
Yale Human Research Protection Program

940 GD.1 Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation

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Purpose

This guidance outlines the roles, review and oversight responsibilities, and governing documents for each Yale University or Yale New Haven Hospital committee that must review human subjects research involving ionizing radiation. This guidance also provides guidance regarding investigator responsibilities when using ionizing radiation in research involving human subjects and applicable reporting requirements.

Scope

The scope of this guidance is limited to human subject research involving the use of ionizing radiation.

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- **Note:** Radiation exposure that is received in a routine standard of care and/or non-research clinical care procedure is outside of the scope of this guidance.

This guidance describes investigator responsibilities and the responsibilities of the following committees for this type of research:

- Yale University Institutional Review Boards (YU IRB) (also referred to as the Human Investigation Committee (YU HIC))
 - Yale University Radiation Safety Committee (YU RSC)
 - Yale University Radioactive Investigational Drug Committee (YU RIDC)
 - Yale University Radioactive Drug Research Committee (YU RDRC)
 - Yale New Haven Hospital Radiation Safety Committee (YNHH RSC)
- **Note:** This guidance does not supersede the authority of any existing applicable guidance or governing documents. In the event of any conflict between this guidance and any applicable policy, such applicable policy supersedes.

Overview

Radiation exposure (other than that received in routine and/or non-research clinical care procedures) must be evaluated to determine the risks posed to research subjects. Depending on the type and location of the research, and the nature of the ionizing radiation used in the research, the following regulations and guidance may apply:

- U.S. Nuclear Regulatory Commission (NRC)
- U.S. Department of Human and Health Services (DHHS), Office of Human Research Protection (OHRP)
- U.S. Food and Drug Administration (FDA)
- Connecticut Department of Energy and Environmental Protection (DEEP)

The YU IRB (and the YU RSC or YNHH RSC) must review all proposed protocols for human subject research involving the use of ionizing radiation. The YU RIDC or the YU RDRC review protocols in cases where radioactive drugs are administered to human subjects under a Yale University research study.

Guidance Statement

To protect the safety of all subjects, employees, staff, students, and the public for any human subject research involving the use of ionizing radiation, the YU IRB and other appropriate committees must review and approve such research prior to the commencement of research activities involving ionizing radiation. The appropriate committee(s) to perform the supplementary review depends on the nature of the research, where the research takes place, and the entity that holds the license/registration for the use of radioactive materials or radiation-producing equipment. In order to facilitate the review of such research, any committee reviewer may ask questions of the investigator and other committees as appropriate to improve their understanding of the proposed research and assist them in performing a thorough review.

Definitions

Absorbed Dose

“Absorbed Dose” is the concentration of energy deposited in tissue as a result of an **exposure** to ionizing radiation.

Authorized User

“Authorized User” means a physician who meets NRC defined requirements and is specifically identified on an NRC license that authorizes the medical use of radioactive material.

Dosimetry

“Dosimetry” is the measurement, calculation, assessment and determination of the ionizing radiation dose absorbed by the human body. This applies both internally, due to injected, ingested or inhaled radioactive substances, and externally, due to sources of radiation external to the body such as X-ray imaging and CT scans, or exposure to sealed sources (transmission scans).

Effective Dose

“Effective Dose” is a measure used to estimate the risk resulting from an exposure to ionizing radiation, calculated as a weighted average of exposure to different body tissues. The effective dose is measured in rems or sieverts.

Exploratory IND

The phrase “Exploratory IND” is intended to describe a clinical trial that occurs very early in phase 1, involves very limited human exposure (up to 7 days of dosing) and has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies). Exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days). This applies to early phase 1 clinical studies of investigational new drug and biological products that assess feasibility for further development of the drug or biological product.

Exposure

The term “Exposure” means being exposed to ionizing radiation or to radioactive material.

Investigational New Drug (IND)

“Investigational New Drug” means a new drug or biological drug that is used in clinical research and whose production and/or use is submitted to the FDA as an application. See, 21 CFR 312.3.

Investigator and Principal Investigator (PI)

“Investigator” refers to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB. Although some research studies are conducted by more than one investigator, usually ***one investigator is designated the “Principal Investigator (PI)” with overall responsibility to supervise the conduct of the study.*** When tasks are delegated, the PI is responsible for providing adequate supervision of those to whom tasks are delegated. The PI is also accountable for regulatory violations from failure to adequately supervise the conduct of the study. See, [HHS Guidance: Investigator Responsibilities](#); [FDA Guidance: Investigator Responsibilities](#). When delegating responsibilities PIs should consider whether:

- individuals who were delegated tasks were qualified to perform such tasks;
- study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study;
- there was adequate supervision and involvement in the ongoing conduct of the study; and
- there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

Radiation

“Radiation” or “Ionizing Radiation” means alpha particles, beta particles, gamma rays, x-rays, neutrons, high-speed electrons, high-speed protons, and other particles or rays capable of producing ions. Radiation, as used in this document, does not include non-ionizing radiation, such as microwaves, laser, visible light, infrared light or ultraviolet light.

Radiologic (Radiological) Procedure

A “Radiologic (Radiological) Procedure” is any procedure involving radiation (e.g., X-ray) or a radioactive agent (e.g., radionuclide used in a nuclear medicine study).

Radiopharmaceutical

A “Radiopharmaceutical” or “Radioactive Drug” is any drug, antibody or metabolic tracer labeled with a radioactive isotope. A radiopharmaceutical emits ionizing radiation. See, 21 CFR 310.3. The terms “radioactive drug” and “radiopharmaceutical” are deemed synonymous for purposes of this guidance.

Standard of Care

“Standard of Care” is defined as the level at which the average, prudent provider in a given situation would manage the patient’s care under the same or similar circumstances. Standard of Care is also defined as treatment that experts agree is appropriate, accepted, and widely used and is also called best practice, standard medical care, and standard therapy. For example, if a patient who is enrolled in a research study is also undergoing a procedure that is part of their prescribed regime/treatment, that exposure would be considered “Standard of Care” and not subject to consideration or review by the policies discussed in this guidance. Radiation exposure that is received in a routine standard of care and/or non-research clinical care procedure is outside of the scope of this guidance.

- “Practice” refers to interventions designed solely to benefit an individual patient and have a reasonable expectation of success.
- “Research” is an activity designed to test a hypothesis and contribute to generalizable knowledge.

United States Nuclear Regulatory Commission (NRC)

The “U.S. Nuclear Regulatory Commission” is an independent federal agency established by the Energy Reorganization Act of 1974 to regulate civilian use of nuclear materials, including the medical use of radioactive materials. The NRC issues radioactive material use licenses and regularly inspects licensee programs to confirm compliance with its regulations. Yale University and Yale New Haven Hospital each have separate NRC licenses and separate radiation safety programs. The NRC requires each licensee to have a Radiation Safety Officer and a Radiation Safety Committee.

Guidance Sections

1. General Requirements related to the Use of Ionizing Radiation in Human Subjects Research

FDA, OHRP, and NRC regulate all human subject research involving the use of a radioactive drug. Human subjects research using radioactive drugs performed at Yale University or Yale New Haven Hospital is conducted under each institution’s respective NRC medical use license.

The FDA allows human subject research involving the use of a radioactive drug without an IND if the research is instead approved by an established and FDA approved Radioactive Drug Research Committee (RDRC). The YU RDRC serves as the radioactive drug research committee for Yale. The NRC and FDA require that the total amount of radioactive material administered to a research subject is the smallest radiation dose practical to perform the study without jeopardizing the benefits obtained from the study. The radiation dose to be received by the subject must also be within the limits specified in 21 CFR 361.1(c)(3)(i) when the protocol is conducted as an RDRC protocol.

An IND is required when the purpose of the study is to determine safety and efficacy of the drug or for immediate therapeutic, diagnostic or similar purposes. If an IND is in effect for a radioactive research drug, then the investigational drug is subject to the IND regulations (21 CFR 312), rather than the regulations at 21 CFR 361.1. Such Yale University studies are reviewed by the YU RIDC rather than the YU RDRC.

As required by the NRC in 10 CFR 33.13 (c)(3)(iii), the Licensee is responsible for the review and approval of protocols detailing this research. The Yale University Radiation Safety Committee (YU RSC) performs this review and approval. The NRC also stipulates provisions for the protection of research subjects in 10 CFR 35.6. Specifically, licensees are responsible for ensuring that research involving human subjects research “obtain review and approval of the research from an IRB and obtain

informed consent as defined and described in the Federal Policy for the Protection of Human Subjects.” See, 10 CFR 35.6(b)(1).

The YU IRB is the last and final committee to approve a protocol involving the use of ionizing radiation and may approve a protocol only after the appropriate radiation safety and radioactive drug committee(s) have approved the protocol. If the YU IRB approved protocol is amended, investigators must update and re-submit protocols for re-review to the appropriate radiation safety/radioactive drug committee(s) that conducted the initial review. Investigators must comply with the applicable protocol requirements regarding timely reporting of adverse events, unanticipated problems and deviations, to the IRB, the appropriate radiation safety committee, and when applicable, the radioactive drug review committee.

Sections [940.2](#) – [940.5](#) below provide general guidance regarding the roles and responsibilities and governing documents for each Yale University or Yale New Haven Hospital committee that must review human subjects research involving ionizing radiation and explains the review and oversight responsibilities of each such committee.

This guidance also provides general requirements for all committees regarding investigator responsibilities when using ionizing radiation and reminds investigators of their obligations regarding reporting PET research incidents.

- **Note:** For an overview of incident reporting requirements, see [Section 7, Reporting Requirements](#).
- **Note:** The subsections below are not meant to comprehensively describe each committee’s policies and procedures.

2. Yale University Institutional Review Board (IRB)

The YU IRB reviews human subjects research conducted at YNHH or Yale University in accordance with applicable laws, regulations, guidelines, including 21 CFR Part 50, 21 CFR Part 56, and 45 CFR Part 46. The requirement for an IRB to review applicable human subjects research, includes human subjects research involving the use of ionizing radiation. See, 10 CFR 35.6.

- **Note:** If the HRPP sends a study involving ionizing radiation to an external IRB for review and oversight, the external IRB shall have the same responsibility and authority as the as YU IRB. See, Yale University Procedure 920 PR.4, Use of External IRBs for Review and Oversight of Research Involving Human Subjects.

2.1 Applicable Policies and Procedures

Relevant Yale IRB policies and procedures include:

- IRB Policy 100, Institutional Review Board (IRB) Review of Human Subject Research Protocols or FDA-Regulated Activities Involving Human Participants
[IRB Policy 100](#)
- IRB Policy 710, Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events
[IRB Policy 710](#)
- IRB 700 PR.1, Reporting Noncompliance and Protocol Deviations to the IRB
[IRB Procedure 700 PR1](#)

For additional YU IRB's policies and procedures, including how to submit a study for review, please refer to the following:

- <https://your.yale.edu/research-support/human-research/yale-irbs-yale-university-institutional-review-boards> (**General Information regarding the Yale IRBs**)
- <https://your.yale.edu/research-support/human-research/ires-irb> (**Link to IRB electronic submission system called IRES-IRB**)

2.2 Scope of YU IRB's Responsibilities

The YU IRB is responsible for ensuring the following, including:

- ✓ Risks to subjects are minimized;
- ✓ Risks to subjects are reasonable in relation to anticipated benefits;
- ✓ Selection of subjects is equitable;
- ✓ Informed consent is sought from each prospective subject or the subject's legally authorized representative;
- ✓ Informed consent language is appropriate;
- ✓ The research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects;
- ✓ There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
- ✓ The underlying science and the research design are sound;
- ✓ The PI and research personnel are current on any required training and are qualified based on their role on the study.

The YU IRB also has the authority to approve, disapprove, or require modifications to the IRB protocol before issuing a final approval letter. Before issuing the final approval letter, however, the YU IRB must ensure that all necessary approvals are received from the appropriate ancillary committees including the applicable radioactive drug review committee prior to issuance.

2.3 Investigator Responsibilities

The Investigator is responsible for the following, including:

- ✓ Submitting a complete and accurate protocol and other requested information to the YU IRB for review through the electronic IRB system;
- ✓ Disclosing to the IRB the planned use of any radioactive drugs and/or any x-ray equipment;
- ✓ Identifying all ionizing radiation procedures that are beyond routine standard of care and for research purposes only;
- ✓ Communicating all decisions or recommendations from relevant ancillary committees to the IRB at initial review, continuing review, any time the protocol is amended, or any time throughout the life of the study as appropriate;
- ✓ Obtaining IRB and other relevant ancillary committee approval prior to implementing the protocol;
- ✓ Submitting "Reportable New Information" in accordance with the IRB's reporting requirements;

- **Note:** For a general overview of IRB reporting requirements and the timeframe for reporting, see Section 7, Reporting Requirements. (This section does not include all IRB reporting requirements.)

- ✓ Carrying out protocols consistent with the directives and approvals of the IRB (and other applicable ancillary review committees);
- ✓ Ensuring that subjects are consented appropriately;
- ✓ Ensuring that all required PI and research personnel training is current and complete;
- ✓ Initiating and/or participating in any required start-up meetings prior to the conduct of the study to work through operational details and to facilitate a smooth running of the protocol in accordance with applicable regulatory requirements and ICH GCP; and
- ✓ Retaining copies of all essential documents for the conduct of the study (e.g., protocols, amendments, consent forms, and study-related documents in the study record).

3. Yale University Radioactive Drug Research Committee (YU RDRC)

The YU RDRC committee is responsible for the review and approval of human subjects research involving radiation exposure and the administration or use of investigational radioactive drugs. This research is typically conducted at the Yale University PET Center.

- **Note:** The YU RDRC may occasionally agree to review human subject research protocols involving the use of investigational radioactive drugs without an IND conducted at other institutions.

Radioactive drugs as defined in 21 CFR 310.3(n), may be administered to research participants *without obtaining an IND* when the purpose of the research is to obtain basic information regarding the metabolism such as kinetics, distribution, dosimetry, and localization of a radioactively labelled drug or regarding human physiology, pathophysiology, or biochemistry. These initial studies are considered basic research within the meaning of 21 CFR 361.1. Such basic research studies must be conducted in accordance with 21 CFR 361.1(b), including review by the YU RDRC, which is an FDA required committee.

In order to be a RDRC protocol, the following criteria must be met:

1. The research is basic science research and is not research that is intended for immediate therapeutic, diagnostic, or similar purposes;
2. The research is not research intended to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product);
3. The Investigator must know that the radioactive drug does not cause any clinically detectable pharmacological effect in humans;
4. The number of protocols using the radioactive drug is limited;
5. The number of human subjects in the study is limited; and
6. The protocol does not include drugs that have no documented previous human experience.

If the above criteria are not met, an IND application may instead be submitted to the FDA and the study must be reviewed by the RIDC.

3.1 Applicable Policies and Procedures

Relevant YU RDRC policies and procedures are as follows:

- [Radioactive Drug Research Committee \(YU RDRC\) Policies and Procedures](#)
[YU RDRC Policies/Procedures](#)

For more additional information regarding the YU RDRC's policies and procedures, including how to submit a study for review, please refer to the following information located here:

- <https://your.yale.edu/research-support/human-research/yale-rdrc-yale-university-radioactive-drug-research-committee> (**Overview; Policies & procedures; Meeting Dates & Deadlines; and link to RDRC Application (see also below)**)
- <https://your.yale.edu/policies-procedures/forms/application-involve-human-subjects-biomedical-research> (**Link to RDRC application**)

3.2 Scope of YU RDRC Responsibilities

The YU RDRC has the responsibility to ensure that the amounts of radioactive materials administered are appropriate, the quality of the radioactive drugs used is high, and pharmacological and radiological dose limits are met. Specifically, the YU RDRC:

- ✓ Ensures the underlying science and research protocol are of sound design such that information of scientific value may result;
- ✓ Reviews and approves the consent form language related to radiation risks;
- ✓ Evaluates radiation dosimetry (i.e., dosimetry is valid, at or below radiation dose limits, meets exposure justification criteria, acceptable rationale for amount of activity to be administered, etc.)
- ✓ The quality of the radioactive drugs used (i.e., appropriate production standards and Chemistry/QC/IDMF)¹;
- ✓ Verifies that:
 - Pharmacological dose limits are met;
 - The rationale for number of subjects is acceptable;
 - The research meets the definition of Basic Science Research (See above criteria set forth in 21 CFR 361.1);
 - The number of human subjects in the study is limited. (If the study has more than 30 subjects, appropriate justification is made and a Special Summary Report to the FDA is submitted.);
 - The drug has documented previous human experience;
 - Requirements for pediatric protocols will be met; and
 - The number of protocols using the radioactive drug is limited.
- ✓ Ensures that the PI and research personnel are current on any required training related to radioactive pharmaceuticals and procedures.

Subject to YU IRB final approval, the YU RDRC has the authority to approve, disapprove or require modifications to the IRB protocol as it relates to the use of radioactive drugs in human subjects for research.

In addition, the RDRC will maintain the following documents or ensure they are made available upon request (e.g., for agency inspections, audits, etc.)

- Specifications established by the PET Center to be met prior to release of the radiopharmaceutical for human use.
- Confirmation that post-release sterility results found to be out of specification, or other out of specification results discovered after the drug is administered, will be reported to the RDRC.
- A copy of the Label template for the specific drug, both the label attached to the shielding and the smaller label attached to the final product vial.
- The dose of the drug known not to cause a pharmacologic effect, and references to support.

¹ The Yale PET Center's radiopharmaceutical production group is responsible to demonstrate that the radioactive drug used in the research study meets appropriate pharmaceutical, radiochemical, and radionuclide standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted.

- The maximum dose of the pharmaceutical (both radiolabeled and unlabeled) that could be present in a dose administered to an enrolled subject.

3.3 Investigator Responsibilities

The Investigator is responsible for the following, including:

- ✓ Submitting a complete application, protocol, and other required study-related documents to the YU RDRC for review and approval;
- ✓ Notifying the YU RDRC if there are any changes to the protocol that impact the use of radioactive materials in the study;
- ✓ Understanding and agreeing to the RDRC Adverse Event reporting requirements;
 - **Note:** This requirement is different than the IRB's reporting requirements and may require reporting to the RDRC and IRB. Reporting to the RSO also may be required. See Section 7, Reporting Requirements.
- ✓ Assuring that the radiation dose to research subjects is as low as reasonably achievable to perform the study and meets the criteria of applicable regulations;
- ✓ Carrying out protocols consistent with the written protocol and the directives and approvals of the YU RDRC (and other applicable review committees, including the IRB);
- ✓ Ensuring that all study personnel have completed required training related to radioactive pharmaceuticals and procedures;
- ✓ Determining who will be the required NRC Authorized User (AU) overseeing the protocol;
- ✓ Communicating with the AU the details of the protocol and seek input on safety improvements; and
- ✓ Incorporating AU guidance into the protocol.

4. Yale University Radioactive Investigational Drug Committee (YU RIDC)

The YU RIDC is Yale University mandated committee. All human subject research protocols involving the use of investigational radioactive drugs with an IND, amended IND or an FDA allowed IND exemption (as well as the use of FDA-approved radiopharmaceuticals) must be reviewed and approved by the YU RIDC. The research that requires YU RIDC review is typically conducted at the Yale University PET Center or another Yale University facility under Yale University's NRC medical use license. The YU RIDC will provide oversight to protocols conducted at Yale New Haven Hospital under review by the YNHH Radiation Safety Committee (YNHH RSC) when requested by the YNHH RSC. Subject to YU IRB final approval, the YU RIDC, has the authority to approve, disapprove or require modifications to the protocol as it relates to the use of radiopharmaceuticals in human subjects for research.

4.1 Applicable Policies and Procedures

Relevant YU RIDC policies and procedures are as follows:

- <https://your.yale.edu/policies-procedures/other/radioactive-drug-research-committee-rdrc-policies-and-procedures>

For more information regarding the YU RIDC's policies and procedures, including how to submit a study for review, please refer to the following information located here:

- <https://your.yale.edu/research-support/human-research/yale-ridc-yale-university-radioactive-investigational-drug-committee>

4.2 Scope of YU RIDC Responsibilities

The YU RIDC is responsible for ensuring that the radioactive materials administered are appropriate. In the committee's review of protocols, the YU RIDC:

- ✓ Ensures the underlying science and research protocol are of sound design;
- ✓ Reviews and approves the consent form language related to radiation ;
- ✓ Evaluates radiation dosimetry (i.e., dosimetry is valid, at or below radiation dose limits, meets exposure justification criteria, acceptable rationale for amount of activity to be administered, etc.);
- ✓ Confirms consistency between the FDA application and Yale University study-related documents.
- ✓ Ensures that the PI and research personnel are trained in relation to use of radioactive pharmaceuticals and procedures.

4.3 Investigator Responsibilities

The Investigator is responsible for the following, including:

- ✓ Submitting a complete application, protocol, and other required study-related documents to the YU RIDC for review and approval;
- ✓ Notifying the YU RIDC if there are any changes to the protocol that impact the use of radioactive materials in the study;
- ✓ Carrying out protocols consistent with the written protocol and the directives and approvals of the YU RIDC (and other applicable review committees, including the IRB);
- ✓ Understanding and agreeing to the RIDC Adverse Event reporting requirements;
 - **Note:** This requirement is different than the IRB's reporting requirements and may require reporting to the RIDC and IRB. Reporting to the RSO also may be required. See Section 7, Reporting Requirements.
- ✓ Ensuring that all study personnel have completed required training related to radioactive pharmaceuticals and procedures;
- ✓ Determining who will be the required NRC Authorized User (AU) overseeing the protocol;
- ✓ Communicating with the AU the details of the protocol and seek input on safety improvements; and
- ✓ Incorporating AU guidance into the protocol.

5. Yale University Radiation Safety Committee (YU RSC)

The YU RSC is a Nuclear Regulatory Commission (NRC) required committee (See 10 CFR 20.1101 *Radiation protection programs* and 10 CFR 35.24 *Authority and responsibilities for the radiation protection program*). All Yale University research protocols involving the use of ionizing radiation with human subjects must be reviewed and approved by the YU RSC. Yale's current NRC medical use license is a specific, limited scope license that allows licensed material to be used in human subjects only at the Yale University PET Center and only for research purposes.

5.1 Applicable Policies and Procedures

Relevant YU RSC policies and procedures are as follows:

- <http://ehs.yale.edu/radiation-safety-committee>

For more information regarding the YU RSC's policies and procedures, including how to submit a study for review, please refer to the following information located here:

- <http://ehs.yale.edu/pet-center> (**General Information**)
- <http://ehs.yale.edu/sites/default/files/files/human-use-protocol-form.pdf> (**YU RSC Application- Human Use Protocol Review Cover Sheet**)

5.2 Scope of YU RSC Responsibilities

The YU RSC is responsible for ensuring that the use of ionizing radiation for human subjects research conducted at Yale University is compliant with applicable licenses and registrations. In their review of protocols, the YU RSC:

- ✓ Reviews procedures at all phases of the protocol to ensure the safety of research subjects.
- ✓ Confirms that the protocol has been submitted to the IRB.
- ✓ Verifies that
 - Yale University is properly licensed for proposed use.
 - The PET Center is authorized for proposed use.
 - The release of subjects following administration of radioactive material is permissible and documented as such appropriately.
 - An NRC Authorized User is listed and approved.
 - The protocol addresses reporting requirements.
 - Dosimetry information in the HIC, RDRC or RIND and RSC documents and consent form is the same.
 - The location(s) of conduct of the study is accurate.
 - Information in the protocol is clear and accurate.
 - There is appropriate consideration of women of childbearing age.
 - Radioactive materials/samples are received and transferred as required.
- ✓ Ensures that practitioners are appropriately authorized and current on any required training related to radiation safety.

Subject to the YU IRB's final approval, the YU RSC has the authority to approve, disapprove or require modifications to the IRB protocol as it relates to the research use of ionizing radiation with human subjects.

5.3 Investigator Responsibilities

The Investigator is responsible for the following, including:

- ✓ Submitting the Yale IRB protocol to be reviewed by the YU RSC to Yale University's Radiation Safety Officer;
- ✓ Ensuring the listed NRC Authorized User (AU) overseeing the protocol is currently active on the Yale University NRC Medical Use license;
- ✓ Communicating with the AU the details of the protocol and incorporating input on safety improvements;
- ✓ Receiving written approval from the AU;
- ✓ Notifying the Yale University Radiation Safety Officer (YU RSO) if there are protocol amendments after Yale IRB approval;
- ✓ Ensuring that all study personnel have completed required training related to radioactive pharmaceuticals and procedures; and
- ✓ Reporting PET incidents as outlined in Section 7, Reporting Requirements.

6. Yale New Haven Hospital Radiation Safety Committee (YNHH RSC)

The YNHH RSC is an NRC required committee. All research protocols involving the use of ionizing radiation in or on human subjects that are conducted under YNHH's NRC license, using YNHH-licensed radioactive material, or involving the use of YNHH-registered radiation-producing equipment must be reviewed and approved by the YNHH RSC. The YNHH NRC license is a comprehensive, broad scope license allowing for significant flexibility with the use of licensed material. Examples of studies requiring YNHH RSC review and approval include:

1. Studies with FDA-approved radiopharmaceuticals that are being used for research purposes but would not normally be a part of the subjects' care and would therefore expose the subjects to a higher radiation dose than they would receive during routine care. Examples include extra 131I studies for thyroid function, extra 99mTc studies (such as MUGA scans for heart function) and 18F FDG PET studies performed for research purposes; and
2. Extra diagnostic imaging studies (e.g., x-rays, CT scans, PET studies, SPECT studies, DEXA studies) using x-rays or radioactive isotopes that are needed for research purposes but would not normally be a part of the subjects' care and would therefore expose the subjects to a higher radiation dose than they would receive during routine care.

6.1 Applicable Policies and Procedures

Relevant policies and procedures are as follows:

- Will be added when central location provided.

For more information regarding the YNHH policies and procedures, including how to submit a study for review, please refer to the following information located here:

- <http://rsc.med.yale.edu/>

6.2 Scope of YNHH RSC Responsibilities

The broad classes of research that must be reviewed by this committee include:

- ✓ Studies using drugs, diagnostics or devices that emit ionizing radiation; and
- ✓ Protocols which propose any additional exposures to ionizing radiation that would not normally be a part of the subject's medical treatment.

Subject to the YU IRB's final approval, the YNHH RSC has the authority to approve, disapprove or require modifications to the protocol as it relates to the use of ionizing radiation in human subjects for research where such research is conducted under YNHH's NRC license, using YNHH-licensed radioactive material, or involving the use of YNHH registered radiation-producing equipment.

6.3 Investigator Responsibilities

When submitting to the YNHH RSC, the Investigator is responsible for the following, including:

- ✓ Requesting the Hospital Health Physicist's survey of the site and the laboratory staff if the proposed study is to be conducted at a site other than the Nuclear Medicine Department;

- ✓ Filing an Application to Use Radioisotopes in Human Investigations to YNHH RSC using the electronic submission portal;
- ✓ Ensuring that an attending physician from Nuclear Medicine Department is listed as a collaborator on protocols to be conducted in that department;
- ✓ Ensuring that the Responsible Investigator and collaborators have documented training and experience in the use of radiolabeled compounds;
- ✓ Ensuring that inexperienced collaborators have completed the required Radiation Safety course; and
- ✓ Notifying the YNHH RSC of IRB approved modifications related to radiation.

7. Reporting Requirements

7.1. PET, RDRC, and RIDC Reporting Requirements

Events that meet reportable criteria: All adverse events experienced by the subject that are potentially associated with the use of the radioactive drug in the research study. This includes ANY adverse event whether or not it is considered to be serious. Examples of adverse events include headache, dizziness and sore throat.

Reporting Steps:

| When | Who | How to Report It |
|---|---|--|
| Immediately, but no later than 24 hours, after learning of the event | The PET Center staff | Notify the following via email: <ul style="list-style-type: none"> • Principal Investigator, • PET Adverse Event Notification Distribution e-mail list², • RIDC/RDRC via email sent to RDRC@yale.edu or RIDC@yale.edu (dependent on the oversight) |
| | The Principal Investigator or his/her designee ³ | Send an email to RDRC@yale.edu or RIDC@yale.edu . The email will be forwarded by the Administrator to the RIDC and RDRC Chairs, and PET Center. |
| Follow up within 3 calendar days, but no later than 7 calendar days (unless the initial report included complete information) | The PET Center staff | Submit <i>Adverse Event Report</i> ⁴ to RDRC@yale.edu or RIDC@yale.edu (dependent on the oversight). |

² PET Center *Post Radiopharmaceutical Injections Adverse Event Notification Policy* requires PET Center to maintain a distribution list of individuals within PET Center who must be notified about the events. That includes members of Radiochemistry, Imaging, Medical, and Regulatory teams.

³ If the event happens after the subject leaves the PET Center and the PI believes it may be related to administration of the radioactive materials.

⁴ The *Adverse Event Report* form is maintained and managed by the PET Center.

7.2. IRB Reporting

Events that meet reportable criteria:

- Events that meet the definition of Unanticipated Problem Involving Risks to Participants or Others (UPIRSO) (Incident, experience or outcome that is unexpected AND related or possibly related AND harmful);
- Multiple occurrences of an event that, based on an aggregate analysis, is determined to be unexpected AND related or possibly related AND harmful;
- Adverse events or IND Safety Reports that require a change to the protocol or consent.

Reporting Steps:

| When | Who | How to Report It |
|---|--|---|
| <p><u>If Yale IRB serves as the IRB of record:</u> Within 5 calendar days upon learning about the event;</p> <p><u>If External IRB serves as the IRB of Record:</u> Follow the IRB of Record's requirements</p> | The Principal Investigator or designee | <p><u>If Yale IRB serves as the IRB of record:</u> Submit Reportable New Information (RNI) in IRES IRB https://your.yale.edu/research-support/human-research/ires-irb</p> <p><u>If External IRB serves as the IRB of Record:</u> Follow the IRB of Record's requirements</p> |

7.3. Radiation Safety Officer Reporting

Events that meet reportable criteria:

- Radioactive material comes in contact with a person or their apparel
- Member of public is exposed to radiation
- Misadministration of a radiopharmaceutical
- The unexpected uptake or intake of radioactive material by the research subject
- Any/other unusual or unanticipated event involving the administration of a radiopharmaceutical

Reporting Steps:

| When | Who | How to Report It |
|-------------|--|---|
| Immediately | <ul style="list-style-type: none"> • The Principal Investigator or designee • PET Center staff | Call Yale Radiation Safety Officer (YRSCO) at 203-785-3550 or email YRSCO directly tammy.stemen@yale.edu |

7.4. Reporting of Injuries

In addition to the reporting requirements detailed above, all injuries to Yale students, faculty, staff, trainees and visitors must be reported using the Online First Report of Injury Form. Search "Yale First Report of Injury" to access the form or [CLICK HERE](#).

7.5. FDA Reporting

| When | Who | What |
|---|-------------------|---|
| Immediately, but no later than 7 calendar days after learning about the event | RDRC | All adverse events probably attributable to the use of the radioactive drug in a research study |
| Annually, by 31st of January | RDRC ⁵ | Annual Report using Form FDA 2915, “Report on Research Use of Radioactive Drug” |

Related Information

Office for Human Research Protections (OHRP)

- 45 CFR 46

Food and Drug Administration (FDA)

- 21 CFR 50, 56, 54, 312, 812
- 21 CFR 361.1
- RDRC Protocol Review Checklist:

<https://www.fda.gov/drugs/science-and-research-drugs/radioactive-drug-research-committee-rdrc-program>

Nuclear Regulatory Commission (NRC)

- 10 CFR Parts 19, 20 and 35
- 10 CFR 35.6 (Provisions for the protection of human research subjects)

Connecticut Department of Energy and Environmental Protection (DEEP)

- <http://www.ct.gov/deep/site/default.asp>
- http://www.ct.gov/deep/cwp/view.asp?a=2713&q=324824&deepNav_GID=1639

⁵ RDRC Administrator reminds all PIs of research studies under RDRC purview of their obligation to submit their annual reports to RDRC by mid-January via an email notification sent to them in December of the preceding year.

Contacts

| Subject | Contact | Telephone |
|----------|--|--------------|
| YU IRB | HRPP@yale.edu | 203-785-4688 |
| YNHH RSC | ravinder.nath@yale.edu | 203-785-2971 |
| YU RSO | tammy.stemen@yale.edu | 203-785-3550 |
| YU RDRC | RDRC@yale.edu | 203-785-5005 |
| YU RIDC | RIDC@yale.edu | 203-785-5005 |

Revision History

| Date | Description of the revision |
|------------|--|
| 01/30/2018 | Initial effective date |
| 12/02/2019 | Clarifications regarding scope of the responsibilities of the RIDC, investigators, and correct typos. |
| 01/20/2021 | Section 5.2. 'YU RSC Responsibilities': Per NRC Guide, adding responsibility of RSC to determine whether the release of subjects following administration of radioactive material is permissible and documented appropriately. |
| 03/25/2022 | Clarified the locations of research studies under purview of RIDC |