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

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ABSTRACT

This manuscript is part of a series developed by the Clinical Trials Network (CTN) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 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 the Code of Federal Regulations that govern clinical research in the US such as 21CFR§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

INTRODUCTION

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., 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 for development and approval of a new therapeutic drug *(1)*. Nuclear medicine and PET technologists play a critical role in collecting research data in the form of patient scans as well as safety data like vital signs and/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 principles discussed are applicable to any clinical trial setting.

GOOD CLINICAL PRACTICE

Good Clinical Practice is a term that 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 GCP framework assures that the rights, safety, and well-being of human subjects involved in research are protected, and that the resulting research data is rigorous and has reliability and integrity.

Often referred to by the acronym GCP, Good Clinical Practice is a document published by an organization called the ICH, which stands for International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 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 twenty 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 6th 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. GCP 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 US Food and Drug Administration (FDA), European Medicines Association, Japan Pharmaceuticals and Medical Devices Agency (PMDA) and other drug regulatory authorities such as 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) which govern human subjects research in the United States and are aligned with GCP *(4)*. The testing of investigational new drugs in human subjects is governed by Title 21 of the Code of Federal Regulations, Part 312 (referred to as 21CFR§312) *(5)*. Radiopharmaceuticals can also be used without an Investigational New Drug (IND) 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 with 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 United States military personnel, are governed by 45CFR§46 under the Department of Health and Human Services *(8)*. Protection of human subjects by development of Institutional Review Boards and the informed consent process are found in 21CFR§50 and §56, respectively *(9,10)*. For an overview of the Investigational New Drug process and regulation, refer to 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, monitoring therapy, or as biomarkers of a disease process. For more information about various types of studies that use radiopharmaceuticals, refer to 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 is subject to similar levels of scrutiny as any other clinical trial data. GCP and federal research regulations are not only designed to protect patient privacy and safety but are in place to ensure that data is collected, documented, and reported with scientific rigor and quality.

COMMON RULE

Research using human subjects that is not for registration of a new drug or device is regulated by federal policy 45CFR§46, Subpart A of which is known as the Common Rule *(12)*. Subpart B of the federal policy includes additional protections for pregnant women, human fetuses, and neonates, while Subpart C includes additional protections for prisoners and Subpart D for children, all 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, FAQs, and other informational material about how recent changes in the Common Rule, effective in 2019, impact academic research centers *(16)*. As with 21CFR§312, Good Clinical Practice is aligned with the Common

Rule and regulators expect that researchers and staff are compliant to both the current regulation 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 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 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 they are a sponsor-investigator. Pharmaceutical sponsors typically contract with investigators (medical experts in the disease or condition under study) to conduct the trial. Sponsors have clearly defined responsibilities cited in GCP and 21CFR312§50 which 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 contained in the IND application, as well as all protocols therein
- Maintaining an effective IND with respect to all clinical trials

- Promptly informing the FDA and all participating investigators of significant new adverse effects or risks *(17,18)*.

Contract Research Organization

Contract Research Organization (CRO) is an entity that can be hired by the Sponsor to conduct various aspects of the trial on the Sponsor's behalf *(19)*. 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 *(20)*. 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 how to obtain, transfer, analyze, and archive image data used in clinical trials. Contract research organizations 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 safety of subjects. The investigator, often referred to as the principal investigator or PI, is the responsible team leader in a group of people who are conducting a trial. They are most commonly a medical doctor, but can also be a PhD, dentist, psychologist, or osteopath, or another licensed professional such as a radiochemist or medical physicist, that is qualified by training and experience to conduct the research *(21)*. Other individuals who work on the clinical trial team are referred to as subinvestigators per 21CFR§312.3 *(22)*.

While the sponsor holds the 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 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 only administering the investigational product to subjects who are under their personal supervision (or under supervision of a subinvestigator) and who have consented to participate in the study *(23,24)*. When a nuclear medicine technologist is responsible for injecting an investigational radiopharmaceutical, their 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** *(25,26)* for all individuals who participate as a subject in a clinical trial, whether receiving investigational drug or as a control subject. This case history includes case report forms (often provided by the sponsor), hospital/progress notes, source documents, follow up reports, and other records. The case history for every individual in the trial must document that informed consent was obtained prior to any research procedures being 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 is signed and on file prior to injection of any radiopharmaceutical *(27,28)*.

Study Coordinator, Clinical Research Coordinator

Study Coordinator or Clinical Research Coordinator works under the direct supervision of the principal investigator at the investigational site. This role is sometimes referred to as a clinical coordinator, or study nurse when applicable. The study coordinator must be knowledgeable about GCP and research regulations, and typically has some form of healthcare training such as nursing, radiology, medical

assistant, etc. The study coordinator can assist with a myriad of administrative, clinical, regulatory, and documentation duties *(29)*.

There are two major professional organizations which support, educate, and certify clinical research coordinators: the Associate of Clinical Research Professionals (ACRP) *(30)* and the Society of Clinical Research Associates (SOCRA) *(31)*. Certification by one of these two organizations is an indication to an investigator and potential sponsor that you are trained in GCP and research regulations and have experience in the conduct of clinical trials.

Clinical Research Associate, Monitor

A Clinical Research Associate (CRA) or monitor is hired by the sponsor (or CRO) to ensure that a clinical study is conducted according to the protocol, and that the principal investigator is complying with their responsibilities to the IRB, trial, and patients. CRAs 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 protocol procedures are followed, and that subjects' safety and privacy rights are protected. Monitors review case reports forms against source documents, ensure that each subject has documented written informed consent in place prior to any study procedures taking place, issues queries for discrepant data points, reviews the drug accountability log for omissions or errors, as well as other tasks. Monitors also conduct study initiation and close-out visits, provide protocol-specific training for the PI, subinvestigators, and other staff involved in research, as well as confirming that all participants in research activities are trained in Good Clinical Practice. Remote monitoring, meaning reviewing documentation electronically without travel to the research site, is more common now because of the impact of the Covid-19 pandemic 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" *(32)*.

Institutional Review Board

The Institutional Review Board (IRB) is a requisite component for research involving FDA-regulated clinical studies. This review board, whose purpose and make-up are described in 21CFR§50 and §56, is a group that has been formally designated to review and monitor biomedical research involving human subjects *(9,10)*. For additional learnings about the IRB, please refer to an earlier paper in this series *(33)*.

KEY DOCUMENTS in CLINICAL TRIALS

Participation in clinical research activities requires knowledge of the key documents that are used to document protocol procedures, adhere to regulations, and ensure safety of subjects. The following documents are discussed: protocol, Form FDA 1572, imaging charter/manual, investigator's brochure, case report form, source document, informed consent form, drug accountability log, and delegation of authority log. Adverse event recording is mentioned, 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). 21CFR§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 proposed objectives are often referred to as endpoints.

- The name and address and a statement of the qualifications of each investigator, the name of each subinvestigator working under the supervision of the principal investigator(s), the name and address of the research facilities to be used, and the name and address of each reviewing Institutional Review Board (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.

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 contained in a separate document referred to as an Imaging Charter or Imaging Manual.

Form FDA 1572 Statement of Investigator

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 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 (21CFR§50) and IRB approval (21CFR§56) are being met; will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21CFR§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 *(34,35)*.

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 also require listing of research nurses or physician assistants who conduct the informed consent.

For additional information about protocol amendments, deviations and variations, Form FDA 1572, and practical advice on how to maximize compliance to the protocol, refer to Trembath and Opanowski, "Clinical Trials in Molecular Imaging: The Importance of Following the Protocol" *(36)*.

Imaging Charter, Imaging Manual

One of the most relevant documents 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. FDA published a guidance document in 2018, "Clinical Trial Imaging Endpoint Process Standards Guidance for Industry", that contains suggestions about what a sponsor should include in an Imaging Charter or manual. This guidance document, while written for sponsors of clinical trials, is useful for molecular imaging researchers and technologists to understand the broad scope of considerations that go into designing an imaging protocol to test a drug. The following standards are recommended for inclusion in an imaging charter:

- Equipment standardization and optimization, including vendor-specific equipment/platforms, equipment technical settings to be used at each site, role of the imaging 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, site qualification process, acquisition quality control and monitoring, data storage and transfer.
- Imaging drug standardization, such as preparative drugs, contrast agents, and radiopharmaceutical agents
- Standards for image interpretation, including image display and interpretation, selection of images for interpretation, randomization for central read process, imaging case report forms, quality control of display and interpretation, etc.

For study protocols that implement a central read process (verses an interpretation by the nuclear medicine physician at the research site), the guidance document offers advice on identifying readers and their background qualifications, reader training for the protocol, timing of reads, the read process or methodology to be employed *(37)*.

Investigator's Brochure, Investigator's Drug Brochure

The Investigator's Brochure (IB), or Investigator's Drug Brochure (IDB) is a critical document 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 the 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" *(38)*. The IB is updated annually by the sponsor and re-issued 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 *(39)*.

Case Report Forms

Case report forms (CRF) and source documents are terms that are often mistakenly used interchangeably, but they each have a specific purpose, and both are needed. A case report form is a document or an electronic document/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 case report forms and submits these CRFs to the sponsor for analysis of all clinical trial 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" *(40)*.

Source Documents

Source documents are the original location of data that is subsequently recorded into a CRF. The first place that data is generated is considered the source. Source documents can be medical records, forms that are filled out by the trial personnel, pieces of paper where data is recorded. GCP states that all information on a case report form must be verified from a source document *(40)*. Digital data can be a source document if it is the first output of data from a test, such as an electrocardiogram (EKG) recording or DICOM headers in a PET scan *(41)*. One of the key roles of a monitor is to compare data entries in the CRF to the original data from the source. When there is a discrepancy, the monitor asks the investigator to clarify which data is 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 will issue a query in writing to the investigator for clarification as to which was the correct scan start time. In another example, if a blood pressure was entered into a case report form as 120/80, but the hospital chart notes that it was 122/80, a monitor will issue a query to 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 for radioactivity to be measured 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 ID, 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 to any future regulatory inspection.

Informed Consent Form

The **informed consent form** (ICF) is a protocol specific document that describes to a patient what the study entails, what procedures will take place, and risks of study participation. This document, the required content of which is defined in 21CFR§50.25, must be signed by the patient prior to any study procedures and indicates they have understood the study and consent to participation. An appropriate translation must be provided to non-native English speakers as needed, and accommodations must be made for subject populations 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 adequate explanation of risks (including any anticipated radiation dose/exposure from the diagnostic or therapeutic procedures) and potential benefits. For clinical trials where molecular imaging is part of a therapeutic study, the informed consent process is conducted by the Principal Investigator or their representative and the imaging department will probably not see or be involved in the informed consent process. For studies where 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 prior to the patient's signature on the ICF. For more information about the importance of the informed consent process, refer to the FDA website which has helpful information for patients, and a guidance document for sponsors and researchers *(42)*.

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., 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, 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 CRA or monitor, in which case vials should be stored for the length of the trial *(23,24)*.

Delegation of Authority Log

While the principal investigator 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" *(43)*. 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 to initiate the informed consent process, a named nurse is delegated the responsibility to take vital signs per protocol, or that a named nuclear medicine technologist is delegated the responsibility to inject an investigational

radiopharmaceutical. Delegation logs typically require an individual's full name in legible print, their signature and initials, their job title or role in the study, and dates of their study involvement. The PI 's signature on the delegation log is an attestation that they approve that these named individuals are authorized to perform the stated protocol tasks. Updates to the delegation of authority log due to staff leaving or joining 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 *(44)*.

Adverse Event Reporting

Imaging departments contribute key data in the developing picture of an investigational drug's side effects, especially in a study where the investigational product is a radiopharmaceutical. Not every adverse event must be *reported*, but every adverse event must be *recorded* in source document and case report form for review and subsequent determination of causality by the sponsor in conjunction with the PI. While a detailed segment on 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, and when to report an event to the sponsor and/or IRB. If you are unsure of your role in recording adverse events in a sponsored trial, reach out to the sponsor or their representative for clarity. For more information on adverse event reporting in a clinical trial, refer to the FDA's draft guidance document "Investigator Responsibilities —Safety Reporting for Investigational Drugs and Devices Guidance for Industry" *(45)*.

CONCLUSION

This article has reviewed Good Clinical Practice 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 Code of Federal Regulations and additional sources of information have been provided where applicable.

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

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