THE HUMAN USE SUBCOMMITTEE, RADIATION SAFETY COMMITTEE AND THE RADIOACTIVE DRUG RESEARCH COMMITTEE
(REVISED 08/2023)

A. Background

1. Human Use Subcommittee – Radiation Safety Committee (HUSC)

Exposure of human subjects to ionizing radiation (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, institutional radiation licenses, 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 prospective review and approval by the Human Use Subcommittee of the University's Radiation Safety Committee (HUSC). Formal HUSC review and approval is required (i.e., in addition to IRB approval) for all clinical research studies that involve the use or evaluation of radiation-emitting drug or device **as an experimental intervention**.

The use of radiation-emitting devices or drugs for routine clinical procedures is also reviewed and approved by the HUSC in accordance with the University's federal and state radiation licensing conditions.

The research protocol and consent form are, however, required to address the risk of these clinical procedures using the recommended risk language [see Section C.4].

Please consult the University of Pittsburgh Radiation Safety website/Human Use Research/ Requirements for Review for guidance (https://www.radsafe.pitt.edu/sites/default/files/husc_guidance_requirements_for_review_033121.pdf). If there are any questions as to whether or not formal HUSC review and approval is required for a clinical research study involving the use or evaluation of a radiation-emitting drug or device, either submit the research study for formal HUSC review (see submission instructions below) or contact the HUSC Chair (i.e., through the University's Radiation Safety Office @ 412-624-2728) for clarification.

2. Radioactive Drug Research Committee (RDRC)

FDA regulations (21 CFR Part 361.1) permit, in lieu of the submission of an Investigational New Drug (IND) application, the clinical research use of non-FDA-approved radioactive drugs; provided that certain specific requirements are met. One of these requirements is that the radioactive drug and applicable clinical

research study must be prospectively reviewed and approved by an institutional Radioactive Drug Research Committee (RDRC). Research studies submitted for RDRC review and approval must include information regarding prior human use of the drug substance, radiation dosimetry estimates, and a detailed description of the radioactive drug preparation and quality control procedures. For information regarding applicability of the FDA regulations governing the RDRC review and approval process and respective submission requirements, contact the RDRC chair (i.e., through the University's Radiation Safety Office @ 412-624-2728).

All clinical research studies approved by the RDRC are also subject to formal review and approval by the HUSC. To facilitate this process, the HUSC and RDRC meetings are held concurrently.

B. Experimental Use or Evaluation of Drugs or Devices that Emit Ionizing Radiation - Submission Requirements

1. Initial submission

Investigators conducting clinical research studies that qualify for formal HUSC or RDRC review and approval (see above) must respond "yes" to Study Scope section, item #11 of the PittPRO application. The completed and signed APPLICATION FOR THE HUMAN RESEARCH USE OR EVALUATION OF PROCEDURES THAT EMIT IONIZING RADIATION (HUSC-RSC Form 1001, available on the University of Pittsburgh Radiation Safety Office website (https://www.radsafe.pitt.edu/sites/default/files/huscform1001revisedjul.18.pdf), should also be uploaded (as a PDF) in the Local Supporting Documents section of PittPRO. The HUSC-RSC Form 1001 should include radiation dosimetry estimates corresponding to the radiation-emitting procedure(s).

Studies involving Positron Emission Tomography (PET) should obtain radiation dosimetry estimates from the University of Pittsburgh PET Facility.

The chair of the HUSC/RDRC will automatically receive notification of the submitted research study through the PittPRO system.

2. Research protocol modifications

Prospective HUSC and RDRC (if applicable) approval is required for any modifications to a HUSC- and/or RDRC-approved clinical research study which affect the number of human subjects exposed to ionizing radiation, the amount of radiation exposure received by the research subjects, or the method of on-site preparation of a radioactive drug; or which involve substantial changes to the scientific design of the study.

Research protocol modifications-continued

In order for modification to be reviewed by the HUSC or RDRC, investigators must respond "yes" to the PIttPRO Modification Information, Additional Reviews, Item #6. The chair of the HUSC/RDRC will automatically receive notification of the submitted research study through the PittPRO system.

3. 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 quarterly basis, a RDRC Research Study Progress Report.

HUSC approval shall remain in effect for the duration of the IRB approval.

4. HUSC/RDRC Meeting Dates and Submission Deadlines

   a. HUSC/RDRC meeting dates:

      1. The HUSC is required by Commonwealth of Pennsylvania regulation to meet as a full-committee to review research studies involving the experimental use or evaluation of radioactive drugs or the experimental use or evaluation of devices that utilize by-product radioactive materials (e.g., gamma knife). The RDRC is required by FDA regulation to meet as a full-committee to review applicable radioactive drug studies. The HUSC and RDRC meet on the third Wednesday of each month to review materials submitted on or before the deadline date for that month.

      2. The HUSC review of research studies involving the experimental use or evaluation of x-ray-emitting devices can be conducted in an expedited manner; i.e., not requiring review by the convened committee. Such research studies will be reviewed by the HUSC as received.

   b. Submission deadline dates:

      1. Research protocols qualifying for formal review by the convened RDRC and/or HUSC must be submitted by 5 p.m. on the Tuesday a week before the monthly meeting to permit their review during that month. The monthly meetings of the RDRC and HUSC are scheduled for the 3rd Wednesday of each month.

      2. There are no deadline dates for research protocols (i.e., involving the experimental use or evaluation of x-ray-emitting devices) which qualify for formal HUSC review using an expedited process.

C. Research Uses of Procedures that Emit (Ionizing) Radiation - General Considerations

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

   In planning a clinical research study, investigators should first consider whether it is necessary to use procedures that emit radiation to obtain the desired information. Any study requiring the use of procedures that emit ionizing radiation must produce the needed information at minimum radiation doses to human subjects, and the use of the radiation-emitting procedures in the research study 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 to oversee the proposed human use of procedure(s) that emit ionizing radiation. An "authorized user" must be involved as the principal investigator or co-investigator in any research study that involves the experimental use or evaluation of procedures that emit ionizing radiation.

   - The designated "authorized user" shall be responsible for compliance with all statements and conditions respective to the preparation, testing, administration and/or use of the radiation-emitting drug or device as specified in the research study submitted to and approved by the RDRC and/or HUSC.

   - The designated "authorized user" shall be responsible for all routine reports (e.g., RDRC Research Study Progress Report, Modification Requests) and special reports (e.g., adverse event, misadministration) required by the IRB, RDRC and/or HUSC.

3. Assessment of radiation risks

A major responsibility of the HUSC and, if applicable, the RDRC is the review of the radiation risks to human subjects attendant with the conduct of the proposed clinical research study. These committees pay 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 committees also review 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 and, if applicable, the RDRC. (Assistance is available from the Radiation Safety Office @ 412-624-2728).

4. Informed Consent statements of radiation risk.

The discussion of radiation exposure and associated risks in the research protocol (i.e., PittPRO application), 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 the HUSC considers reasonable include the following:

a. For whole body (i.e., systemic) radiation exposures (e.g., radioactive drugs): Effective Dose (ED) < 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 "mrem" is a unit of radiation dose), which is approximately (*indicate multiplication factor, fraction, or percentage of*) of the average radiation dose (300 mrem) that each member of the general public receives per year from naturally occurring radiation sources. 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 participation in this study is considered to be low when compared to everyday risks."

b. For a whole body (i.e., systemic) 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 "rem" is a unit of radiation dose), which is approximately

(*indicate fraction or percentage of*) the annual radiation dose (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 everyday risks."

c. For a <u>whole body</u> (i.e., systemic) radiation exposures (e.g., radioactive drugs): Effective Dose Equivalent (EDE) of > 5000 mrem (5 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 "rem" is a unit of radiation dose), which is approximately (*indicate multiplication factor*) the annual radiation dose (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 <u>single</u> 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 "rem" is a unit of radiation dose) 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 50 rem 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).

f. Risk statement(s) related to therapeutical procedures that emit ionizing radiation shall address the specific risks (e.g., bone marrow depression, skin erythema, etc.) known to be associated with the respective procedure.

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 (e.g., research subject is greater than 1 year post- menopause or has undergone a surgical sterilization procedure) or by a urine or serum test performed within a short time frame (e.g., 24 hours) prior to exposure.

      Studies involving ionizing radiation that are deemed low risk (due to study procedure and/or anatomical location) may include women of childbearing potential, so long as:

   - The PI clearly identifies the pregnancy risk within the consent.
   - The PI provides for research participant acknowledgment of risk within the consent (separate from full informed consent form acknowledgment/ signature).
   - The consent form documents the research subject's decision regarding pregnancy testing.
   - If requested by research subject, PI to provide urine pregnancy testing and document negative result prior to subject participation.

   b. Nursing females should not be included in any research study that involves 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 IRB and to the HUSC. Such events should be submitted as Reportable New Information (RNI) through the PittPRO system. Questions regarding RNI can be routed to Allison Gerger, RN, MPH, CIP who serves as the IRB Regulatory Affairs Specialist in the Office of Research Protections. The University of Pittsburgh IRB shall immediately notify the chair of the HUSC regarding any unanticipated problems involving unintentional exposure to radiation or adverse reaction to a radioactive drug. ***All adverse events (regardless of severity) felt to be associated, or possibly associated, with a radioactive drug approved under the RDRC process must be immediately reported to the Chair of the RDRC. When reporting adverse events to the RDRC, please use the following form.*** (https://www.radsafe.pitt.edu/sites/default/files/rdrc_adverse_event_reporting_form_0.pdf).