Overview of Review Processes for the Human Use of Radioisotope Studies

The Nuclear Regulatory Commission (NRC) and the Food and Drug Administration (FDA) have regulatory responsibilities concerning medical devices, drugs, and biological products using radioactive material.

REGULATORY ENTITY	DESCRIPTION
NRC	Regulates the use of radioactive materials. The University of Michigan (U-M) is authorized under various licenses issued by the NRC to conduct research and clinical activities using radiopharmaceuticals, radioactive compounds, and radioactive sources
FDA	Assures the safety, effectiveness, and proper labeling of medical products, such as drugs, devices, and biologics
Michigan Department of Licensing and Regulatory Affairs (LARA)	Regulates the use of radiation-producing equipment including CT scanners, fluoroscopy machines, radiographic x-ray machines, x-ray diffraction units, cyclotrons, medical linear accelerators, and electron microscopes

The following U-M committees and department ensures that U-M is in compliance with the regulatory requirements for using human subjects for radioisotope studies.

REGULATORY ENTITY	DESCRIPTION
Radiation Policy Committee (RPC)	• Implements, maintains, and oversees radiation safety at U-M • Establishes policies and enforces compliance with the program • Provides advice through the Associate Vice President for Facilities & Operations to the Executive Vice President & Chief Financial Officer regarding the regulatory compliance and the safe, authorized use of ionizing radiation • Along with the Radiation Safety Officer (RSO): o Approves the use of radioactive material and radiation-producing devices o Evaluates the training, experience, and qualifications of applicants who request such authorizations **NOTE**: The RPC or RSO can revoke or suspend a user's authorization for health, safety, environmental, or regulatory compliance concerns.
Environment, Health & Safety (EHS)	• Ensures that radioactive materials and radiation-producing equipment are used safely and in accordance with applicable regulations • Ensures that doses to employees and research subjects are maintained As Low As Reasonably Achievable (ALARA) • Provides administrative and technical assistance to the U-M: o RPC o Radioactive Drug Research Committee (RDRC) o Subcommittee on the Human Use of Radioisotopes (SHUR)

REGULATORY ENTITY	DESCRIPTION
Radioactive Drug Research Committee (RDRC)	Reviews research protocols involving radiopharmaceuticals as required by the FDA regulations (21 CFR 361.1)
Subcommittee on the Human Use of Radioisotopes (SHUR)	• Approves the applications for the clinical use of radioactive materials in or on humans submitted by medical authorized users • Reviews human research subject protocols involving the administration of radiopharmaceuticals to research subjects that are **not** covered under 21 CFR 361.1
Institutional Review Boards IRBMED	Grants final approval for the protocols

RADIATION POLICY COMMITTEE (RPC)

The committee consists of the following faculty and staff appointed by the Executive Vice President & Chief Financial Officer:

- U-M administration
- RSO and representatives from clinical and research disciplines
- Other U-M program areas

The Executive Director of EHS and the Associate Vice President for Facilities & Operations serve as ex officio members of the RPC. The RPC meets once each calendar quarter.

RDRC

The RDRC is a subcommittee of the RPC.

The RDRC oversees basic human research, as permitted under 21 CFR 361.1, for the purpose of advancing scientific knowledge. The research is intended to obtain *basic* information regarding the metabolism of radiopharmaceuticals including:

- Kinetics
- Distribution
- Dosimetry
- Localization
- Basic information about:
  - Human physiology
  - Pathophysiology
  - Biochemistry of radiopharmaceuticals

Research conducted under the RDRC approval process is **not** intended:

- For the immediate therapeutic, diagnostic, or preventive benefit to the human research subjects involved
- To determine the safety and effectiveness of a radiopharmaceutical in human research subjects as a therapy, diagnostic, or preventive medical product

RDRC Responsibilities

The RDRC:

- Reviews, approves, request modifications or clarifications, or defers approval of human research protocols involving the administration of radiopharmaceuticals to research subjects solely because they are involved in a research study
- Ensures that radiopharmaceuticals are only administered to human research subjects by or under the direct supervision of physicians meeting the specific training and experience requirements specified in the NRC medical regulations (10 CFR 35)
- Documents meeting minutes including voting results
- Communicates comments and expectations to the principle investigator
- Submits an annual report by January 31st to the FDA as required by 21 CFR 361.1

  NOTE: The annual report **must** include a summary of each RDRC-approved study and a list of the current RDRC membership.

- Maintains approval by the FDA and ensures compliance with 21 CFR 361.1

  NOTE: The FDA monitors the activities of each institution's RDRC through on-site inspections, annual reports, notification of deficiencies, and withdrawal of RDRC approvals.

Protocols the RDRC is Authorized to Review

The RDRC reviews research protocols, as required by FDA regulation 21 CFR 361.1, involving radiopharmaceuticals *WITHOUT*:

- A New Drug Application (NDA) filed with the FDA
- An approved Investigational New Drug (IND) application
- An IND Exemption that may be subject to review by the RDRC in compliance with 21 CFR 361.1

To be eligible for review by the RDRC under 21 CFR 361.1, a protocol **must**:

- Involve certain radioactive compounds generally recognized as safe and effective
- Be designed to use radioactive compounds to obtain *basic* information regarding the metabolism of the compound or regarding human physiology, pathophysiology, or biochemistry
- **Not** be intended for immediate therapeutic use, diagnostic use, diagnostic studies, or clinical trials
- **Not** be intended to determine the safety and effectiveness of a drug (carry out a clinical trial)
- **Not** be designed as part of the routine clinical medical management of patients
- **Not** allow a pharmacological dose to cause a clinically detectable effect
- Be limited with respect to the annual and total radiation dose commitment to the numerical limits specified in 21 CFR 361.1

An example of a RDRC study would be an investigator wanting to study the expression of a specific neurotransmitter receptor in the brain.

SHUR

The SHUR is a subcommittee of the U-M's RPC and is comprised of the identical membership as the RDRC.

SHUR Responsibilities

The SHUR:

- Reviews, approves, requests modifications or clarifications, or defers research studies involving:
  - FDA-approved NDAs
  - FDA-approved IND
  - IND Exemptions

- Reviews, approves, request modifications or clarifications, or defers the clinical administration of radiopharmaceuticals intended for therapeutic use, diagnostic use, or similar purposes or to determine the safety and effectiveness of a drug (clinical trials)
- Ensures that radiopharmaceuticals are only administered to patients or human research subjects by or under the direct supervision of physicians meeting the specific training and experience requirements specified in the NRC medical regulations (10 CFR 35)
- Documents committee meeting minutes including voting results
- Communicates committee members comments and expectations to the authorized user physician or principle investigator
- Ensures compliance with NRC medical regulations (10 CFR 35) and the FDA research subject regulations for studies conducted under an IND, NDA, or IND exemption.

  NOTE: The NRC monitors the activities of the SHUR, respectively, through on-site inspections and notification of deficiencies or non-compliance issues.

An example of a SHUR study would be an investigator wants to study a new radioligand to monitor the treatment response of a brain tumor.

Any human research subject protocol submitted to the SHUR for review and approval is also required to receive IRBMED approval. IRBMED approval is contingent upon SHUR review and approval. Any revisions or modifications required by the SHUR must be incorporated into the protocol before final, full approval by the IRB will be granted.

RDRC/SHUR Membership

The RDRC is comprised of the identical membership as the SHUR; thus, RDRC/SHUR. The RPC Chair appoints the members and chairperson of the RDRC/SHUR.

In accordance with FDA regulations (21 CFR 361.1), an RDRC **must** have at least five members that include the following professional disciplines:

- The U-M RSO
- A physician recognized as a specialist in nuclear medicine
- An individual qualified by training and experience to formulate radiopharmaceuticals
- An individual with special competence in radiation dosimetry
- An individual that has special training and experience in various disciplines pertinent to the need of the committee in reviewing a research project such as:
  - Radiology
  - Internal Medicine
  - Radiation Therapy/Radiation Oncology
  - Clinical Pathology
  - Hematology
  - Endocrinology
  - Radiation Physics
  - Radiation Biophysics
  - Health Physics
  - Medical Physics
  - Cardiology
  - Pediatrics
  - Nuclear Pharmacy
  - Biochemistry

RDRC/SHUR Meetings

RDRC/SHUR meetings are typically scheduled on the third Monday of every month and the FDA allows traditional face-to-face meetings and teleconferencing when reviewing new or amendments to RDRC applications. The FDA does **not** approve of e-mail correspondences for the initial review of new RDRC applications or amendments.

The RDRC/SHUR members vote on each protocol reviewed at the meeting. Any member having involvement in a protocol or some other conflict of interest **must** abstain from voting on it.

For each protocol, members may vote to do the following:

- Approve unconditionally
- Approve pending minor changes in the protocol which may be approved after review by the Chair of the RDRC/SHUR
- Defer, requiring substantial or major changes or more information which will be reviewed at another committee meeting
- Disapprove

Committee meeting minutes are drafted by the RDRC/SHUR secretary and signed by the RDRC/SHUR chair. The minutes include a list of the members who were present for the meeting, voting results and committee members comments regarding the reviewed protocols.