GUIDELINES FOR CONDUCTING RESEARCH STUDIES UNDER THE
AUSPICES OF THE COLUMBIA UNIVERSITY RADIOACTIVE DRUG
RESEARCH COMMITTEE

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GUIDELINES FOR CONDUCTING RESEARCH STUDIES UNDER THE AUSPICES OF THE COLUMBIA UNIVERSITY RADIOACTIVE DRUG RESEARCH COMMITTEE

These Guidelines describe what a principal investigator (PI) needs to know if he/she intends to conduct a research study under the auspices of the Columbia University Radioactive Drug Research Committee (RDRC) to ensure compliance with governmental regulations and University policies.

The principal regulatory documents that relate to RDRC studies are:


Please refer to these documents for more complete information on the topics covered in these Guidelines.

I. What is RDRC Research?

In 1975, the FDA issued 21 CFR 361 to provide for the use of radioactive drugs for basic science and medical research in humans without being subject to the same requirements for investigational use as other new drugs. Under 21 CFR 361, certain basic science studies may be conducted without an IND if approved by a Radioactive Drug Research Committee. The term radioactive drug, as used in 21 CFR 361, is defined in 21 CFR 310.3 and includes radioactive biological products labeled with a radionuclide. (21 CFR 310.3) RDRC studies do not involve radiopharmaceuticals that have an IND or FDA approval.

Human research using a radioactive drug or biological product may be conducted under the auspices of the RDRC only when the research is basic science research. In the RDRC context, basic science research is research that

- Is intended to obtain basic information regarding the metabolism (including kinetics, distribution, dosimetry and localization) of a radioactive drug or regarding human physiology, pathophysiology or biochemistry and
- Is not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of a radioactive drug in humans. (21 CFR 361.1(a))

The following are examples of types of basic science research that would be appropriate to conduct under a RDRC without an IND:

A. Metabolism and excretion studies. These studies usually employ non-imaging radionuclides. Following administration of the radioactive drug, samples can be obtained at
various times from blood, urine, feces, accessible fluid or tissues, or expired gas. Samples can be analyzed to determine the amount, structure, and persistence of the parent molecule and various metabolites formed. Separate studies of metabolism or excretion can be conducted. A combined study is commonly known as a Mass Balance study. Carbon-14 and H-3 are commonly used for these studies, but other radionuclides can also be used, including gamma emitting radionuclides that can be imaged.

B. Noninvasive functional imaging/molecular imaging studies. For most other types of research studies, the radioactive drug is usually selected for its imaging properties (e.g., positron emission tomography (PET), single photon emission computed tomography (SPECT), or gamma scintigraphy). The terms noninvasive functional imaging and molecular imaging are widely used to describe this category of studies, including the following:

1. **Biodistribution.** Investigation of the time course for delivery, uptake, and retention of a radioactive drug at various tissue sites in the body. The goal is to determine whether there are any sites in the body in which the radioactive drug is excluded or in which the radioactive drug preferentially accumulates. An understanding of the variation of these processes within the population is often the main objective.

2. **Pathophysiology.** Studies to determine whether the presence or absence of pathophysiological conditions (e.g., preferential uptake or exclusion by tumors compared with adjacent tissues) influences the distribution and persistence of the radioactive drug.

3. **Receptor binding or occupancy.** Characterization of the kinetics between the radioactive drug and receptors or other binding sites throughout the body, and characterization of the radioactive drug binding affinity to these receptors. The primary objective is to determine whether localization is specific or nonspecific. In some cases, the observed variation within the population or among populations is a major endpoint. In other studies, the goal may be to develop hypotheses related to disease states, receptor polymorphisms, or therapeutic interventions.

4. **Transport processes.** Many transport proteins regulate the extracellular and intracellular distribution of ions and other endogenous compounds in the body, as well as exogenous molecules, such as drugs. Radioactive drugs can be used to determine the relative abundance and specificity of such transporters in various tissues.

5. **Enzyme activity.** Enzymes help to control the concentrations of critical signaling molecules. Radioactive drugs can serve as molecular probes to determine rates of synthesis or degradation of signaling molecules through enzymes.

6. **Multistep biochemical processes.** Many biochemical and molecular processes represent the net effect of a complex array of serial and parallel pathways. Radioactive drugs can be used as markers to study processes such as DNA synthesis, cellular proliferation, or apoptosis. (Guidance, Section III(A))

II. What Steps are Needed to Obtain RDRC Approval?

No RDRC research may be conducted prior to review and approval by RDRC. You must take the following steps in order to obtain approval of a RDRC study:
A. With certain limited exceptions (see Section III(G) below), all investigational radiopharmaceuticals will be produced in the Columbia University Pet Center (the **PET Center**) Radiochemistry and Radiopharmaceutical Laboratories (collectively, the **Laboratory**). Prior to submitting an Application to the RDRC, notify the Director of the Laboratory as to your intention to conduct a RDRC study. The Director of the Laboratory and you will determine whether the particular study should be conducted under an IND or with RDRC approval. If the Director of the Laboratory agrees that the study can be conducted with RDRC approval, you may proceed with the subsequent steps described below.

B. Meet with the Chair of the RDRC and the Director of Quality and Regulatory Affairs of the PET Center to review 21 CFR 361, the Guidance, the RDRC Application and these Guidelines and to answer any questions that you might have about conducting a RDRC study.

C. A Clinical Authorized User is a physician who is an expert in the clinical use of radiation or radioactive materials, has the requisite training and qualifications for such use and has been authorized by the JRSC to prescribe the administration of radioactive material to humans. If you are not yourself a Clinical Authorized User, select a Clinical Authorized User from the list of Clinical Authorized Users that can be found on the Radiation Safety Program website ([http://www.ehs.columbia.edu/RadiationJRSC.html](http://www.ehs.columbia.edu/RadiationJRSC.html)) in the category of study to which the protocol relates and obtain his/her approval to act as the Clinical Authorized User on your study.

D. Complete the RDRC Application for the Use of Radiopharmaceuticals in Certain Basic Research Studies (the **Application**) which can be found in the Hazardous Materials section of Rascal as Appendix H. and will be further described herein. If you need assistance on filling out the Application, you may contact the Columbia University Medical Center Radiation Safety Program office at (212) 305-0303.

E. Prior to filing the Application with the RDRC, have the Clinical Authorized User sign the Application in Rascal.

F. Submit the Application as hazardous Materials Appendix H to the related Columbia University or New York State Psychiatric Institute IRB protocol (the **Protocol**). The IRB review process will run parallel to the RDRC process, but IRB approval will not be granted until the RDRC has approved your application.

G. Make sure that your and each of your Co-Investigators’ C.V.s are attached to the Application.

III. **What Information Does the RDRC Need In Its Review?**

21 CFR 361 and the Guidance set forth requirements as to what information must be reviewed by the RDRC before approval may be given. Approval may be given only if the RDRC is satisfied that these requirements have been met. Most of this information is provided to the RDRC in the Application. The section of the Application to which each requirement relates is referenced below. Your Clinical Authorized User should be able to help you address these questions.

A. **IRB Protocol [Application, Section I]**. As indicated above, the Application, Protocol and related Informed Consent Form (ICF) must be submitted together. You should use the same study title on both the Application and the Protocol. The IRB and RDRC processes will be undertaken in parallel tracks, but there will be communication between the RDRC and the IRB
during the course of the review so that each Committee will be up to date on issues that may arise prior to approval and the language that must be included in the ICF.

B. Sound Study Design [Application, Section I]. No study may be approved by the RDRC unless it concludes that scientific knowledge and benefit is likely to result from that study. Therefore, you must:

- Provide a rationale for the research derived from appropriate animal studies or published literature.
- Provide a design of the study that will result in information of scientific value.
- Confirm that the radiation dose to research subjects is sufficient and no greater than necessary to obtain valid measurement.
- Verify that the number of research subjects is sufficient and no greater than necessary for the purpose of the study. The number of subjects must be limited to a number needed for basic research and not for immediate therapeutic, diagnostic or similar purposes, or to carry out a clinical trial to determine the safety and effectiveness of the drug. (See Section D below.) (21 CFR 361.1(e)(7))

C. Qualified Study Investigators [Application, Section II]. You and all of your Co-Investigators must provide information about your and their training and experience to show that you and they are qualified to conduct their proposed research study. This information is contained in the C.V.s of the PI and Co-Investigators that are attached to the Application. (21 CFR 361.1(d)(5)). A Clinical Authorized User must be included on the Application.

D. Radiopharmaceutical Information [Application, Section III]. In the table in Section III(A), you are asked to identify for each radiopharmaceutical used in the study, the name of the radiopharmaceutical (i.e., F-18, Tc-99m, etc.), the chemical form (i.e., Sestimibi), the minimum pharmacologic dose (i.e., the lowest dose at which any pharmacologic effect has been found), the physical amount of radiation to be administered to the subject and the supplier.

The dose of the radioactive drug to be administered in an RDRC study must not be known to cause any clinical detectable pharmacological effect (21 CFR 361.1(b)(2)).

You must provide pharmacological dose calculations based on clinical data in the published literature or from other valid human studies to show that the radioactive drug has no clinically detectable pharmacological effect. This requirement means that RDRC protocols may not include the use of drugs that have no documented previous human experience. Please note that for a study that involves subjects of less than 18 years of age, you should provide data from a similar pediatric age group for evidence that the administered dose does not cause any clinically detectable pharmacological effect.

If the same active ingredients (exclusive of the radiopharmaceutical) are to be administered simultaneously, e.g., under an IND or for a therapeutic use in accordance with labelling for a drug, the total amount of active ingredients including the radiopharmaceutical shall be known not
to exceed the dose limitations applicable to the separate administration of the active ingredients excluding the radiopharmaceuticals.

Although the term *clinically detectable pharmacological effect* is not defined under 21 CFR 361.1, the FDA’s current recommendation is that a drug be considered to have a clinically detectable pharmacologic effect if any of the following occur:

- After the drug is administered, research subjects report symptoms in response to questions about how they are feeling.
- An adverse event occurs.
- A change outside the range of normal variation from baseline vital signs is observed (e.g., change in baseline systolic blood pressure, diastolic blood pressure, heart rate, temperature, mental status or respiratory rate).
- Targeted monitoring based on the drug’s pharmacology, such as blood testing, urine analysis, papillary reactions or an EKG reveals a pharmacologic effect.

The FDA does not regard effects such as changes in receptor binding visualized on PET scanning, with no associated changes to the above parameters, as clinically detectable pharmacological effects. The term No Observed Effect Level (NOEL) is sometimes used to define that level below which there are no observed short-term pharmacological effects. Pharmacological doses below this NOEL are usually considered acceptable for RDRC research.

**E. Radiation Doses to Subjects from Research Study Procedures [Application, Section IV].** In the tables in Sections IV and V, you are asked to provide dose calculations for the following unless dosimetry data on the particular tissue or organ is not available:

- The three organs or tissues receiving the highest doses
- Active blood-forming organs such as bone marrow
- Lens of the eye
- Gonads.

In addition, you are asked for the whole body “effective dose” which is used to compare the stochastic risk of non-uniform exposure to radiation to the risk caused by uniform whole body exposure.

Please note that you must include dose calculations from any significant radiopharmaceutical contaminants or impurities as well as from the radionuclide itself.

The amount of radioactive material to be administered may not exceed the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study (21 CFR 361.1(b)(3)). You must therefore provide radiation dose calculations based on biologic distribution data from published literature or other valid studies.

The Application calls for information applicable to a “representative subject in your study”. In many cases, the actual individual radiation dose can only be estimated using standard adult and child reference models published by organizations such as the Society of Nuclear Medicine’s
Medical Internal Radiation Dosimetry (MIRD) Committee, the British Health Protection Agency (formerly the National Radiological Protection Board) for x-ray sources, including CT, and the FDA for conventional x ray. The FDA believes that the determination of radiation dose to specific tissue or organs using currently accepted methods, such as the system set forth by the MIRD Committee, or the system set forth by the International Commission on Radiological Protection, is sufficiently accurate for estimating radiation risk from radiolabeled drugs used in RDRC research.

The Radiation Safety Program website (http://www.ehs.columbia.edu/RadiationJRSC.html) provides dosimetry information for many of the common uses of radiation. Please refer to the following link when you are completing the Application: Radiation Dose Estimates for Human Research Protocols Using Nuclear Medicine Scans, CT Scans and/or General Radiographic Examinations: http://www.ehs.columbia.edu/RadiationHumanDoseEstimates.html. The sources used must be included in the Application.

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 be generally recognized as safe if such dose exceeds the following:

<table>
<thead>
<tr>
<th>Organ or System</th>
<th>Single Dose Sieverts (Rems)</th>
<th>Annual and Total Dose Sieverts (Rems)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Active blood-forming organs</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Lens of the eye</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Other organs</td>
<td>0.05 (5)</td>
<td>0.15 (15)</td>
</tr>
</tbody>
</table>

The radiation dose to an individual subject consists of the sum total of all sources of radiation associated with the research protocol including the following:

- The radiation absorbed dose from the radioactive drug, which consists of the dose from the radionuclide associated with the drug and any significant contaminant or impurity;
- The radiation absorbed dose from any associated x-ray procedures (related procedures such as PET transmission scans, CT scans and dual energy x-ray absorptiometry (DEXA) should also be included); and
- The radiation from any follow-up studies.

Note: The radiation limits for a research subject under 18 years of age at his or her last birthday may not exceed 10% of the radiation values given in the above table.

Please see Appendix D to the Guidance for a list of reference documents and software for determining radiation dose.

When there is no published reference literature, you may provide a specific reference to unpublished data, together with a listing of your assumptions for your specific study.
If there is insufficient human biodistribution or pharmacokinetic data, absorbed dose calculations may be based on animal data extrapolated to humans to approve the proposed research study.

F. Human Research Subjects [Application, Section VII]. Although the IRB is responsible for assuring the protection of human research subjects, including that proper consents are obtained, RDRC studies have certain special criteria for human subjects.

1. Number of Subjects. At Columbia, a RDRC study may not enroll more than 30 subjects initially. If you increase the number of subjects beyond 30 during the course of the study, you must provide special justification for a higher number. 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.

2. Women of Childbearing Potential. 21 CFR 361.1(d)(5) requires that a woman of childbearing potential 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 an RDRC study. The FDA recommends that the absence of pregnancy be confirmed by a pregnancy test. Lack of pregnancy in women of childbearing potential is usually confirmed by a negative urine pregnancy test. Postmenopausal or surgically sterile women are not regarded as having childbearing potential. Postmenopausal is defined as 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. The FDA recommends that women of childbearing potential use a reliable form of contraception, such as an IUD, hormonal contraception, tubal ligation, partner’s vasectomy, latex condom, diaphragm, or cervical cap throughout the at-risk period. The FDA recommends that women of childbearing potential use a reliable form of contraception, such as an IUD, hormonal contraception, tubal ligation, partner’s vasectomy, latex condom, diaphragm, or cervical cap throughout the at-risk period. The FDA recommends that IUD use and hormonal contraception begin at least 1 month before radioactive drug administration. The FDA recommends that women not become pregnant after exposure to a radioactive drug until the potential fetal dose from remaining radionuclide(s) is < 1 mSv (<100 mrem).

3. Pediatric Subjects. 21 CFR 361.1(d)(5) requires that for RDRC studies, subjects should be at least 18 years of age and legally competent. Exceptions to this rule are permitted only when it can be demonstrated to the RDRC that:

- The study represents a unique opportunity to gain information not currently available;
- The study requires the use of research subjects less than 18 years of age; and
- The study is without significant risk to the subject.

21 CFR 361.1(d)(5) refers to pediatric research that is “without significant risk.” In 2001, the FDA adopted 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, which sets the regulatory guidelines for IRB review. These regulations do not use the term “without significant risk,” but rather refer to “minimal risk” and “greater than minimal risk.” Minimal risk is defined in § 50.3(k) as “the probability and magnitude of harm or discomfort anticipated in the research are not
greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

The FDA recommends that risk assessment of proposed pediatric studies include consideration of the magnitude, probability, and duration of each protocol intervention, the age-related changes in risk profile, and factors such as the use of venipuncture (both the frequency and total blood volume needed for the study), the use of enclosed or confining equipment, the length of any proposed immobilization (including the possibility that the immobilization may be prolonged), concomitant medications, any additional protocol interventions, and the need for sedation (if any). You may be asked by the IRB to provide this data.

G. Quality of Radioactive Drug. Under 21 CFR 361.1, all radioactive drugs produced under an approved RDRC protocol are required to meet appropriate chemical, pharmaceutical, radiochemical and radionuclidic standards of identity, strength, quality and purity as needed for safety. They must also be of such uniform and reproducible quality as to give significance to the research study conducted. In addition, radioactive materials for parenteral use are required to be prepared in a sterile and pyrogen-free form.

With limited exceptions, all radiopharmaceuticals used in RDRC studies at Columbia must be produced in the Laboratory. In certain circumstances, investigators will be permitted to use radiopharmaceuticals produced by an external radiopharmaceutical manufacturer or pharmaceutical company (a Vendor). Therefore, either the Laboratory or the Vendor will be responsible for producing such radiopharmaceuticals in accordance with all regulatory standards.

If the radiopharmaceutical is produced in the Laboratory, a Quarterly Quality Assurance Report (Lab QA Report) will be delivered to you within 10 days following the end of each calendar quarter for each of your studies for which radiopharmaceuticals were produced during the preceding quarter. The QA Report will identify radiopharmaceutical release and administration data for all batches produced by the Laboratory, including both radiopharmaceuticals injected and radiopharmaceuticals not injected due to cancellation or production failure.

IV. What Ongoing Responsibilities Does a PI Have During the Course of a Study?

After approval by the RDRC and the IRB, you may commence the study. During the course of the study, you as PI will have certain ongoing responsibilities, which are described below.

A. Quality Assurance

You or a qualified member of your research staff will be required to confirm the following:

1. Radiopharmaceutical Quality.

   Confirm that a Certificate of Analysis for each radiopharmaceutical administered was obtained prior to its administration. The Certificate of Analysis will be provided to you either by the Laboratory or the Vendor.
Confirm that a RDRC-approved label for each radiopharmaceutical dispensed by the PET Center was received following its administration. You may assume that a label received from the PET Center meets all regulatory standards.

2. **Subject Safety**

Confirm that subject safety requirements set forth in the study’s IRB protocol have been met prior to each administration of a radiopharmaceutical.

3. **Image Quality**

Confirm that each image produced in your study has been reviewed by the Clinical Authorized User and certified as having met the criteria for acceptability.

**B. Quarterly and Annual Reports.**

The following describes a PI’s reporting responsibilities:

1. **Quarterly Reports.** You must submit to the RDRC a Quarterly Report for each of the first three quarters of the calendar year summarizing subject activities during the quarter. The Report should be submitted by the 15th day of the first month following the end of the quarter being reported on.

   Each Quarterly Report should be submitted on FDA Form 2915 (*Form 2915*). Please note that radiation dose and radiopharmaceutical information must be provided with respect to each subject receiving a radiopharmaceutical during the period covered by the Report. A Form 2915 should be completed for each study that is open and ongoing even if you did not enroll any subjects during the period being reported on.

2. **Annual Report.** You must submit to the RDRC an Annual Report on Form 2915 summarizing subject activities for the year. The Report should be submitted by the 15th day of January of the year following the year being reported on.

3. **QA Reports.** You should provide the RDRC with (a) a certified copy of each Lab QA Report that you receive from the PET Center and (b) a certification that a RDRC-approved label was used for each administration of a radiopharmaceutical in your studies during the quarter. The QA Reports should be submitted with either the Quarterly Report or Annual Report referenced above. If no radiopharmaceuticals were administered during the quarter, you should so notify the RDRC.

Each of the foregoing Reports will be uploaded into Rascal by the Radiation Safety Committee Coordinator.

**C. Special Summaries**
Following notification by the RDRC of its approval of (a) your Application for a study that includes research subjects of less than 18 years of age (a **Pediatric Subject**) or (b) a modification of your Application to include more than 30 subjects or Pediatric Subjects, you are required to submit a Special Summary on Form 2915 to the RDRC within three days of receiving such notification.

The Special Summary must include a justification for the number of subjects or for the inclusion of pediatric subjects. In addition, the maximum radiation dose commitment for each critical organ, active blood forming organs, lens of the eye and gonads and the whole body, for each radiopharmaceutical used in study, should be provided for a representative subject.

Each Special Summary will be uploaded into Rascal by the Radiation Safety Committee Coordinator.

**D. Adverse Reactions**

You must report to the RDRC immediately, but in no event later than seven calendar days following the incident, any adverse reaction associated with the use of the radiopharmaceutical in your study.

In addition, you must forward to the RDRC copies of (1) any other adverse event report submitted to a sponsor or a governmental agency or (2) any report of an unanticipated problem involving risks to subjects submitted to the IRB, in each case resulting from the use of radiation or a radiopharmaceutical in your study, promptly after submission of such report.

Each of the foregoing Reports will be uploaded into Rascal by the Radiation Safety Committee Coordinator.

**E. Modifications**

If you wish to modify any information in the Application for this study, you should provide the RDRC with a revised Application at the same time that the related IRB Protocol Modification is submitted to the IRB. The Application is amended by creating a clone of the original Application and revising the clone. You must indicate the changes in the Application and the rationale for each change in the Rascal Notes. A copy of each IRB Protocol Renewal or Modification that involves a change to the research radiation exposure should also be sent to the RDRC upon submission to the IRB.