

Policy and Procedure Manual
Massachusetts General Hospital
Radioactive Drug Research Committee
RDRC #0032

PURPOSE

This document defines the membership, authority, responsibilities and operating rules of the Hospital's Radioactive Drug Research Committee (RDRC).

DEFINITIONS

Radioactive Drug: The term radioactive drug means any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any non-radioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides.

Drug master File: a file is maintained in the office of the chairman of the RDRC for each radioactive drug approved by the RDRC. The file becomes an official compendium of drug information, including data on the materials, methods, syntheses, quality control and radiation dosimetry associated with the drug. All subsequent protocols submitted to the RDRC using the previously approved drug will reference the original drug master file.

POLICY

Approval. The Radioactive Drug Research Committee shall be specifically approved by the Center for Drug Evaluation and Research of the Food and Drug Administration. The Radioactive Drug Research Committee (RDRC) is the governing body for all aspects of the use of radioactive drugs for certain research uses as described in 21 CFR Part 361. Duly constituted Radioactive Drug Research Committees are authorized and approved by the U.S. Food and Drug Administration to review and approve or disapprove certain uses of radioactive drugs in the conduct of basic research in humans. The committee applies RDRC review criteria to all human research applications involving the use of radioactive drugs to determine the appropriateness of a given protocol being reviewed by the RDRC process. Protocols not meeting RDRC criteria are referred to the Radiation Safety Committee for alternate regulatory review. The RDRC fulfills all reporting requirements of 21 CFR 361(c)(3) including annual and special reports.

The RDRC can approve the use of radioactive drugs in humans in research projects 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). Research projects designed to conduct a clinical trial of a radioactive drug must be conducted under a Notice of Claimed Exemption for an Investigational Drug (IND) submitted to the FDA and approved by the Radiation Safety Committee.

The conditions under which use of radioactive drugs for research are considered safe and effective are:

1. **Approval by Radioactive Drug Research Committee.** A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration in accordance has determined, in accordance with the standards set forth that:
 - 1.2 The pharmacological dose is within the limits set forth in paragraph 2 of this section;
 - 1.3 The radiation dose is within the limits set forth in paragraph 3 of this section;
 - 1.4 The radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;
 - 1.5 The study meets the other requirements regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent of research subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee;
 - 1.6 The use of the radioactive drug in human subjects has the approval of the Radioactive Drug Research Committee.
2. **Limit on pharmacological dose.** The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.
3. **Limit on radiation dose.** The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

3.1 Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following:

3.1.1 Whole body, active blood-forming organs, lens of the eye, and gonads:

	<u>Rems</u>
Single dose	3
Annual and total dose commitment	5
Other organs:	
Single dose	5
Annual and total dose commitment	15

3.1.2 For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph 2 of this section.

3.1.3 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. 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.

- 3.1.4 Numerical definitions of dose shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.

Membership

A Radioactive Drug Research Committee shall consist of at least five individuals. Each committee shall include the following three individuals: (i) A physician recognized as a specialist in nuclear medicine, (ii) a person qualified by training and experience to formulate radioactive drugs, and (iii) a person with special competence in radiation safety and radiation dosimetry. The remainder of the committee shall consist of 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, health physics, and radiopharmacy). Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. A list of current members is shown in Appendix 1.

Joint committees involving more than one medical institution which have been established in order to achieve a high level and diversity of experience will be acceptable. In this regard, in June 2003, the MGH RDRC assumed responsibility for reviewing appropriate human research protocols being submitted by the Dana Farber Cancer Institute that require RDRC oversight. This agreement is in effect until such time that the volume of protocol review exceeds a workable level, i.e., at such time that a full PET Center becomes operational in the Longwood area campus.

Function

The Radioactive Drug Research Committee shall select a chairman, who shall sign all applications, minutes, and reports of the committee. The committee shall meet at least once each quarter in which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present with appropriate representation of the required fields of specialization. Minutes shall be kept and shall include the numerical results of votes on protocols involving use in human subjects. No member shall vote on a protocol in which he/she is an investigator.

Reports

The Radioactive Drug Research Committee shall submit an annual report on or before January 31 of each year to the Food and Drug Administration, Center for Drug Evaluation and Research, HFD-160, 5600 Fishers Lane, Rockville, MD 20857. The annual report shall include the names and qualifications of the members of, and of any consultants used by, the Radioactive Drug Research Committee, and, for each study conducted during the preceding year, a summary of information presented in the following format:

Annual Report on Research Use of Radioactive Drug

1. Title of the research project.
2. Brief description of the purpose of the research project.
3. Name of the investigator responsible.
4. Pharmacological dose: (a) Active ingredients, (b) Maximum amount administered per subject

5. Name of the radionuclide(s) used, including any present, as significant contaminants or impurities.
6. Radiation absorbed dose. Provide the maximum dose commitment to the whole body and each organ specified in 21 CFR 361.1(b)(3)(i) that was received by a representative subject and the calculations or references that were used to estimate these maximum dose commitments. The report shall include the dose contribution of both the administered radionuclide(s) and any X-ray procedures associated with the study. If the study elicits data on the uptake or excretion of the radioactive drug pertinent to the estimation of dose commitment, report the mean value and range of values. For each subject provide:
 - 6.1 Age, sex, and approximate weight.
 - 6.2 Total activity of each radionuclide administered for each radioactive drug used in the study. Report each X-ray procedure used in conjunction with the study.
 - 6.3 If the subject has participated in other radioactive drug research studies, report the name of the radioactive drug used in these other studies, the date of administration, and the total activity of each radionuclide administered. If any X-ray procedures were used, identify the X-ray procedure(s) and include an estimate of the absorbed radiation doses.
 - 6.4 If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides.
7. A claim of confidentiality, if any.

Special Reports

At any time a proposal is approved which involves exposure either of more than 30 research subjects, or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Administration a special summary of information.

Review Procedures

In making the determination required by this policy and federal regulations the Radioactive Drug Research Committee shall consider the following requirements and assure that each is met. A RDRC review criteria checklist used by reviewers is included in Appendix 2.

1. **Radiation dose to subjects.** To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the following criteria. The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.
 - 1.1 Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following:
 - 1.2 Whole body, active blood-forming organs, lens of the eye, and gonads:

	<u>Rems</u>
Single dose	3
Annual and total dose commitment	5
Other organs:	
Single dose	5
Annual and total dose commitment	15

- 1.3 For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph 2 of this section.
- 1.4 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. 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.
- 1.5 Numerical definitions of dose shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.

The Radioactive Drug Research Committee shall require that:

- 1.6 The investigator must provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies.
 - 1.7 The investigator provide for an acceptable method of radioassay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.
 - 1.8 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.
 - 1.9 The investigators utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.
2. **Pharmacological dosage.** To determine that the amount of active ingredients to be administered does not exceed the regulatory limits the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.

3. **Qualifications of investigators.** Each investigator shall be qualified by training and experience to conduct the proposed research studies.
4. **License to handle radioactive materials.** The responsible investigator or institutions shall be a listed investigator under the hospital's broad license, and be named on a human use permit.

5. **Human research subjects.** Each investigator shall select appropriate human subjects and shall obtain the review and approval of the partners Human Research Committee. The research subject shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before she may participate in any study. Current procedures approved by the MGH Radiation Safety Committee shall be followed in pregnancy testing.
6. **Quality of radioactive drug.** The radioactive drug used in the research study shall meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic 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 Radioactive Drug Research Committee shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form. All documentation of drug product quality identity and strength shall be contained in a Drug Master File to be prepared in conjunction with the protocols application process.

A radioactive drug prepared, packaged, distributed, and primarily intended for use in accordance with the requirements of this section shall be packaged and labeled in compliance with Federal, State, and local law regarding radioactive materials and if the label of the immediate container and shielded container, if any, either separate from or as part of any label and labeling required for radioactive materials by the State or local radiological health authorities bear the following:

- 6.1 The statement “Rx only”,
- 6.2 The statement “To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 361.1)”;
- 6.3 The established name of the drug, if any;
- 6.4 The established name and quantity of each active ingredient;
- 6.5 The name and half-life of the radionuclide, total quantity of radioactivity in the drug product’s immediate container, and amount of radioactivity per unit volume or unit mass at a designated referenced time;
- 6.6 The route of administration, if it is for the other than oral use;
- 6.7 The net quantity of contents;
- 6.8 An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;
- 6.9 The name and address of the manufacturer, packer, or distributor;
- 6.10 The expiration date, if any;
- 6.11 If the drug is intended for parenteral use, a statement as to whether the contents are sterile;

6.12 If the drug is for other than oral use, the names of all inactive ingredients, except that:

6.12.1 Trace amounts of harmless substances added solely for individual product identification need not be named.

6.12.2 If the drug is intended for parenteral use, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust pH or to make the drug isotonic may be declared by name and a statement of their effect; if the vehicle is water for injection, it need not be named. Provided, however, that in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information may be placed on the shielded container only.

7. **Research protocol.** No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, to research subjects shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and 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).
8. **Adverse reactions.** The investigator shall immediately report to the Radioactive Drug Research Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radioactive Drug Research Committee to the Food and Drug Administration, Center for Drug Evaluation and Research, HFD-160, 5600 Fishers Lane, Rockville, MD 20857.
9. **Approval by an institutional review board.** The investigator shall obtain the review and approval of the Partners Human Research Committee.

Appendix 1

Members of the Radioactive Drug Research Committee

Ronald J. Callahan, Ph.D., Chairman
Nuclear Medicine

Gordon L. Brownell, PhD
Radiology

Rex Woodleigh, M.M.Sc.
Radiation Safety Officer

John F. Burke, MD
Surgical Service

Ming-Yong, Yu, M.D., Ph.D.
Surgery

John A. Correia, PhD
(Vice Chairman)
Radiology

Ralph Weissleder, M.D., Ph.D.
Radiology

Alternates

Alan J. Fischman, MD, PhD
Nuclear Medicine

Stephen Dragotakes
Nuclear Medicine

Bob Liu, Ph.D.
Radiology

Carlos Rabito, M.D., Ph.D.
Nuclear Medicine

Keith W. Miller, PhD
Anesthesia

Tara Medich, Ms, CHP

Appendix 2

RDRC Review Criteria Checklist

CHECKLIST

To approve a proposed research study, the RDRC must consider the following:

- 1. Is the pharmacological dose within the following limits?** Yes ___ No ___
- a. The amount of active ingredient or combination of active ingredient shall be known to not cause any clinically detectable pharmacological effect in humans. Yes ___ No ___
- *Sufficient Documentation Provided: Yes ___ No ___
- b. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously (e.g. under an IND or for a therapeutic use), the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredient excluding the radionuclide. Yes ___ No ___ N/A ___
- *Sufficient Documentation Provided: Yes ___ No ___
- 2. Were pharmacological dose calculations based on data available from published literature or from other valid studies?** Yes ___ No ___
- 3. Is the radiation dose within the following limits?** Yes ___ No ___
- a. Subject must receive the smallest radiation dose practical to perform the study Yes ___ No ___
- *Absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies was provided Yes ___ No ___
- *An acceptable method of radioassay of the radioactive drug prior to its use was provided Yes ___ No ___
- *Adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide will be utilized Yes ___ No ___

*The radioactive drug has the combination of half-life, type of radiation, radiation energy, metabolism and chemical properties which results in the lowest dose to the whole body or specific orifices which is passable to obtain the necessary information.

Yes ___ No ___

b. For adult subject: under no circumstances may radiation dose from single study or cumulatively from a number of studies conducted within 1 year exceed:

*Whole body, active blood-forming organs, lens of eye, and gonads:

Yes ___ No ___

Single Dose	3 Rems
Annual & Total Dose	5 Rems

Yes ___ No ___

Yes ___ No ___

*Other Organs:

Single Dose	5 Rems
Annual & Total Dose	15 Rems

Yes ___ No ___

Yes ___ No ___

c. For subject under 18 years of age: radiation dose may not exceed 10 percent of dose set forth above.

Yes ___ No ___

d. When determining total radiation dose and dose commitments must consider:

*All radioactive material included in drug either as essential material or as significant contaminant or impurity;

Yes ___ No ___ NA ___

*X-ray procedures that are part of the research study;

Yes ___ No ___ NA ___

*Possibility of follow-up studies

Yes ___ No ___ N/A ___

e. Are the numerical definitions of dose based on absorbed fraction method of radiation absorbed dose calculation (e.g. system set forth by Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine or by the International Commission on Radiological Protection)?

Yes ___ No ___ N/A ___

*Sufficient Documentation Provided

Yes ___ No ___

4. Is the radiation exposure justified by the quality of the study being undertaken and the importance of the information it seeks to obtain?

Yes ___ No ___

5. Is each investigator qualified by training and experience to conduct the proposed research studies?

Yes ___ No ___

6. Is the investigator's or institutions license to handle radioactive materials appropriate? Does the investigator meet the following requirements?

- a. For reactor-produced isotopes: the investigator or institution shall be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license; Yes ___ No ___ N/A ___
- b. For non-reactor-produced isotopes: the investigator or institution shall be licensed by other appropriate State or local authorities, when required by state or local law. Yes ___ No ___ N/A ___

7. Is the use of human subjects appropriate and does it meet the following requirements?

- a. Number of subjects should not exceed 30. Yes ___ No ___
- b. Research must be reviewed and approved by an institutional review board and consent must be obtained from the subjects or legal representatives. Yes ___ No ___
- c. Research subjects must be at least 18 years of age and legally competent. Yes ___ No ___
- d. Exceptions to preceding requirement only permitted if:
- *Investigator can demonstrate that 1) the study presents unique opportunity to gain information not currently available; 2) requires use of subjects less than 18, 3) is without significant risk to subject; Yes ___ No ___ N/A ___
- *RDRC review is supported with review by qualified pediatric consultant Yes ___ No ___ N/A ___
- e. Female subjects of childbearing potential must: 1) state in writing that they are not pregnant or 2) on basis of pregnancy test be confirmed as not pregnant Yes ___ No ___ N/A ___

8. Does the radioactive drug meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality and purity? Yes ___ No ___ N/A

Were radioactive materials for parenteral use prepared in sterile and pyrogen-free form? Yes ___ No ___ N/A ___

9. Is the research design appropriate in that:

a. Scientific knowledge and benefit is likely to result from the study and the research shall be based upon sound rationale derived from appropriate animal studies or published literature; Yes ___ No ___ N/A ___

b. Scientific knowledge and benefit should be of sound design such that information of scientific value may result Yes ___ No ___ N/A ___

c. Will the radiation dose be sufficient and no greater than necessary for purpose of study? Yes ___ No ___ N/A ___

d. Will the projected number of subjects shall be sufficient and no greater than necessary and should reflect the fact that the study is intended to obtain basic research information are not intended for other purposes. Yes ___ No ___ N/A ___

10. Is the packaging, label, and labeling of the radioactive drug in compliance with Federal, State, and local law regarding radioactive materials? Yes ___ No ___ N/A ___

Is the label of the immediate container and shielded container, if any, in compliance with RDRC requirements? Yes ___ No ___ N/A ___