

APPENDIX D

THE HUMAN USE SUBCOMMITTEE, RADIATION SAFETY COMMITTEE, AND THE RADIOACTIVE DRUG RESEARCH COMMITTEE

A. Background

Exposure of human subjects to ionizing radiation in the course of a biomedical research study involves several considerations in addition to those applied to clinical research studies which do not incorporate such an intervention. The risks of involved radiation exposure must be appropriately addressed and delineated in the consent form. Also, the research study must be conducted in accordance with institutional policies and procedures and with state and/or federal regulations that govern the safe use and handling of radioactivity. To ensure that these special considerations are properly addressed, biomedical research studies involving the experimental exposure of human subjects to ionizing radiation are subject to review and approval by the Human Use Subcommittee of the Radiation Safety Committee (HUSC). Approval of the HUSC for research involving the experimental evaluation of drugs or devices which emit ionizing radiation is in addition to the requirement for approval by the Institutional Review Board (IRB).

It is noted that these guidelines apply to research studies involving the use of devices or drugs that emit ionizing radiation. The use of (ionizing) radiation-emitting devices or drugs for routine clinical procedures is also subject to review and approval by the HUSC in accordance with the University's federal and state radiation licensing conditions.

B. Research Uses of Ionizing Radiation - Submission Requirements

1. Use of standard procedures for research subject screening or medical management.

Biomedical research studies frequently involve the use of 1) a standard diagnostic procedure (e.g., nuclear medicine procedure, chest X-ray, computerized tomography, angiography) in a routine clinical manner and frequency for research subject screening and/or to evaluate a therapeutic response; or 2) a standard radiation therapy procedure indicated for medical management of the patient. Such uses of standard clinical procedures do not require prior review and approval by the HUSC.

If the investigator or IRB is uncertain if the proposed research use of (ionizing) radiation-emitting drug or device is consistent with routine clinical practice, the research protocol should be submitted for review and approval by the HUSC in accordance with the requirements listed under B.2.a. (for a device) or B.2.c (for a radioactive drug).

2. Experimental evaluation of a (ionizing) radiation-emitting device or drug.

Review and approval of the HUSC is required to initiate biomedical research studies directed at the experimental evaluation of a drug or device that emits ionizing radiation. The specific information to be submitted to the HUSC will depend on the FDA-approval status of the drug or device and its intended use.

a. Experimental evaluation of an FDA-approved device (e.g., for an "Off-label" indication) or an unapproved device which emits ionizing radiation:

Food and Drug Administration policies permit the experimental evaluation, in human subjects, of an FDA-approved device for an open-label indication or device that is not the subject of an approved IDE or 510K application provided that it is classified as a "nonsignificant risk device" based on review by the IRB (see Appendix F). To be considered as presenting a "nonsignificant risk", the proposed

experimental use of the device must not be of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health. Failure to meet the criteria for "nonsignificant risk" requires that the sponsor of the device obtain FDA approval of an Investigational Device Exemption (IDE).

The following materials should be submitted to the HUSC:

- four (4) copies of a completed Application for the Research Use of Ionizing Radiation ([HUSC-RSC Form 1001](#), see IRB web site (www.irb.pitt.edu); IRB Forms);
 - four (4) copies of the research protocol and informed consent document (IRB format); and
 - four (4) copies of the device manufacturer's clinical protocol and/or investigator's brochure or the investigator-sponsored IDE application.
- b. Experimental evaluation of a FDA-approved radiopharmaceutical prepared using a non-approved (i.e., not according to product labeling) method; and/or administered by a non-approved (i.e., not according to product labeling) route; and/or used for a non-approved (i.e., "off-label") indication. For research involving the experimental evaluation of an "off-label" preparation and/or "off-label" use of a FDA approved radiopharmaceutical, submit:

- nine (9) copies of a completed Application for the Research Use of Ionizing Radiation ([HUSC-RSC Form 1001](#), see IRB web site (www.irb.pitt.edu); IRB Forms);
- nine (9) copies of the research protocol and informed consent document (IRB format).
- nine (9) copies of completed [HUSC-RSC Form 1002](#), "Information Required in Support of the Research Use of a Non-Approved Radioactive Drug" (see IRB web site (www.irb.pitt.edu); IRB Forms).

- c. Experimental evaluation of a radioactive drug which is the subject of a FDA-accepted Investigational New Drug (IND) exemption:

For research involving the experimental evaluation of a radioactive drug conducted under an FDA-accepted IND application, submit:

- nine (9) copies of a completed Application for the Research Use of Ionizing Radiation ([HUSC-RSC Form 1001](#), see IRB web site (www.irb.pitt.edu); IRB Forms);
- nine (9) copies of the research protocol and informed consent document (IRB format).
- five (5) copies of the manufacturer's clinical protocol and/or investigator's brochure or the investigator-sponsored IND application.

- d. Experimental evaluation of a radioactive drug that is not FDA-approved:

FDA regulations (21 CFR Part 361.1) permit the research use, in human subjects, of radioactive drugs that are not currently the subject of an FDA-accepted IND or new drug application (NDA), provided that certain special conditions are met. These special conditions are outlined as part of HUSC-RSC Form 1002, Information Required in Support of the Research Uses of a Non-Approved Radioactive Drug (see IRB web site (www.irb.pitt.edu); IRB Forms). To facilitate the review and approval of research studies that meet these conditions, the HUSC also serves in the capacity of the Radioactive Drug Research Committee (RDRC) mandated by these FDA regulations. The following information should be submitted to permit both HUSC and RDRC review of the research use of a non-approved radioactive drug that is not currently the subject of an FDA-accepted IND application:

- nine (9) copies of a completed Application for the Research Use of Ionizing Radiation ([HUSC-RSC Form 1001](#), see IRB web site (www.irb.pitt.edu); IRB Forms);
- nine (9) copies of the research protocol and informed consent document (IRB format).
- nine (9) copies of completed [HUSC-RSC Form 1002](#), "Information Required in Support of the Research Use of a Non-Approved Radioactive Drug" (see IRB web site (www.irb.pitt.edu); IRB Forms)).
- nine (9) copies of a written notification that the proposed research study has been approved by a scientific review committee representing the principal investigator's primary academic or center affiliation.

3. Modifications

Modifications to a HUSC or RDRC-approved research study which affect the number of human subjects exposed to ionizing radiation; the amount of radiation exposure to subjects or the method of preparation of a radioactive drug exposure of human subjects to ionizing radiation or require prior approval of the HUSC and RDRC (if applicable).

- a. If the modification involves the experimental evaluation of a (ionizing) radiation emitting device, submit:
 - four (4) copies of a completed, revised Application for the Research Use of Ionizing Radiation ([HUSC-RSC Form 1001](#), see IRB web site (www.irb.pitt.edu); IRB Forms);
 - four (4) copies, each, of the following information submitted to the IRB:
 - (i) New IRB Cover Sheet
 - (ii) Completed and signed Modification Request form.
 - (iii) Revised research protocol and informed consent document with modifications highlighted.
- b. If the modification involves the experimental evaluation of a radioactive drug, submit:
 - nine (9) copies of a completed, revised Application for the Research Use of Ionizing Radiation (HUSC-RSC Form 1001, see IRB web site (www.irb.pitt.edu); IRB Forms);
 - (if the modifications are limited to the radioactive drug preparation) nine (9) copies of a revised HUSC-RSC Form 1002, "Information Required in Support of the Research Use of a Non-Approved Radioactive Drug" (see IRB web site (www.irb.pitt.edu); IRB Forms) with the modifications highlighted.
 - (if the modifications involve the experimental use of the radioactive drug) nine (9) copies, each, of the following information submitted to the IRB:
 - (i) New IRB Cover Sheet
 - (ii) Completed and signed Modification Request form.
 - (iii) Revised research protocol and informed consent document with modifications highlighted.

4. Renewal/Termination

The RDRC will monitor the status of approved research projects by requiring that the principal investigator and/or authorized user complete, on a periodic basis, a Research Study Progress Report. HUSC approval shall remain in effect for the duration of the IRB approval.

5. Location for submissions

Materials submitted for review and approval by the HUSC and the RDRC should be delivered to the Ground Floor of 3500 5th Avenue, using the McKee Place Entrance. Such material should be clearly marked "ATTENTION: HUSC/RDRC."

6. HUSC/RDRC Meeting Dates and Deadlines

a. HUSC/RDRC meeting dates:

- The HUSC/RDRC is required by regulation to meet as a full-committee to review research studies involving the experimental evaluation of radioactive drugs or devices that utilize by-product radioactive materials (e.g., gamma knife). The HUSC/RDRC meets on the third Wednesday of each month to review materials submitted on or before the deadline date for that month.
- The review of research studies involving the experimental evaluation of x-ray-emitting devices can be expedited by a limited review process. Such research studies will be reviewed as received.

b. Deadline dates:

- Research protocols (i.e., involving the experimental evaluation of a radioactive drug or a device that utilizes by-product material) which require RDRC and/or HUSC review by the full committee should be submitted to 3500 5th Avenue, Ground Floor (i.e., using the McKee Place Entrance), by 4 p.m. the first Tuesday of each month in order to permit their review during that month.
- There are no deadline dates for research protocols (i.e., involving the experimental evaluation of x-ray-emitting devices) which can be reviewed by the HUSC using an expedited process. Such research protocols should be submitted to Ground Floor of 3500 5th Ave (i.e., using the McKee Place Entrance).

C. Research Uses of Ionizing Radiation - General Considerations

1. Use of (ionizing) radiation-emitting devices or drugs in a research study.

In planning a research study, investigators should first consider whether it is necessary to use ionizing radiation to obtain the desired information. Any investigation requiring the use of ionizing radiation must produce the needed information at minimum radiation doses to human subjects and the research must be defensible in terms of clinical and scientific relevance.

2. Required involvement of an "authorized user"

An "authorized user" is a physician or dentist approved by the University's Radiation Safety Committee as possessing the appropriate qualifications for the proposed human use of the (ionizing) radiation-emitting device or drug. An "authorized user" must be involved in the research study as either the principal investigator or a listed co-investigator.

- a. The "authorized user" listed on the research study shall be responsible for compliance with all statements and conditions respective to the preparation, testing, administration and/or use of the (ionizing) radiation-emitting drug or device as submitted to and approved by the HUSC and RDRC.
- b. The "authorized user" listed on the research study shall be responsible for all routine reports (e.g., Research Study Progress Report, Modification Requests) and special (e.g., adverse event, misadministration) reports required by the HUSC and RDRC.

3. Assessment of radiation risks

A major responsibility of the HUSC is the review of the radiation risks to human subjects attendant with the conduct of the proposed research project. The HUSC pays special attention to the radiation risks associated with a single study (i.e., inclusive of all procedures performed on the subject during a single study session) and the cumulative risks (i.e., inclusive of all single studies performed on the subject) associated with total project participation. The HUSC also reviews the methods or sources of information that were used to approximate these risks. Estimates of radiation exposure to human subjects must be made in advance and included as part of the research protocol submitted to the HUSC. (Assistance is available from the Radiation Safety Office (412-624-2728).

4. Informed Consent statements of radiation risk.

The discussion of radiation risks in the informed consent document and patient dialogue should include comparisons with natural background (i.e., for low risk procedures) or occupational worker limits. Examples of statements that are reasonable include the following:

- a. For whole body radiation exposures (e.g., radioactive drugs: Effective Dose Equivalent (EDE) < 1000 mrem:

"Participation in this research study involves exposure to radiation from (specify respective procedure(s) to be performed). The amount of radiation exposure that you will receive from this (these) procedure(s) is equivalent to a uniform whole body dose of ____ mrem (a unit of radiation exposure) which is approximately (indicate multiplication factor, fraction, or percentage of) the average amount of natural environmental radiation exposure (300 mrem dose) that each member of the general public receives per year. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low when compared to other everyday risks."

- b. For a whole body radiation exposures (e.g., radioactive drugs): Effective Dose Equivalent (EDE) of 1000 mrem - 5000 mrem:

"Participation in this research study involves exposure to radiation from (specify respective procedure(s) to be performed). The amount of radiation exposure that you will receive from this (these) procedure(s) is equivalent to a uniform whole body dose of ____ rem (a unit of radiation exposure) which is approximately (indicate fraction or percentage of) the annual radiation exposure (5 rem) permitted to radiation workers by federal regulations. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low and comparable to other everyday risks."

- c. For a whole body radiation exposures (e.g., radioactive drugs): Effective Dose Equivalent (EDE) of > 5000 rem.

"Participation in this research study involves exposure to radiation from (specify respective procedure(s) to be performed). The amount of radiation exposure that you will receive from this (these) procedure(s) is equivalent to a uniform whole body dose of ____ rem (a unit of radiation exposure) which is approximately (indicate multiplication factor) the annual radiation exposure (5 rem) permitted to radiation workers by federal regulations. Excess cancer risk associated with this level of radiation exposure is estimated to be (specify BEIR III, BEIR V, or ICRP 64 factor*) the standard risk."

* Contact the University Radiation Safety Office (624-2728) for assistance in obtaining this data.

- d. For single organ radiation exposures (e.g., x-ray procedures):

“Participation in this research study involves exposure to radiation from (specify respective procedure(s) to be performed). The amount of radiation exposure that you will receive from this (these) procedure(s) is approximately ___ rem (a unit of radiation exposure) to your (specify organ/tissue exposed) with minimal exposure of other body areas. For comparison, radiation workers are permitted, by federal regulation, a maximum annual radiation exposure of 20 rems to the most sensitive organs of their body. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low and comparable to everyday risks.

- e. Note: Comparisons of radiation exposures or risks from radioactive drugs to those from X-ray procedures shall not be approved unless the risks are stated in comparable units (i.e., Effective Dose Equivalents).

5. Restrictions on human subject recruitment.

- a. If a research study involving exposure to ionizing radiation involves female subjects or patients, pregnancy must be ruled out on the basis of the research subject's clinical history or by a urine or serum test performed within a short time frame prior to exposure.
- b. Nursing females should not be included in any research study involving the administration of a radioactive drug.

6. Notification of auxiliary personnel.

All auxiliary personnel involved directly (e.g., radiologic or nuclear medicine technologists) or indirectly (e.g., nursing staff, laboratory technologists) in the conduct of a research study involving the use of a radioactive drug, in the care of human subjects or patients participating in such research, or in the handling of respective radioactive samples should be adequately informed of the nature of the research study and any radiation risks (including methods to reduce such risks) that may be associated with their involvement.

7. Misadministration and Adverse Reactions.

Any unintentional exposure to radiation (i.e., misadministration) or adverse reaction to a radioactive drug occurring during the research study must be reported immediately to the HUSC/RDRC. A copy of the "IRB Adverse Event Report Form (see IRB web site (www.irb.pitt.edu); IRB Forms) submitted to the IRB may be used to provide information concerning the latter.