocol-specific training for the PI, subinvestigators, and other staff involved in research; and confirm that all participants in research activities are trained in GCP. Remote monitoring, or review of documentation electronically without travel to the research site, is more common now because of the impact that the coronavirus disease 2019 pandemic has had on in-person site visits. In a guidance document published by the FDA in March 2020 about the impact of the pandemic on clinical trials, the FDA encouraged sponsors to "consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites" (*25*).

IRB

The IRB is a requisite component for research involving FDA-regulated clinical studies. The IRB, whose purpose and makeup are described in 21CFR§50 and §56, is formally designated to review and monitor biomedical research involving human subjects (*9,10*). Additional information about the IRB can be found in an earlier paper in this series (*26*).

KEY DOCUMENTS IN CLINICAL TRIALS

Participation in clinical research activities requires knowledge of the key documents used to verify adherence to protocol procedures and regulations and to ensure the safety of subjects. The following documents are discussed in this article: protocol, form FDA 1572, imaging charter/manual, investigator's brochure (IB), CRF, source document, informed-consent form, drug accountability log, and delegation-of-authority log. Recording of adverse events is also discussed, and additional resources are provided.

Protocol

A protocol is a document that describes the objectives, design, methodology, statistical considerations, and organization of the trial (*1*). According to 21CFR§312, a protocol document must contain the following elements: a statement of the objectives (often referred to as endpoints) 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; the name of each subinvestigator working under the supervision of the PI; the name and address of the research facilities to be used; the name and address of each reviewing 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; and a description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug on human subjects and to minimize risk.

The term *protocol* is commonly used in imaging departments to describe the dose, injection, scanning, and processing protocols for an imaging procedure. In clinical research, especially pharmaceutical research, scanning details are typically not in the study protocol but are in a separate document referred to as an imaging charter or imaging manual.

Form FDA 1572

Form FDA 1572 is a statement that includes a commitment that the investigator will conduct the study in accordance with the relevant, current protocols and will make changes to a protocol only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects; will comply with all clinical investigator obligations and other pertinent requirements; will personally conduct or supervise the investigations; will inform any potential subjects that the drugs are being used for investigational purposes and ensure that the requirements on informed consent (21CFR§50) and IRB approval (21CFR§56) are being met; will report to the sponsor any adverse experiences that occur (21CFR§312.64); has read and understands the information in the IB, including the potential risks and side effects of the drug; and will ensure that all associates, colleagues, and employees assisting with the study are informed about their obligations in helping the investigator meet this commitment (*27,28*).

All nuclear medicine physicians who participate in the trial by reading images, administering investigational products, 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 participates in the study be listed on form FDA 1572 and that training and licensure be documented and submitted to the sponsor for regulatory filing. Some sponsors or institutions also require listing of research nurses or physician assistants who obtain the informed consent.

Additional information about protocol amendments, deviations, and variations; form FDA 1572; and practical advice on how to maximize compliance with the protocol can be found in a previous publication (*29*).

Imaging Charter

An important document for molecular imaging researchers and technologists to be aware of is the imaging charter (sometimes referred to as an imaging manual or technical manual). This document contains detailed instructions, usually not provided in the study protocol, that describe how, when, and with what parameters research subjects should be imaged to ensure standardization and harmonization of imaging results. The FDA published a guidance document in 2018, "Clinical Trial Imaging Endpoint Process Standards Guidance for Industry," that suggests what a sponsor should include in an imaging charter or manual (*30*). This guidance document, although written for sponsors of clinical trials, helps molecular imaging researchers and technologists understand the broad scope of considerations that go into designing an imaging protocol to test a drug.

Several standards are recommended for inclusion in an imaging charter. One standard is equipment standardization and optimization, including vendor-specific equipment and platforms; equipment technical settings to be used at each site; the role of technologists in the imaging process; phantoms to be used for site qualification and monitoring of quality; subject preparation, positioning, and comfort measures; schedules for imaging, off-protocol imaging; imaging risks; the site qualification process; acquisition quality control and monitoring; and data storage and transfer. Another standard is for the imaging drug, such as preparative drugs, contrast agents, and radiopharmaceutical agents, and a third standard is for image interpretation, including image display, selection of images for interpretation, randomization for the central read process, imaging CRFs, and quality control of display and interpretation, among others.

For study protocols that implement a central read process (vs. an interpretation by the nuclear medicine physician at the research site), the guidance document offers advice on identifying readers and their background qualifications, training readers for the protocol, timing reads, and determining the read process or methodology to be used (*30*).

IB

The IB, or investigator's drug brochure, is critical for any investigator in a clinical trial to read and understand. Per the GCP guidelines, "The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the

investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration[,] and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial." (*17*). The IB is updated annually by the sponsor and reissued to all investigators. It is critical to review the IB for any changes in the safety profile of the drug. For example, if there has been a significant increase in side effects or adverse events, the consent language may require revision (*31*).

CRF

CRFs and *source documents* are terms that are often mistakenly used interchangeably, but each has a specific purpose, and both are needed. A CRF is a physical document or an electronic document or repository that contains the records and results from all observations and clinical procedures that are performed to monitor the effects of the investigational drug in humans and to fulfill the objectives of the study. The investigator records all study data onto subject-specific CRFs and submits them to the sponsor for analysis of data across subjects and investigational sites. Per GCP, "data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained" (*17*).

Source Documents

Source documents are the original location of data that is subsequently recorded into a CRF. The first place that data are generated is considered the source. Source documents can be medical records, forms that are filled out by the trial personnel, or pieces of paper on which data are recorded. GCP requires that all information on a CRF be verified from a source document (*17*). Digital data can be a source document if they are the first output of data from a test, such as an electrocardiogram recording or DICOM (Digital Imaging and Communications in Medicine) headers in a PET scan (*32*). One key role of a monitor is to compare data entries in the CRF with the original data from the source. When there is a discrepancy, the monitor asks the investigator to clarify which data are correct. For example, if a CRF states that the scan start time is 12:07 but the PET scan DICOM header says the scan started at 12:12, a monitor will flag that discrepancy. The monitor writes to the investigator to ask which was the correct start time. In another example, if a blood pressure measurement was entered into a CRF as 120/80 but the hospital chart notes that it was 122/80, a monitor will ask the investigator for clarification and correction. This clarification is required even if the discrepancy results in a measurement that is considered within normal limits and might not be clinically meaningful to patient care.

Trials using radiopharmaceuticals will often take advantage of the ability to measure radioactivity in samples of blood or urine. Analog data from a well counter that prints out a strip of numbers should be annotated with the date, time, subject identification number, and what sample is represented by the number (e.g., 5-min plasma). Because ink from analog printouts is prone to fading over time, it is recommended that the technologist make a certified copy of the source document for clarity and accessibility in any future regulatory inspection.

Informed-Consent Form

The informed-consent form is a protocol-specific document that describes to a patient what the study entails, what procedures will take place, and what the risks of study participation are. This document, the required content of which is defined in 21CFR§50.25, must be signed by patients before they undergo any study procedures and indicates that they understand the study and have consented to participate. An appropriate translation must be provided to nonnative English speakers if needed, and accommodations must be made for subjects incapable of giving consent themselves (e.g., medical power of attorney for dementia patients). The informed-consent document is reviewed by the IRB to ensure an adequate explanation of risks (including any anticipated radiation dose or exposure from the diagnostic or therapeutic procedures) and potential benefits. For clinical trials in which molecular imaging is part of a therapeutic study, the informed-consent process is conducted by PIs or their representatives, and the imaging department will probably not see it or be involved. For studies in which a radiopharmaceutical is the investigational agent, the imaging staff may be involved in the consent process or be responsible for ensuring that no study procedures are performed before the patient signs the informed-consent form. More information about the importance of the informed-consent process can be found on the FDA website, which has helpful information for patients and a guidance document for sponsors and researchers (*33*).

Drug Accountability Log

The investigator is responsible for the control of all investigational drugs in a study per GCP and 21CFR§312.62. To facilitate that control, and document how and when each dose of an investigational product is administered, a drug accountability log should be used. This log is typically provided by the sponsor and maintained by the department or entity that administers the investigational product (e.g., the dispensing nuclear pharmacy). For therapeutic investigational drugs, often this is a hospital pharmacy. For studies in which the radiopharmaceutical is investigational, the imaging department may be responsible for tracking receipt, administration, decay, and disposal each time a subject is administered a dose. Even though administration of radioactive materials is carefully documented via dose-ordering systems in a nuclear medicine department, a drug accountability log for investigational radiopharmaceuticals is required above and beyond departmental dose records. At the completion of a clinical trial or if the investigation is terminated for any reason, the

investigational product must be either returned to the sponsor or destroyed. For radiopharmaceuticals, the typical disposition consists of allowing decay to background levels, discarding or destroying the nonradioactive vial, and documenting that disposal. Sometimes a sponsor will request that disposal of the nonradioactive vial be done in the presence of a clinical research associate or monitor, in which case vials should be stored for the length of the trial (*17,21*).

Delegation-of-Authority Log

Although the PI is ultimately responsible for everything that happens in a clinical trial, for practical reasons many of the protocol tasks are delegated to qualified and trained individuals. GCP advises in section 4.6.2 of the guidance, "If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated" (*17*). To document that the PI has ensured that only qualified personnel are performing protocol-required tasks, a delegation-of-authority log is often used even though it is not specifically required in 21CFR§312. A delegation-of-authority log maintains a record of which specific tasks and procedures are delegated by the PI and to whom they are delegated. For example, the log may state that a named study coordinator is delegated the responsibility for initiating the informed-consent process, that a named nurse is delegated the responsibility for taking vital signs per the protocol, or that a named nuclear medicine technologist is delegated the responsibility for injecting an investigational radiopharmaceutical. Delegation logs typically require an individual's full name in legible print, signature and initials, job title or role in the study, and dates of study involvement. The PI's signature on the delegation log is an attestation that the PI approves authorization of these individuals to perform the stated tasks. Updates to the delegation-of-authority log due to staff departure from or entrance into the study should be documented and a new signature from the PI obtained. A good example of a delegation-of-authority log can be found on the National Center for Complementary and Integrative Health website (*34*).

Adverse-Event Reporting

Imaging departments contribute key data to the developing picture of an investigational drug's side effects, especially when the drug is a radiopharmaceutical. Not every adverse event must be reported, but every adverse event must be recorded in a source document and CRF for review and subsequent determination of causality by the sponsor in conjunction with the PI. Although a detailed discussion of adverse-reporting definitions and procedures is beyond the scope of this article, it is recommended that imaging technologists and researchers have a clear understanding of their role in monitoring patients for adverse effects, how to document them, and when to report them to the sponsor or IRB. Individuals who are unsure of their role in recording adverse events in a sponsored trial should reach out to the sponsor or the sponsor's representative for clarity. More information on adverse event reporting in a clinical trial can be found in the FDA's draft guidance document "Investigator Responsibilities: Safety Reporting for Investigational Drugs and Devices—Guidance for Industry" (*35*).

CONCLUSION

This article has reviewed GCP definitions and application of its principles to clinical trials that use molecular imaging, as well as presenting key roles, documents, and procedures essential for clinical trial work. Relevant references to the CFR and additional sources of information have been provided when applicable.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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