# SNMMI Clinical Trials Network Research Series for Technologists: Clinical Research Primer—Regulatory Process, Part II: The Role of the Institutional Review Board in Food and Drug Administration–Regulated Radiopharmaceutical Research

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The goal of clinical research is to advance medical knowledge in hopes of improving patient care. At the core of clinical research is the need to perform research on human volunteers. This is absolutely required for the eventual approval of drugs and certain therapies. Unfortunately, history is replete with stories involving exploitation and abuse of individuals in research. Clinical research using radiopharmaceuticals introduces additional apprehension. Although the past few decades have witnessed significant improvements in safety and ethics, there remain indelible images seared into the psyche of the general population. Those new to clinical research may find themselves asking questions such as, What are the ethical guidelines and regulations for clinical research, How are they enforced and by whom, and How do we ensure the safety of participants? The answer, in large part, is the oversight and actions of the institutional review board. This article will focus on familiarizing the reader with the institutional review board and its role in protecting the rights and welfare of humans participating as subjects in Food and Drug Administration–regulated radiopharmaceutical research.

**Key Words:** radiopharmaceutical; clinical research; clinical trial; institutional review board

**J Nucl Med Technol 2022; 50:97–102**
DOI: 10.2967/jnmt.122.264034

This article builds on an earlier publication, "SNMMI Clinical Trials Network Research Series for Technologists: Clinical Research Primer—Regulatory Process, Part I: How and When Radiopharmaceuticals Can Be Used" (*1*). The reader may wish to review the earlier material to fully benefit from this discussion. In addition, institutional review board (IRB) websites are another resource to review an institution's processes, policies, and procedures.

In the United States, the Department of Health and Human Services (HHS) is the principal federal agency for protecting the health of all Americans and providing essential human services. The mission of the HHS is to enhance the health and well-being of all Americans by providing for effective health and human services and by fostering sound, sustained advances in the sciences underlying medicine, public health, and social services. This mandate is fulfilled through several HHS agencies and offices, including the Office of the Assistant Secretary for Health through its Office for Human Research Protections (OHRP), as well as the Food and Drug Administration (FDA) (*2*).

The OHRP provides leadership in the protection of the rights, welfare, and well-being of human subjects involved in research conducted or supported by the HHS. (*3*) The FDA is responsible for protecting public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biologic products, and medical devices and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation (*1,4*). To help fulfil their respective mandates, the OHRP and the FDA have established requirements for the oversight and actions of the IRB in clinical research performed under their respective purview. Differences in the rules are due to differences in the statutory scope or requirements (*3*). The OHRP and the FDA have actively worked to enhance human subject protection and reduce regulatory burden by harmonizing the agencies' IRB regulatory requirements and guidance for human subject research (*5–7*). For

Received Feb. 17, 2022; revision accepted Apr. 25, 2022.
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the purposes of this discussion, we will focus on IRB requirements only for FDA-regulated radiopharmaceutical research.

IRBs must comply with OHRP and FDA regulations in 45 *Code of Federal Regulations* (CFR) §46 and 21 CFR §50 and §56, respectively, when reviewing research subject to those regulations (*6,7*). The purpose of the IRB is to review research studies to ensure that they comply with applicable regulations, meet commonly accepted ethical standards, follow institutional policies, and adequately protect research participants (*5*).

As evidenced by OHRP and FDA regulatory joint promulgation, the IRB is an integral and requisite component for research involving FDA-regulated clinical studies. But what is the IRB and why is it important? The focus of this article is to acquaint the reader with the IRB and its role in FDA-regulated clinical research involving radiopharmaceuticals.

## DEFINITIONS AND TERMS

To facilitate further discussion, the following terms and definitions are provided.

*Central (single) IRB* is the IRB that conducts reviews on behalf of all study sites that agree to participate in the centralized review process. For sites at institutions that have an IRB that would ordinarily review research conducted at the site, the central IRB should reach agreement with the individual institutions participating in centralized review and those institutions' IRBs about how to apportion the review responsibilities between local IRBs and the central IRB (*8*).

*Clinical investigation* or *clinical research* means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. The terms *clinical investigation, clinical study, clinical research,* and *clinical trial* are deemed to be synonymous for purposes of this article unless otherwise identified (*9*).

*CFR* is the codification of the general and permanent rules and regulations FDA-Institutional in the *Federal Register* by the executive departments and agencies of the federal government of the United States. The CFR has 50 titles; each title is dedicated to a particular agency or branch of the federal government. Title 21 is dedicated to food and drugs, and title 45 is dedicated to public welfare (*1,10*).

*Contract research organization,* as defined in 21 CFR §312, means a person or group that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, such as design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA (*9*).

*FDA approval* of a drug means that data on the drug's effects have been reviewed and the drug has been determined to provide benefits that outweigh its known or potential risks for the intended population. An FDA-approved drug may be lawfully marketed (*9*).

*Good clinical practice* is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the clinical trial data are credible (*11*).

*Institution* means any public or private entity or agency (including federal, state, and other agencies). The term *facility* is deemed to be synonymous with the term *institution* for purposes of this article unless otherwise identified (*9*).

*IRB,* also called an independent ethics committee, means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such a review is to ensure protection of the rights and welfare of the human subjects (*9*).

*IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements (*9*).

*Investigational new drug* means a new drug that is used in a clinical investigation. The term also includes a biologic product that is used in vitro for diagnostic purposes. The terms *investigational drug, investigational new drug,* and *test article* are deemed to be synonymous for purposes of this article unless otherwise identified (*9*).

*Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event that an investigation is conducted by a team, the investigator is the responsible leader of the team. The lay term used frequently is *primary investigator*. *Subinvestigator* includes any other individual member of that team. The terms *investigator* and *primary investigator* are deemed to be synonymous for purposes of this article unless otherwise identified (*9*).

*Multisite clinical trial* involves the implementation of the same clinical protocol at 2 or more independent investigational sites where participants are seen for an intervention or an outcome assessment. In a multisite trial, investigational sites are typically administratively or corporately distinct from each other (*8*).

*Single-site clinical trial* utilizes 1 investigational site to conduct and coordinate the protocol. Although a single-site clinical trial may enroll participants from multiple locations, those participants will receive an intervention or undergo outcome assessments under the direction and oversight of 1 research team located at 1 investigational site (*8*).

*Sponsor* means the person or organization taking responsibility for and initiating a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor–investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated

is a sponsor, not a sponsor–investigator, and the employees are investigators. The terms *sponsor* and *sponsor–investigator* are deemed to be synonymous for purposes of this article unless otherwise identified (*9*).

*Sponsor–investigator* means an individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor–investigator under 21 CFR part 312 include both those applicable to an investigator and those applicable to a sponsor. The terms *sponsor* and *sponsor–investigator* are deemed to be synonymous for purposes of this article unless otherwise identified (*9*).

*Subject* means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease (*9*).

## IRB PURPOSE, REGISTRATION, AND MEMBERSHIP

Under FDA regulations, as outlined in 21 CFR §50 and §56, an IRB is an appropriately constituted group that has been formally designated or charged to review and monitor biomedical research involving human subjects. The purpose of IRB review is to ensure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed-consent documents and investigator brochures). An IRB has the authority to approve, require modifications to (to secure approval), or disapprove research (*12*).

### IRB Registration and Approval

In 2009, the FDA, in consultation with the OHRP, enacted a regulation (21 CFR §56.106) requiring IRB registration for IRBs reviewing clinical investigations involving FDA-regulated products. The OHRP issued a companion rule (45 CFR §46) requiring registration for IRBs reviewing federally supported research (*13*).

All IRBs that review human subject research conducted or supported by the HHS, and that are designated under assurances of compliance approved for federal use by the OHRP under 45 CFR §46.103(a), must be registered with the OHRP. The database of registered IRB organizations and IRBs includes information on IRBs that are regulated by the OHRP only, the OHRP and the FDA, or the FDA only (*14*).

The fact that an IRB is registered with the OHRP does not mean that the OHRP has determined that the IRB reviews research in accordance with the requirements of the HHS Protection of Human Subjects regulations, 45 CFR §46, and does not mean that the IRB has the appropriate competence or expertise to review a particular research project (*14,15*).

### IRB Membership

As outlined in 21 CFR §56.107, each IRB must have at least 5 members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience, expertise, and diversity of its members, including consideration of race, sex, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to having the professional competence necessary to review the specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB therefore includes persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration is given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects (*13*).

Additional criteria for IRB membership include the following. Every nondiscriminatory effort must be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of sex. No IRB may consist entirely of members of a single profession. Each IRB must include at least 1 member whose primary concerns are in the scientific area and at least 1 member whose primary concerns are in nonscientific areas. Each IRB must include at least 1 member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. No IRB can have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. An IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available in the IRB. These individuals cannot vote with the IRB. (*13*) The FDA regulations do not preclude a member from being compensated for services rendered. Payment to IRB members should not be related to or dependent on a favorable decision. Expenses, such as travel costs, can also be reimbursed (*12*).

## TYPES OF IRBS

Although IRBs may differ from one institution to another, the 2 main types of IRBs are local (institutional) and centralized (single).

### Local (Institutional) IRB

Institutions engaged in research involving human subjects usually have their own IRBs to oversee research conducted within the institution or by the staff of the institution. An IRB that is affiliated with an institution may serve only that institution or may serve as a central IRB for multisite

studies. FDA regulations permit an institution without an IRB to arrange for an outside (external) IRB to be responsible for initial and continuing review of studies conducted at the non-IRB institution (*8*). The institution's policies will dictate under what circumstances the institution's IRB can participate in a review process and the role of the institution's IRB in that process, leading to various differences between institutions.

Types of research that may use an institutional or local IRB include single-site or multisite clinical trials (sponsored), radioactive drug research committee studies, investigator-initiated single-site or multisite studies, and single-site clinical trials or other research projects under IND exemption.

### Centralized (Single) IRB

The advent of multisite studies introduced complexity and placed significant burdens on IRBs, sponsors, and investigators. In many instances, the IRB at each center of a multisite study would conduct a comprehensive review of the study, resulting in unnecessary duplication of effort, increased time and expense, and confusion. The centralized IRB review process for joint review of cooperative research has become an effective method to address this issue. This type of review process involves an agreement under which multiple study sites in a multicenter trial rely in whole or in part on the review of an IRB other than the IRB affiliated with the research site. Because the goal of the centralized process is to increase efficiency and decrease duplicative efforts that do not contribute to meaningful human subject protection, it may be preferable that a central IRB take responsibility for all aspects of IRB review at each site participating in the centralized review process. Other approaches may be appropriate as well. For example, an institution may permit a central IRB to be entirely responsible for initial and continuing review of a study or may apportion IRB review responsibilities between the central IRB and its own IRB. At clinical sites that are not already affiliated with an IRB, investigators and sponsors typically rely on the review and oversight of a central IRB (*8*).

Although some exemptions are allowed, 45 CFR §46.114(b) requires all institutions located in the United States that are engaged in cooperative research conducted or supported by a federal department or agency to rely on approval by a centralized IRB for the portion of the research that is conducted in the United States (*16*).

Types of research that may use a centralized IRB include multisite commercially funded clinical trials. Types of research that must use a centralized IRB include cooperative research conducted or supported by a federal department or agency.

## IRB FUNCTIONS AND OPERATIONS: 21 CFR §56[C]

Each IRB must follow written procedures for the following: conducting initial and continuing review of research at intervals appropriate to the degree of risk, but not less than once a year; determining which projects require review more than annually and which projects need verification (from sources other than the investigator) that no material changes have occurred since previous review; ensuring prompt reporting to the IRB of proposed changes in a research activity; ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the human subjects; and ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head for research conducted for FDA-regulated research of any unanticipated problems involving risks to human subjects or others, instances of serious or continuing noncompliance with the applicable FDA regulations or the requirements or determinations of the IRB, and suspension or termination of IRB approval.

Except when an expedited review procedure is allowed, as outlined in §56.110, each IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least 1 member whose primary concerns are in nonscientific areas. Proposed research cannot be approved unless a majority of the members at the meeting approve it (*17*).

IRBs may decide to make their written procedures available to ensure that others (e.g., investigators or sponsors) are aware of the IRB's requirements and to facilitate compliance. Some IRBs post their written procedures on a website to provide broad access (*17*).

## IRB APPROVAL OF CLINICAL RESEARCH, AMENDMENTS, AND DEVIATIONS

To approve research covered by OHRP and FDA regulations, the IRB must determine that all of the following requirements are satisfied:

- Risks to subjects are minimized by using procedures that are consistent with sound research design and do not unnecessarily expose subjects to risk and, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may be expected from the results. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as part of those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, and economically or educationally disadvantaged persons.
- Informed consent is obtained from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required.

- Informed consent is appropriately documented, in accordance with and to the extent required.
- When appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, the IRB must ensure that additional safeguards have been included in the study to protect the rights and welfare of these subjects. To approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with 21 CFR §50[D] (*18*).

The IRB should receive and review all research activities. The documents reviewed should include the complete documents received from the clinical investigator, such as the protocol, the investigator's brochure, a sample consent document, and any advertising intended to be seen or heard by prospective study subjects. Some IRBs also require the investigator to submit an institutionally developed protocol summary form. A copy of all documentation reviewed must be maintained for at least 3 y after completion of the research at that institution. However, when the IRB makes changes, such as in the wording of the informed-consent document, only the finally approved copy needs to be retained in the IRB records (*18*).

### IRB Amendments for Clinical Protocols

Although a clinical investigation is ongoing, IRBs review and consider changes in research as they are received, including protocol amendments. They also review changes to the informed-consent document, reports from investigators or sponsors of unanticipated problems, and other information about the investigation. IRB review of a proposed change in research during the period for which approval is authorized does not constitute continuing review of the research as a whole and thus does not extend the date by which continuing review must occur (e.g., beyond 1 y from the effective date of the initial approval or the most recent continuing review approval). Although an IRB may become familiar with various individual aspects of the study's conduct, such familiarity does not relieve the IRB of the responsibility to conduct continuing review, which provides an opportunity to reassess the totality of the study and ensure that, among other things, risks to subjects are minimized and still reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result (21 CFR §56.111(a) (1) and (2)) (*18*).

### Protocol Deviations

FDA drug regulations do not explicitly address protocol deviations. However, the issue is directly addressed in the *FDA Compliance Program Guidance Manual,* program 7348.811, chapter 48—"Bioresearch Monitoring, Clinical Investigators and Sponsor–Investigators," December 8, 2008. (*19*) The manual states that a protocol deviation or violation is generally an unplanned departure from the protocol procedures or treatment that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective departure from the protocol (e.g., agreement between the sponsor and the investigator to enroll a single subject who does not meet all inclusion and exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor before implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR §312.66) or to protect the life or physical well-being of the subject (21 CFR §812.35(a)(*2*)) and generally communicated to the FDA. The term *protocol deviation* is also used to refer to any other unplanned instances of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol, or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations (*19*).

The IRB must determine whether changes to the protocol were documented by an amendment, dated, and maintained with the protocol; reported to the sponsor (when initiated by the clinical investigator); and approved by the IRB and the FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazards to human subjects) (*19*).

## HOW IS THE IRB MONITORED?

Both the OHRP and the FDA may conduct IRB inspections to determine whether they are operating in compliance with current regulations and statutory requirements and whether the IRBs are following their own written procedures. OHRP regulations for IRBs are FDA-Institutional in 45 CFR §46. The FDA regulations pertinent to IRBs include 21 CFR §50 ("Protection of Human Subjects"), §56 ("IRBs"), §312 ("Investigational New Drug Application"), and §812 ("Investigational Device Exemptions") (*17,20,21*).

FDA inspections of IRBs generally fall into 1 of 2 categories: surveillance inspections (periodic scheduled inspections to review the overall operations and procedures of the IRB) and directed inspections (unscheduled inspections focused on the IRB's review of a specific clinical trial or trials; directed inspections generally result from a complaint, clinical investigator misconduct, or safety issues pertaining to a trial or site) (*20*).

## CONCLUSION

Essential to all clinical research is the need to use human volunteers. Although much progress in ethics and safety has been made in the last few decades, past abuses to individuals involved in research are difficult to forget. Protecting the rights and welfare of individuals participating as subjects in clinical research is of paramount importance. To safeguard these fundamental principles, the federal government, through the offices and agencies of the OHRP and the FDA, has

established regulations for the IRB to ensure safety for participants involved in FDA-regulated radiopharmaceutical research.

## DISCLOSURE

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

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