

Radioactive Drug Research Committee (RDRC)

Standard Operating Procedures¹

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1 Radioactive Drug Research Committee (RDRC)

1.1 Policy

The State University of New York at Stony Brook (University or Institution as used in this document) fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, and participating in, research conducted by or under the auspices of the University. In the review and conduct of research, actions by the University will be guided by the U.S. Nuclear Regulatory Commission (NRC); U.S. Department of Health and Human Services (DHHS), and the U.S. Food and Drug Administration (FDA). Stony Brook University RDRC will conform to all applicable state and local laws.

The RDRC serves as the Radioactive Drug Research Committee for Stony Brook University. The University Standard Operating Procedures for Radioactive Drug Research Committee (RDRC) detail the policies, procedures and regulations governing research with humans and the requirements for submitting research proposals for review by the Stony Brook University RDRC. This is not a static document. The policies and procedures are regularly amended by the Assistant Vice President for Research Compliance, in consultation with applicable institutional entities (e.g., Institutional Official (IO), Office of Research Compliance staff, Radioactive Drug Research Committee, University counsel, etc.).

The RDRC has responsibility for verifying that proper licensing of the medical facility and the ability of the facility to possess and handle radioactive materials 361.1(d)(1)-(9) is in place prior to allowing research with human subjects to proceed.

The Assistant Vice President for Research Compliance will keep the University research community apprised of new information that affects the RDRC, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures will be available on the University's Human Research website and copies will be available upon request.

1.2 Mission

The mission of the RDRC is to:

- Protect the safety of all subjects, employees, staff, students, and the public involving the use of ionizing radiation
- Perform required reviews for the use of radioactive drugs (radiopharmaceuticals)

The RDRC includes mechanisms to:

- Establish a formal process to monitor, evaluate and continually improve the protection of human research subjects
- Dedicate resources sufficient to do so
- Exercise oversight of research protection
- Educate investigators and research staff about their ethical responsibility to protect research subjects; and
- When appropriate, intervene in research and respond directly to concerns of research subjects.

1.3 Definitions

Absorbed Dose

“Absorbed Dose” is the energy deposited per unit mass by any ionizing radiation to any absorbing medium. The unit of expression for Absorbed Dose is in units of Rad[®] or Gray (Gy).

Adverse Event

“Adverse Event” means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It does not include an **adverse event** or suspected **adverse reaction** that, had it occurred in a more severe form, might have caused death.

Authorized User

“Authorized User” means a physician, dentist or podiatrist who meets Nuclear Regulatory Commission (NRC) defined requirements and is specifically identified on an NRC or agreement state 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 and its

response expressed as if the whole body were irradiated. The effective dose is measured in rems (Rem) or sieverts (Sv).

Exploratory IND

“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.

External Dose

“External Dose” means that portion of the dose equivalent received from any source of radiation outside the body.

Food and Drug Administration (FDA)

“Food and Drug Administration” monitors the activities of each institution’s RDRC through on-site inspections, notification of deficiencies, and withdrawal of RDRC approvals.

Human Use

“Human Use” means the internal or external administration of radiation of radioactive material to human beings.

Individual

“Individual” means any human being.

Institutional Official (IO)

The “Institutional Official” is the person designated by the University to be responsible for the University’s RDRC. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution’s Assurance. The IO is the point of contact for correspondence addressing human subject research with OHRP, FDA, and other federal regulatory agencies.

Internal Dose

“Internal Dose” is that portion of the dose equivalent received from an uptake of radioactive material into the body.

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. The RDRC must review human research protocols involving radioactive drugs that are without a New Drug Application (NDA) filed with the FDA, or an approved Investigational New Drug (IND) application (an IND Exemption may be subject to review by the RDRC in compliance with 21 CFR 361.1.)

Investigator and Principal Investigator (PI)

“Investigator” refers to an individual performing various tasks related to the conduct of human subject research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the RDRC. 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 physician under tutelage.

Ionizing Radiation Exposure

“Ionizing Radiation Exposure” a measure of charge generation per unit mass and is only applicable to photons and not particulate radiation.

Medical Use

“Medical Use” means the intentional internal or external administration of byproduct material or the radiation from byproduct material to patients or human research subjects under the supervision of an authorized user.

Misadministration

The medical administration of; (1) a radiopharmaceutical from a source other than one ordered. (2) A radiopharmaceutical or radiation to the wrong person. (3) a radiopharmaceutical by a route of administration or to a part of the body other than that intended by the ordering physician. (4) An activity of a radiopharmaceutical for diagnostic purposes that differs from the prescribed dosage by more than 50%.

Prescribed Dosage

A “prescribed dosage” is the specified activity or range of activity of unsealed byproduct material as documented in a written directive, or in accordance with the directions of the authorized user for procedures performed pursuant to 10 CFR 35.100 and 10 CFR 35.200.

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.

Radioactive Materials Licensing

“Radioactive Materials Licensing” includes New York States being one of many states that have agreements with the federal government under the Atomic Energy Act. This agreement regulates all sources of radiation in the State, except reactors, federal facilities and large quantities of special nuclear materials which are regulated by the U.S. Nuclear Regulatory Commission. The Department of Labor's radioactive materials program was merged with the Department of Health's program in 2006. The Radioactive Materials Licensing program of the Bureau of Environmental Radiation Protection is responsible for licensing and inspecting approximately 1300 radioactive materials licensees including commercial, medical, academic and government facilities.

Radiologic (Radiological) Procedure

“Radiologic (Radiological) Procedure” is any procedure involving the medical use of externally penetrating radiation (e.g., X-ray) or an internally administered Radiopharmaceutical”)

Radiopharmaceutical

“Radiopharmaceutical” or “Radioactive Drug” is any drug, antibody or metabolic tracer labeled with a radioactive isotope. The term “radioactive drug” is defined in 21 CFR 310.3(n) and includes a “radioactive biological product” as defined in 21 CFR 600.3. A radiopharmaceutical emits ionizing radiation [See, 21 CFR 310.3]. The terms “radioactive drug” and “radiopharmaceutical” are deemed synonymous for purposes of these Standard Operating Procedures. Radioactive drugs when administered to human research subjects during the course of a research project are intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but **not** intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the

drug in humans for such purposes (*i.e.*, to carry out a clinical trial). Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research.

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)

“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 or ‘Agreement State’ issues radioactive material use licenses and regularly inspects licensee programs to confirm compliance with its regulations. New York State being an ‘Agreement State’ issued Radioactive Material License to Stony Brook University (including its Medical Center) through its Bureau of Environmental Radiation Protection (BERP) New York State Department of Health (NYSDOH). Stony Brook being an agreement state licensee is required to comply with the provisions of federal regulatory code 10 CFR 35 which is incorporated by reference in NYSDOH code 10 NYCRR 16. Stony Brook University and Stony Brook University Hospital operate under one license and have a Radiation Safety Committee with a Radiation Safety Subcommittee at the hospital. The NRC requires that a licensee have a Radiation Safety Officer and a Radiation Safety Committee.

The actions of the University will also conform to all other applicable federal, state, and local laws and regulations.

1.4 RDRC Organization and Operation

The RDRC is administered by the Office of Research Compliance (ORC), which also monitors compliance and promulgates policies and procedures to ensure that the RDRC membership is duly constituted in accordance with 21 CFR 361.1.

A Radioactive Drug Research Committee shall consist of at least five individuals. Each committee shall include the following three individuals:

- A physician recognized as a specialist in nuclear medicine [§ 361.1(c)(1)]
- An individual qualified by both training and experience to formulate radioactive drugs [§ 361.1(c)(1)].
- An individual with competence in radiation safety and radiation dosimetry [§ 361.1(c)(1)]

Individuals qualified in various disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, and radio pharmacy) [§ 361.1(c)(1)]. The addition of consultants in other pertinent medical disciplines is encouraged.

All of the required members must be in attendance. The RDRC chair is selected from the RDRC members by the members and the Vice President for Research. This individual signs all applications, minutes and reports of the RDRC.

Applications (i.e., Curriculum Vitae) for new members are submitted to the RDRC administrator and brought to the RDRC meeting for review. The RDRC members determine if the individual meets the requirements for membership on the committee. Once the review of the CV is complete, the individual is notified regarding their status as a potential RDRC member. The potential new member may observe a RDRC meeting. The individual must be approved by the Food and Drug Administration prior to membership on the RDRC. The name of the new member must be submitted to the FDA as soon as, or before, vacancies occur and new members are appointed to the RDRC.

Changes in membership and applications for new members must be submitted as soon as, or before, vacancies occur on the committee. Submission of Form 2914 (Membership Summary) and a current, signed and dated Curriculum Vitae for each proposed committee member must be received by the FDA for membership additions to occur. Updated Curriculum Vitae must be submitted to the Office of Research Compliance by each committee member every 3 years.

The RDRC meets at least once during each calendar quarter, or more frequently, at the discretion of the Chair. No member may vote on a protocol in which he/she is an investigator. Any member having involvement in a protocol or some other conflict of interest must abstain from voting on it. Members who do not attend at least 50% of meetings in a calendar year may be dropped from membership. Meetings require a quorum to occur (more than 50%). Meetings are held via videoconferencing. Protocols that involve special populations such as pediatrics, should include a specialist with expertise in that area as a consultant. The RDRC members vote on each protocol reviewed at the meeting. A majority of the members must vote to approve the application for the application to be approved.

Members are under strict requirements to maintain confidentiality regarding service on the RDRC. This requirement remains in full force during the entire term of service with the RDRC and continues in effect after such affiliation terminates.

Decisions of the committee are documented in the minutes. Minutes are confidential documents and are not available outside of committee members. Minutes are available to auditors or individuals required to review the minutes. The minutes are drafted by the RDRC Administrator. The minutes will include a listing of the members who were present for the meeting, voting results and outcome of review 361.1(c)(2). The minutes will include the numerical results of votes on protocols involving human subjects 361.1(c)(2). Comments from the protocol reviews will be communicated to the Principal Investigator by the RDRC Administrator. Each quarter, a copy of the minutes from the previous quarter will be sent to the Radiation Safety Committee for review. A summary of each new protocol will also be sent to the Radiation Safety Committee for review on a quarterly basis.

The RDRC must submit immediately, but no later than 7 calendar days, a special summary (using form 2915) to the Food and Drug Administration if a proposal includes more than 30 research subjects (or a previously approved protocol enrolment is expanded to include more than 30 subjects) or research subjects will be enrolled in the study who are <18 years of age.

It is the responsibility of the Principal Investigator to report all adverse events. If the RDRC receives an adverse event report, the RDRC will review the adverse event at a convened meeting. If it is determined that the adverse event is possibly related to the radiopharmaceutical, the RDRC has the responsibility for reporting to the Food and Drug Administration.

1.5 Radiation Dose Limits

The Radiation Safety Committee must review and approve the dosimetry for all active RDRC protocols. 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.

Dosimetry Calculations need to be defined in the proposed protocol, including all doses of radiopharmaceuticals and all external exposure from associated transmission scans such as CT and DEXA. Dosimetry calculations should be based on the most comprehensive sources available. Studies using human subjects are preferable to studies in preclinical species. If these are not available, studies in nonhuman primates are preferable to studies in other species. Peer-reviewed studies are preferable to unpublished studies. In all cases, the source of the dosimetry data shall be referenced and readily verifiable. Subjects may be enrolled in multiple studies involving radioactive drugs. The Principal Investigator is responsible for the amount of exposure experienced by these subjects.

The cumulative radiation dose for subjects who have been enrolled in multiple studies during the prior year must be compiled by a member of the study team prior to the study intervention and verified in writing by the RDRC Chair or Chair designee.

The adult subject's radiation dose resulting from the enrollment in other studies should be considered in the total dose, not to exceed the limits detailed in the table below. Under 361.1(b)(3)(i) the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year may not generally be recognized as safe if such dose exceeds the following:

Organ or System	Single Dose Sieverts (Rems)	Annual and Total Dose Sieverts (Rems)
Whole body	0.03 (3)	0.05 (5)
Active blood-forming organs	0.03 (3)	0.05 (5)
Lens of the eye	0.03 (3)	0.05 (5)
Gonads	0.03 (3)	0.05 (5)
Other organs	0.05 (5)	0.15 (15)

For a research subject under 18 years of age at the individual's last birthday, the radiation dose shall not exceed 10 percent of the limits provided in the above table.

Subjects will be asked regarding exposure based on participation in other studies (particularly those outside of Stony Brook University). This will be done prior to enrolment of the subject into the study. The source of the dosimetry data shall be referenced and readily verifiable. Radiation doses from x-ray procedures that are part of the research study (*i.e.*, would not have occurred but for the study) shall also be included. The possibility of follow-up studies shall be considered for inclusion in the dose calculations.

All radioactive material included in the drug either as essential material or as a significant contaminant or impurity shall be included when determining the total radiation doses and dose commitments

1.6 Drug Master File

A Drug Master File approach will be used to define the Chemistry, Manufacturing, and Controls for production of the radiopharmaceutical. The Drug Master File will be used for all studies involving that particular radiopharmaceutical. The Drug Master File may be expanded to include a definition of the no observable effect levels, literature references for the drug's bio-distribution, in humans, calculated dosimetry for the radiopharmaceutical at a targeted adult dose to be administered, etc. The Drug Master File for each radiopharmaceutical is reviewed, modified, and approved by the RDRC. The Drug Master File then serves as a reference for each protocol employing that drug. Occasionally, there will be a need to describe non-Drug Master File aspects. Examples include different targeted doses to be administered, a different route of administration, a different patient population such as patients with renal insufficiency or other conditions that may impact drug metabolism.

When something related to the drug changes, such as synthesis method, labelling, new information in the literature, etc. the master file will be updated. Literature on its own has no impact unless it leads to specific changes.

1.7 Research Covered by the RDRC

The University's RDRC covers all research involving human subjects that is under the auspices of the University. The research may be externally funded, funded from internal University sources, or conducted without direct funding. No matter how small the amount of

radioactivity, no study involving administration of a radioactive drug, to research subjects under this section, shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge is likely to result from that study. The University's RDRC has the responsibility to ensure that the amounts of radioactive materials administered are appropriate, the pharmacological and radiological dose limits are met (as specified in 21 CFR 361.1), and the radioactive compounds are generally recognized as safe and effective. Specifically, the RDRC:

- ✓ Ensures the underlying science and research protocol are of sound design such that information of scientific value may result
- ✓ Ensures that this is not the first use in humans as required in 21 CFR 361.1
- ✓ Ensures that the radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;
- ✓ Ensures the quality of the radioactive drugs used (i.e., appropriate production standards and Chemistry §361.1(d)(6)) and that appropriate standards comply with cGMP;
- ✓ 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 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);
- ✓ There is appropriate selection and consent of research subjects
 - The drug has documented previous human experience;
 - Requirements for pediatric protocols will be met;
- ✓ Ensures that the PI and research personnel are current on any required training related to radioactive pharmaceuticals and procedures
- ✓ Ensures that the study investigators are qualified (by training or experience) to conduct the study
- ✓ Ensures that the study is not intended as a clinical trial for the product
- ✓ Determines that the study is not designed as part of the routine clinical medical management of patients
- ✓ Determines that the dose of the radioactive drug to be administered is known not to cause a clinically detectable effect in humans
- ✓ Determines that the radiation dose to be administered is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain 361.1(b)(1)(iii) and is within the limits specified in 361.1(b)(3).

- ✓ 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.)

In order to assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of § 361.1(b)(3), the Radioactive Drug Research Committee shall require that:

- The investigator provides the absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies
- The investigator provides an acceptable method of radio assay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.
- The radioactive drug chosen for the study has that combination of half-life, types of radiations, radiation energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.
- The investigator utilizes adequate and appropriate instrumentation for the detection and measurement of the specific radionuclides.
- The investigator provides pharmacological dose calculations based on data available from published literature or from other valid human studies.

The Stony Brook University RDRC has the authority to approve, require modifications to the protocol, defer, or disapprove the protocol.

The Stony Brook University RDRC reviews all new research, amendments, and adverse events. Changes to a protocol without prior approval of the RDRC is considered non-compliance. It is important to regularly track enrollment in approved studies to ensure that the enrollment is not exceeding the number of human subjects approved for the protocol. On a quarterly basis a report will be given to the RDRC regarding number of subjects approved for each RDRC study. This report will include a comparison between the number of approved subjects and the actual number of subjects accrued.

1.8 Reporting

An annual report must be submitted to the Food and Drug Administration on or before January 31st of each year 361.1(c). The annual report includes the names and qualification of the members of the RDRC and of any consultants used by the RDRC (Form FDA 2914). The annual report includes the title of the study, name of the investigator, a brief description of the purpose of the research, pharmacological dose, name of the radionuclide(s) used, including any

contaminants or impurities, radiation absorbed dose, a claim of confidentiality if any and a summary of study information for each active study conducted during the preceding year (Form FDA 2915).

A special summary (Form FDA 2915) must be submitted to the FDA at the time a proposal is approved that involves more than 30 research subjects (or when a previously approved protocol is expanded to include more than 30 subjects) or at the time a research proposal is approved that involves exposure to a research subject under 18 years of age (studies involving minors are subject to dose limitations as specified in 21 CFR 361.1(b)(3) and must be supported with a review by a qualified pediatric consultant to the RDRC).

The special summary should include a justification for continued human subject enrollment to ensure that research is considered basic science and not moving towards immediate therapeutic or diagnostic purposes, or determining the safety and effectiveness of a drug in humans (i.e., carrying out a clinical trial for safety and efficacy). Reasons for increasing subject enrollment might include the study of the radioactive drug in different subpopulations related to age, sex, or disease types, such as subjects with impaired renal function or diabetes. Reasons such as statistical powering for non-basic research endpoints, grant requirements, or making decisions about patient treatment are not valid justifications for continued subject enrollment in RDRC studies. Contents of these special summary reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 20.61.

1.9 Institutional Official

The ultimate responsibility of the RDRC resides with the Vice President for Research (VPR). The Institutional Official (IO) is the primary contact at the University for the Office for Human Research Protections, Department of Health and Human Services, and the Food and Drug Administration. The IO, in close partnership with the Assistant Vice President for Research Compliance, has ultimate responsibility for oversight of:

- The development, management, and evaluation of policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the compliance program.
- The RDRC and University Investigators, ensuring that all are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations

- Keeping other appropriate institutional officials apprised on key matters regarding research at the University.
- Implementation the University's RDRC policy.
- Assessment of the resources of the University's RDRC including, but not limited to:
 - Staffing commensurate with the size and complexity of the research program;
 - Appropriate office space, meeting space, equipment, materials, and technology;
 - Resources for the production, maintenance, and secure storage of RDRC records;
 - Resources for auditing and other compliance activities and investigation of noncompliance;
 - Access to legal counsel;
- Ensuring assistance for investigators in their efforts to carry out University's research mission.
- Development and implementation of needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.

1.10 University Counsel

The University's RDRC relies on the University Counsel for the interpretation and application of New York State law and the laws of any other jurisdictions where research is conducted as they apply to human research.

1.11 The Investigator

The investigator is the ultimate protector of the human subjects who participate in research and must be qualified to conduct such activities. The investigator is expected to abide by the highest ethical standards and to develop a protocol that incorporates the ethical principles 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 Investigator is responsible for the following, including:

- ✓ Submitting a complete application, protocol, and other required study-related documents to the RDRC for review and approval;
 - ✓ Notifying the RDRC of any significant alteration of the original proposed research plan.
- Examples of amendments that need to be submitted to the RDRC:
- Change of inclusion and exclusion criteria
 - Change of radiation exposure

- Addition of a radiotracer
- Change of PI
- ✓ Reporting all protocol violations/deviations to the RDRC, including misadministration's as defined in this document. If the protocol deviation is minor, it may not require reporting to the FDA. However, the Principal Investigator should document the deviation, identify the root cause of the deviation, any additional risk to subject, if it is an isolated event or repeated deviation, a planned deviation, etc. and establish corrective action. Additionally, protocol deviations must be reported to the IRB as well;
- ✓ Understanding and agreeing to the RDRC Adverse Event reporting requirements; (Reporting immediately to the RDRC, all adverse effects potentially associated with the use of the radioactive drug in the research study.) The subject will be contacted within 48 hours after exposure to the radioactive drug to ask about adverse events. All adverse events reported by the subject will be submitted to the RDRC for review. If it is determined that the adverse event was probably attributable to the radiopharmaceutical, the adverse event must be reported to the FDA by the RDRC Chair, immediately (21 CFR 361.1(d)(8)). The reported adverse event will be tracked in a spreadsheet whereby each approved study is listed. This spreadsheet is internal to the RDRC and is kept confidential.** Examples of adverse events that need to be reported to the Food and Drug Administration:
 - Over-enrollment: A study is approved for 30 subjects and the researcher has enrolled (and administered a radiotracer dose) to greater than 30 subjects
 - Age of Subject: Enrollment of a subject who was less than 18 years old, and the study did not have a special approval for pediatrics
 - Over-dosing the subject: The subject was given a dose of a radiotracer that meant his or her radiation dose exceeded the limits that are acceptable under RDRC regulations.
 - Radiotracer didn't meet agreed-upon specifications: and the radiotracer was administered.
- ✓ Ensuring that female research subjects of childbearing potential state in writing that they are not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before they may participate in any study.
- ✓ Ensuring that all rules and regulations as related to the use of radioactive materials under Stony Brook's Radioactive Materials License is adhered to by all those working under approved protocols.
- ✓ Submitting a completed FDA form 2915 for each active study on or before January 5th of each year. The form should include the details of all subjects scanned during the prior calendar year.

****Note:** This requirement is different than the IRB's reporting requirements and requires reporting to the RDRC.

- ✓ Assuring that the radiation dose to research subjects is as low as is reasonably achievable to perform the study and meets the criteria of applicable regulations;
- ✓ Demonstrating that the radioactive drug used in the research study meets appropriate pharmaceutical, radiochemical, and radionuclide standards of identity, strength, quality, In order to assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of § 361.1(b)(3), the Radioactive Drug Research Committee shall require that:
 - ✓ The investigator provides the absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies
 - ✓ The investigator provides an acceptable method of radio assay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.
 - ✓ The radioactive drug chosen for the study has that combination of half-life, types of radiations, radiation energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.
 - ✓ The investigator utilizes adequate and appropriate instrumentation for the detection and measurement of the specific radionuclides.
 - ✓ The investigator provides pharmacological dose calculations based on data available from published literature or from other valid human studies.
- ✓ and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted;
- ✓ Carrying out protocols consistent with the written protocol and the directives and approvals of the 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 Authorized User the details of the protocol and seek input on safety improvements;
- ✓ Ensuring that a physician is listed as study personnel.

Investigators who want to enroll individuals who have prior exposure (within the preceding 12 months) must obtain approval by the chair of the RDRC prior to enrollment. The chair of the RDRC will review all reported exposure of the potential enrollee and make a recommendation.

If the RDRC chair requests that the individual not be enrolled, the decision will stand and the individual must not be enrolled.

All subjects must give informed consent and the investigator must establish and maintain an open line of communication with all research subjects participating in his/her studies. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete appropriate training and must obtain all required approvals prior to initiating research.

1.11.1 IND Requirements

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. If the study is covered under an IND after the study has been approved by the RDRC, the Investigator must notify the RDRC of this change within 30 days.

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 RDRC, which is an FDA required committee.

1.12 Institutional Review Board

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 the research. The NRC stipulates provisions for the protection of research subjects in 10 CFR 35.6. Specifically, licensees are responsible for ensuring that research involving human subjects “obtain review and approval of the research from the 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 Stony Brook IRB will approve a protocol involving the use of ionizing radiation after the radioactive drug committee approval. If the approved protocol is amended, investigator must submit the amendment to the IRB for review and approval. Institutional Review Boards are

required to conduct continuing review of research at intervals appropriate to the degree of risk, but not more than once a year § 56.109(f). The PI is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process.

1.13 Radiation Safety Committee

The Radiation Safety Committee (RSC) of the university is responsible for the oversight of the use of radioactive materials, both for research and for clinical use. The University possesses a Medical-Research Broad Scope License from the New York State Department of Health/Bureau of Environmental Radiation Protection allowing for the possession and use of radioactive materials/radiation-producing equipment 10 NYCRR Part 16 – Ionizing Radiation; 10 CFR 35 Specific Domestic Licenses of Broad Scope). A Broad Scope radioactive materials license puts the responsibility for developing all elements of a radiation safety program on the licensee, i.e., Stony Brook University. The RDRC assures the Radiation Safety Committee through the review process that studies undertaken under the radiation license are performed in accordance with 10 NYCRR 16 (title: Part 16 – Ionizing Radiation / New York codes, Rules and Regulations (ny.gov) and the limits and conditions of Stony Brook's radiation license

2 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:
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm085838.pdf>

New York State Department of Health

- 10 NYCRR 16
- PUBLIC HEALTH LAW ARTICLE 35 - PRACTICE OF RADIOLOGIC TECHNOLOGY
- Part 89 PRACTICE OF RADIOLOGIC TECHNOLOGY

Nuclear Regulatory Commission (NRC)

- 10 CFR Parts 19, 20 and 35

Human Subject Guidance 940 GD.1

- Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation
- 10 CFR 35.6 (provisions for the protection of human research subjects)

RDRC Forms

- FDA 2914 (PDF - 747KB) Report on Research use of Radioactive Drugs: Membership Summary
- FDA 2915 (PDF - 2MB) Report on Research use of Radioactive Drugs: Study Summary

Guidance for Industry

- [RDRC Final Guidance: Human Research without an Investigational New Drug Application \(PDF - 417KB\)](#) (August, 2010)
- Developing Medical Imaging Drug and Biological Products
 - [Part 1: Conducting Safety Assessments \(PDF - 471KB\)](#)
 - [Part 2: Clinical Indications \(PDF - 231KB\)](#)
 - [Part 3: Design, Analysis, and Interpretation of Clinical Studies \(PDF - 307KB\)](#)
 - [PET Drug Products - Current Good Manufacturing Practice \(CGMP\) \(PDF - 399KB\)](#)

FDA Radioactive Drug Research Committee Program Presentations

- [Society of Nuclear Medicine and Molecular Imaging \(SNMMI\) Annual Meeting \(June 10 to 14, 2016\)](#)
- [Updates from the Division of Medical Imaging Products \(DMIP\) - Louis Marzella MD, PhD](#)
- [Expanded Access to Investigational Imaging Drugs - Phillip B. Davis, MD](#)
- [Extending Imaging Applications to Pediatric Patients - Ira Krefting, MD](#)
- [PET Drug Inspections and Compliance Update - Krishna Ghosh, MS, PhD](#)
- [FDA Update - 68Ge - 68Ga Generators and 68Ga radiolabeled Approved Kit - John K. Amartei, PhD](#)
- [Peptides as Radiopharmaceuticals - CMC Perspectives - Ravindra K. Kasliwal, PhD](#)
- [Good Analytical Chemistry Practices in PET Radiopharmaceuticals – \(poster presentation\) - Elise Luong, PhD, Eldon Leutzinger, PhD & Danae Christodoulou, PhD](#)

Contact Food and Drug Administration

RDRC Team at RDRC@cder.fda.gov.

- CAPT (ret.) Richard Fejka, RPh, MS, BCNP, Senior Manager, Radioactive Drug Research Committee Program
- Modupe Fagbami, RDRC Regulatory Health Project Manager

- Ira Krefting, MD, Deputy Director of Safety, Division of Medical Imaging Products

All reports (i.e., annual reports, special summaries, changes in membership, and adverse reaction reports) are sent to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
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Rockville, MD 20857

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