

RDRC/SHUR Committees Role in Research

Training Course Material

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Radioactive Drug Research Committee

The Radioactive Drug Research Committee (RDRC) is a subcommittee of the U-M's Radiation Policy Committee. The RDRC reviews certain research protocols involving radiopharmaceuticals or radioactive drugs as required by the Food and Drug Administration (FDA) regulations (21 CFR 361.1).

The RDRC research pathway involves the oversight of basic human research for the purpose of advancing scientific knowledge. The research is intended to obtain **basic information** regarding the metabolism of radioactive drugs including kinetics, distribution, dosimetry, and localization or obtain basic information regarding human physiology, pathophysiology, and biochemistry of radioactive drugs. Only basic research studies are permitted under 21 CFR 361.1.

Research conducted under the RDRC approval process is **not** intended for the immediate therapeutic, diagnostic, or preventive benefit to the human research subject involved. In addition, RDRC research is **not** intended to determine the safety and effectiveness of a radiopharmaceutical or radioactive drug in human research subjects as a therapy, diagnostic, or a preventive medical product.

The RDRC reviews human research protocols involving radiopharmaceuticals or radioactive drugs without: (1) a New Drug Application (NDA) filed with the FDA, (2) an approved Investigational New Drug (IND) application, or (3) an IND Exemption may be subject to review by the RDRC in compliance with 21 CFR 361.1.

Subcommittee on the Human Use of Radioisotopes

The Subcommittee on the Human Use of Radioisotopes (SHUR) is a subcommittee of the U-M's Radiation Policy Committee and is comprised of the identical membership as the RDRC. The SHUR is responsible for the review and approval of applications for the clinical use of radioactive materials in or on humans submitted by medical authorized users and the review of human research subject protocols involving the administration of radiopharmaceuticals to research subjects that are not covered under 21 CFR 361.1.

The SHUR reviews studies involving FDA-approved New Drug Applications (NDA), Investigational New Drugs (IND), and IND Exemptions and the clinical (standard of care) administration of radiopharmaceuticals intended for therapeutic use, diagnostic use, or similar purposes or to determine the safety and effectiveness of a drug (clinical trials).

RDRC/SHUR Hints and Tips

RDRC/SHUR applications involving the human use of radioisotopes for research are primarily covered by Section 21 ('Ionizing Radiation') of the eResearch application.

In addition to Section 21 (Ionizing Radiation), the RDRC/SHUR committee reviews the following eResearch application sections:

SECTION	SECTION TITLE	NOTES
1	General Study Information	Team member information needs to agree with Section 21-1.1
5	Research Design	N/A
6.5 or 6.7	Benefits and Risks	<ul style="list-style-type: none">Needs to agree with Informed Consent (Section 5.1)From the EHS Web site, read the content under Radiation Risk Language
7-2.3	Special Considerations	N/A
8	Subject Participation	8.2 Needs to agree with 21-2.1 and 21-2.2
9-1	Subject Population	Needs to agree with Section 21-2.1.1
10	Informed Consent (Section 5.1)	Needs to agree with Section 6.5-6.7

When making changes to any of the sections listed above, be sure to make changes to the corresponding sections in Section 21 (Ionizing Radiation).

Criteria Changes to Research Studies Requiring RDRC/SHUR Review

The RDRC/SHUR **must** review an amendment to a previously-approved eResearch project if **any** of the following changes have been made:

- Change in Principle Investigator (PI)
- Change in radiopharmaceutical / radionuclide tracer use in the protocol (additions or deletions)
- Change in radiopharmaceutical activity (increase or decrease) administered to a research subject
- Change in the anticipated radiation exposure to a research subject
- Increase in the number of research subjects to be studied
 - RDRC-approved studies **must** submit FDA Form 2915 ("Special Summary") to the RDRC when requesting approval to study more than 30 research subjects
 - Check the FDA website for the most current version of this form (expired versions will **not** be accepted by the FDA)

If the study team / PI / study coordinator notices that the RDRC/SHUR does **not** respond when any of the above items are amended in the previously approved research project, you are encouraged to post a correspondence within eResearch to either the RDRC or SHUR ancillary committee so that the amendment can be reviewed.

Types of Reports Associated with RDRC/SHUR Approved Research Studies

RDRC Adverse Events

As a PI of an RDRC-approved research study involving the use of a radiopharmaceutical or radioactive tracer, be aware of your requirement to **immediately** notify the U-M RDRC of all adverse effects or adverse reactions (mild or severe) that are probably attributable to the use of the radiopharmaceutical or radioactive tracer in your research study.

You need not confirm a causal relationship between the drug and the event, but the likelihood that the event and the use of the drug were related.

The U-M RDRC **must** be notified no later than 3 calendar days after the identification of an adverse effect or adverse reaction that was probably attributable to a radioactive drug or radioactive tracer. Notification should be made by contacting Radiation Safety Service (RSS) (764-6200) or e-mailing the Radiation Safety Officer (Mark Driscoll / drisc@umich.edu) or EHSRadSafety@umich.edu.

This requirement to report adverse effects or adverse reactions to the U-M RDRC is in addition to the formal reporting requirement using the eResearch system. In accordance with FDA regulations, the U-M RDRC only has 7 days to assess and report adverse effects or reactions to the FDA.

FDA Warning Letter – Columbia University Medical Center

In a letter dated September 20, 2011, the Food and Drug Administration (FDA) issued a warning letter to Columbia University Medical Center (CUMC) noting that the CUMC Radioactive Drug Research Committee failed to adhere to the applicable statutory requirements and FDA regulations governing the use of radioactive drugs for human research. Refer to the FDA Warning Letter issued to CUMC in the link below:

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm273526.htm>

Specifically, refer to non-compliance item #2 in the warning letter: 'The RDRC failed to assure that investigators immediately report all adverse events (effects) associated with the use of the radioactive drug in a research study [21 CFR 361.1(d)(8)].'

Please do not hesitate to contact RSS (764-6200) should you have any question, comments, or concerns regarding this notification.

RDRC Quarterly Reporting

The RDRC requires completion and submission of Quarterly Reports. These reports are generated by the RDRC and distributed to the study groups. These reports are used for tracking the number of approved "Unique Subjects" as they are studied each quarter. This means that the subject is counted only one time when they receive the first administration of the radiopharmaceutical. The study team is encouraged to keep an excel spreadsheet to track when each subject is studied and what the organ doses were for each administration of radiopharmaceutical. Please see template for suggested format which makes it easy to keep track of each subject as they progress thru the protocol.

RDRC ‘Annual Reporting’ (FDA Form 2915)

The FDA requires that the U-M RDRC submits an "Annual Report" by January 31 of each year. The report **must** contain a summary of study information for each study conducted during the preceding year. Each PI **must** submit a completed FDA Form 2915 ('Annual Report') for each of their RDRC-approved research projects to the U-M RDRC. These reports are reviewed, revised if necessary, and sent to the FDA by the U-M RDRC. These reports show the number of "Unique Subjects" that are studied during the calendar year. Please note that the sum of the Quarterly Reports and the Annual Report totals of "Unique Subjects" studied for each calendar year **must** match.

Current versions of the FDA Form 2915 ("Annual Report / Special Summary") are posted on the FDA website. The FDA will not accept an outdated version of FDA Form 2915. Check the FDA website each time before completing the form. See [Supplemental Information](#) section for the website.

RDRC ‘Special Summary’ (FDA Form 2915)

The U-M RDRC **must** immediately, but no later than 7 calendar days, submit a completed 'Special Summary' (using the FDA Form 2915) 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. If additional research subjects are needed to be studied for scientific reasons, additional "Special Summary" (FDA Form 2915) **must** be completed by the study team and submitted to the U-M RDRC for approval and submittal to the FDA.

RDRC ‘Study Termination Reporting’ (FDA Form 2915)

A study team **must** complete an FDA Form 2915 ('Special Summary') when an RDRC-approved study closes enrollment and ceases administration of radiopharmaceuticals or radioactive tracers. Be sure to enter the date of 'Termination' in Section 1(d). This notifies the FDA that the study is no longer active. Submit this completed FDA Form 2915 to the U-M RDRC.

SHUR ‘Annual Reporting’

The SHUR requires that the PI / Study Team submit an 'Annual Report' to show the number of "Unique Subjects" that are studied each calendar year. The SHUR generates the reports and distributes them to the study groups.

SHUR ‘Study Termination Reporting’

While there is no regulatory requirement to report the "termination" of SHUR-approved studies at U-M, the study team is requested to notify the SHUR committee when the study is terminated within eResearch. At this time, it is suggested that a "Correspondence" be posted within eResearch to advise the SHUR committee of the impending termination of a research study. This could be done at the same time that the Institutional Review Board (IRBMED) is given notice of the intent to terminate.

RDRC/SHUR FAQ's

What is the difference between a RDRC and a SHUR application?

- RDRC

An application involving the administration of radiopharmaceuticals or a radioactive tracer to a human research subject for the **basic research** of advancing scientific knowledge. The research is intended to obtain basic information regarding the metabolism of a radiopharmaceutical or radioactive drug including kinetics, distribution, dosimetry, and localization ... or ... obtain basic information regarding human physiology, pathophysiology, and biochemistry of radioactive drugs.

An RDRC research application is **not** intended to determine the safety and effectiveness of a radiopharmaceutical or radioactive drug in human subjects as a therapy, diagnostic, or preventive medical product. The research is **not** intended for the immediate therapeutic, diagnostic, or preventive benefit to the research subject and is not designed to involve the routine medical management of clinical patients.

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

RDRC research applications can involve human research protocols involving radiopharmaceuticals or radioactive drugs without either: (1) a New Drug Application (NDA), (2) an approved Investigational New Drug (IND) application, or (3) an IND exemption. Any human research subject protocol submitted to the RDRC is also required to receive IRBMED approval. IRBMED approval is contingent upon RDRC review and approval. Any revisions or modifications required by the RDRC **must** be incorporated into the protocol before final, full approval by the IRBMED will be granted.

- SHUR

An application involving the clinical administration of radiopharmaceuticals or radioactive drugs for routine medical patients or the administration of radioactive drugs to human research subjects involving (1) FDA-approved New Drug Applications (NDA), (2) FDA-approved Investigational New Drugs (IND), or (3) FDA-approved IND Exemptions.

A SHUR application can involve the clinical administration of radiopharmaceuticals or radioactive drugs intended for therapeutic use, diagnostic use, or similar purposes or to determine the safety and effectiveness of a drug (clinical trials).

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

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

What is the maximum radiation dose allowed per year per human research subject?

- RDRC Protocols (FDA Regulatory Limits – 21 CFR 361.1)
 - Smallest dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study
 - When determining the total radiation doses (effective dose) and dose commitments, the following **must** be considered:
 - All radioactive material included in the radioactive drug either as essential material or as significant contaminant or impurity
 - X-ray procedures that are part of the research study
 - Possibility of follow-up studies
 - 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:

Whole Body / Active Blood-Forming Organs / Lens of Eye / Gonads (FDA Limits)

DOSE...	EQUALS...
Single Dose (Effective Dose)	3 rem (30 mSv)
Annual & Total Effective Dose Commitment	5 rem (50 mSv)

Other Organs:

DOSE...	EQUALS...
Single Dose	5 rem (50 mSv)
Annual and Total Dose Commitment	15 rem (150 mSv)

- SHUR Protocols (No Stated Limits)
 - There are no stated regulatory dose limits for SHUR applications; however, the SHUR will evaluate each research study for safety on a case-by-case basis.

Can I exceed the maximum allowed number of subjects?

- RDRC Protocols
 - YES...however, a Principal Investigator PI **must** never study more than the maximum number of research subjects approved by the RDRC. For example, if the RDRC approved a research protocol for n=20 subjects, the PI or study group **must** not exceed n=20 without first seeking and obtaining approval from the RDRC.
 - In addition, RDRC studies **must** never exceed the FDA limit of 30 research subjects (21 CFR 361.1) without prior approval by the RDRC.

SPECIAL NOTE: Multi-arm study protocols may have a different number of approved research subjects authorized by the IRBMED for the 'total' protocol; however, there may be a more limited RDRC or SHUR approval for research subjects undergoing a research procedure with administration of a radiopharmaceutical or radioactive drug. Thus, the IRBMED 'maximum' number of approved research subjects may not be the same maximum number approved by the RDRC/SHUR.

- At any time a RDRC proposal is approved which intends to involve the exposure of more than 30 research subjects, the ~~Principal Investigator~~ PI **must** notify the U-M RDRC/SHUR in advance of exceeding the approved 30 research subjects, complete and submit to the RDRC/SHUR a FDA Form 2915 **and** justification cover-letter, and the RDRC/SHUR **must** approve the request and submit to the FDA.
- SHUR Protocols
 - There is no limit on the number of research subjects allowed for a given SHUR study. However, the SHUR will evaluate the number of requested research subjects and determine if the number appears appropriate for the study.

Questions for the RDRC and SHUR committees may be emailed to EHSRadSafety@umich.edu.

Recommended Resource

- RDRC/SHUR Resource Links
 - [Overview of Review Processes for the Human Use of Radioisotope Studies](#)
- NRC
 - [NRC – Report and Notification of a Medical Event](#)
 - [NRC – Risks Associated with Medical Events](#)
 - [NRC - Determination of Dosages of Unsealed Radioactive Material for Medical Use](#) [Incorrect Dosage Administered - 10 CFR 35.63(d)]
 - <https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/part035-0063.html>
- FDA
 - [FDA Regulations for Radioactive Material \(21 CFR 361.1\)](#)
 - [FDA – RDRC Guidance Documents](#)
 - [FDA Form 2915 \('Report on Research Use of Radioactive Drugs – Study Summary'\)](#)
- RDRC
 - [RDRC Protocol Review Checklist](#)
 - [Guidance for Industry and Researchers – 'The RDRC: Human Research without an Investigational New Drug \(IND\) Application'](#)
 - [Contact the FDA Radioactive Drug Research Committee \(RDRC\) Staff](#)

Revision History

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1 (OSEH to EHS)	5/8/17						
2 (Updated template)	5/31/18						