POLICY AND COMMUNICATIONS BULLETIN
THE CLINICAL CENTER

Medical Administrative Series

M93-1 1 September 1993

MANUAL TRANSMITTAL SHEET

SUBJECT: Research Involving Human Subjects at the Clinical Center: Structure and Process

1. Explanation of Material Transmitted: This issuance transmits the processes by which the Clinical Center, in the design and approval of biomedical studies, protects the rights and welfare of human subjects. The policy is currently under review. It is based on the NIH Multiple Project Assurance of Compliance, which describes the NIH policies and procedures related to research involving human subjects, and which is maintained by the Office of Human Subjects Research, NIH. **You are encouraged to refer to that document while this policy is revised.**

2. Material Superseded:
   - MAS 77-1, dated 1 February 1977
   - MAS 81-1, dated 2 February 1981
   - MAS 82-2, dated 3 May 1982
   - MAS 82-3, dated 3 May 1982
   - MAS 83-1, dated 12 May 1983
   - MAS 84-1, dated 3 April 1984
   - MAS 85-2, dated 17 October 1985
   - MAS 86-1, dated 21 March 1986
   - MAS 87-1, dated 12 January 1987

   and
   - MAS 87-1(a), dated 2 April 1987.

3. Filing Instructions: Informed Consent Section
   Remove: Ten above-listed issuances
   Insert: No. M93-1, dated 1 September 1993

DISTRIBUTION

Physicians, Dentists, and Other Practitioners Participating in Patient Care

M93-1: Research Involving Human Subjects at the Clinical Center: Structure and Process

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SUBJECT: Research Involving Human Subjects at the Clinical Center: Structure and Process

I. INTRODUCTION

PURPOSE

The primary mission of the Warren Grant Magnuson Clinical Center (the Clinical Center) is to support the Institutes of the National Institutes of Health (NIH) in the performance of clinical research designed to advance biomedical knowledge and to improve the health of the citizens of the United States.

Each clinical investigation is the result of a partnership between the principal investigator, the other members of the research team, and the subjects who volunteer for the study. It is of the utmost importance, therefore, that research carried out at the Clinical Center be designed and conducted so as to promote the rights and welfare of human subjects.

Furthermore, it is the stated policy of the Department of Health and Human Services (DHHS) that research involving human subjects may be undertaken only after appropriate review and approval. Regulations governing this policy have been published as Title 45 Code of Federal Regulations Part 46 (45 CFR 46), "Protection of Human Subjects." The Intramural Research Program at NIH has given its assurance — through its *Assurance of Compliance with DHHS Regulations for the Protection of Human Subjects (45 CFR 46)*, submitted to and accepted on behalf of DHHS by the Office for Protection from Research Risks (OPRR) in 1992, and herein referred to as the Multiple Project Assurance (MPA) — that NIH conducts or supports human subjects research at the Clinical Center and elsewhere in compliance with these regulations. The MPA described NIH policies and procedures, including (1) a statement of principles relating to the protection of the rights and welfare of human subjects of research conducted at or sponsored by NIH, regardless of the source of funding, (2) the designation of and support for a number of Institutional Review Boards (IRBs), (3) maintaining lists of IRB members and their qualifications, and (4) provision of written procedures for the conduct of initial and continuing review of protocols. Copies of the MPA may be obtained from NIH's Office of Human Subjects Research.

POLICY

It is the policy of the Clinical Center that biomedical and behavioral research involving human subjects, carried out in the Clinical Center or involving Clinical Center personnel, regardless of the site of the activity, will be designed and carried out with the highest regard for the rights and welfare of those subjects.

No research, development, or related activities involving human subjects to be conducted at the Clinical Center or under its sponsorship shall be carried out unless they have been subjected to scientific and ethical review and have been approved by appropriate IRBs in one or more of the Institutes and by the Director of the Clinical Center.

No person shall undergo procedures relating to evaluation or treatment at the Clinical Center unless those procedures are part of an IRB-approved protocol.

APPLICABILITY

Except as provided below, this policy shall apply to all protocols involving human subjects developed by investigators of any of the Institutes of the NIH that carry out clinical research or by investigators of any of the departments of the Clinical Center (CC).

Similar activities connected with intramural clinical programs but conducted at sites other than the CC shall be subject to the same review process if they (a) are funded through Institute intramural clinical programs or the CC portion of the Management Fund; (b) are conducted by employees of intramural Institute programs or of the CC who are acting in connection with their relationships or responsibilities to the CC, or who intend to use the name of the CC in any report of the activity; (c) involve the records of the CC; or (d) use the CC records or personnel to identify and/or contact current clients, patients, or normal volunteers to be subjects.

EXEMPTIONS

Research in which the only involvement of human subjects will be in one or more of the following categories is exempt from coverage under the Federal regulations, the NIH MPA, and this policy:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special education instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless information taken from these sources is recorded in such a manner that subjects can be identified, directly or through identifiers linked to the subjects, and any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) above if the human subjects are elected or appointed public officials or candidates for public office, or if federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the

information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs.

Exemptions are not to be determined by the researcher alone. The Office of Human Subjects Research (OHSR) is the only NIH component authorized to grant an exemption. Before a researcher begins activities that he/she thinks are exempt from the MPA, he/she must get approval in writing from the OHSR.

DEFINITIONS

For the purposes of this policy, *research* means a systematic investigation designed to develop or contribute to generalizable knowledge. At the Clinical Center, biomedical research is any process that seeks to secure new information from humans or about humans and that differs from customary medical (or other professional) practice. *Development* and related activities are those which, though not primarily research, have a research component.

DHHS states *minimal risk* to mean that 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.

Subjects registered at the CC who may participate in research projects fall into three classes: patients, patient volunteers, and normal volunteers:

Patients are individuals who have been referred by a physician or dentist because they have a disease of research interest to staff members.

Patient volunteers are individuals with a disease whose participation in research is related to their disease but unlikely to benefit them, or individuals who have a disease but volunteer for research totally unrelated to that disease.

Normal volunteers are healthy persons who have volunteered to participate in clinical investigation at the CC. Such persons may be employees of NIH (*see* Medical Administrative Series issuance no. 86-3), relatives of patients on occasions when it is appropriate to investigate the familial aspects of a specific disease, or others chosen to participate as normal controls or a participants in the development of preventive therapy regimens.

STUDIES REQUIRING REVIEW

Protocols must be prepared for most diagnostic, therapeutic (i.e., where benefit is expected), and non-therapeutic (i.e., where there is no expectation of benefit) clinical studies. Diagnosis and treatment within non-investigational, accepted practice for intercurrent illness need not be covered by a protocol.

Protocols must be written, either individually or in "omnibus" fashion (i.e., describing the clinical workup of a rather broadly defined set of subjects for the purpose of determining their suitability for other, more narrowly defined, research protocols). Removal of, or the use of, removed organs, tissues, blood and other fluids, and other materials from human subjects for research activities must also be written in protocol form for review and approval, unless the activities fall under one of the exemptions listed above.

PRINCIPAL INVESTIGATORS AND MEDICAL ADVISORS

The principal investigator (PI) is responsible for the design, conduct, and monitoring of a clinical research protocol. There shall be only one PI on a protocol.

The PI must be a health professional, qualified in the judgment of the Institute's Clinical Director and IRB — on the basis of education, training, experience, and demonstrated professional competence — to be capable of assuming responsibility for the study.

When the PI is not a physician, or when the Clinical Director, the IRB, or the Director, CC, consider it warranted, a medical advisor (MA) shall be identified in the protocol. The MA must be a member of the CC's Junior or Senior Medical Staff. There may be only one MA per protocol.

Consultants and students may not serve as PIs or as MAs on a clinical research protocol.

RESPONSIBILITY FOR IMPLEMENTATION AND ADMINISTRATION

The overall responsibility for the implementation of NIH's MPA rests with the Deputy Director for Intramural Research (DDIR), NIH. The DDIR will be assisted in the resolution of policy questions by the Human Subjects Research Advisory Committee (HSRAC), formerly called the Human Research Review Panel (HRRP). The structure and function of this committee and of the Institutional Review Boards (IRBs) (formerly called Institute Clinical Research Subpanels, ICRSs) which it represents, will be described below. Guidance is available to the DDIR concerning bioethical matters from the CC's Bioethics Program and on regulatory human subjects matters from the OHSR.

This Medical Administrative Series policy statement, approved by the Medical Board and issued by the Clinical Center, shall be implemented and administered by the Director, Clinical Center. Copies of the policy may be obtained from the Office of Medical Board Services, and questions about the policy may be directed to the Chief of that office.

II. STRUCTURE

GENERAL

To fulfill DHHS and NIH requirements, all research projects involving human subjects that require review and approval as enumerated above will be examined by an IRB. Research projects conducted away from the CC or conducted by NIH intramural clinical staff via a collaboration with an outside individual or organization must be reviewed in the same manner as projects to be carried out intramurally. NIH researchers may participate in protocols that have received appropriate review by the IRB of an outside organization.

The responsibility for determining the adequacy of facilities, resources, and personnel in off-site locations rests with the Institute under whose auspices a project is supported. The primary mandate of IRBs is to protect the rights and safeguard the welfare of human research subjects, Therefore, the appropriate IRB(s) will be concerned with considerations of risks, burdens, benefits to subjects (and others), scientific design, and the importance of the knowledge to be gained by the proposal.

The participation of certain vulnerable populations in research is subject to additional safeguards because of legal and ethical considerations regarding their ability to comprehend the risks and consequences of their participation and thus to provide informed consent. These populations include:

- pregnant women or fetuses, including studies of *in vitro* fertilization (45 CFR 46, subpart B);

Regulations require that no pregnant woman may be involved in a research activity unless the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or unless the risk to the fetus is minimal.

- prisoners (45 CFR 46, subpart C);

Such research is subject to additional safeguards because prisoners may be under constraints due to their incarceration that could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research.

- children (45 CFR 46, subpart D);

Not only does the law generally deny children the right to give legally valid consent to participate in biomedical or behavioral research, but their role as research participants may be

inherently compromised by a limited ability to comprehend the risks and consequences of such participation.

- the cognitively impaired;

Special consideration should be given to those subjects participating in biomedical research studies who are mentally disabled or who are or will become cognitively impaired. This subject is treated at greater length in Medical Administrative Series issuance no. 87-4.

- other potentially vulnerable people such as those who are economically or educationally disadvantaged.

Investigators are advised to contact their IRB Chair, the Bioethics Program, or the Office of Human Subjects Research when there are research design questions regarding the adequacy of protection afforded these subject populations.

It is the policy of the NIH intramural research program that women, minorities, and other groups shall be included as subjects in clinical trials as appropriate. If a study proposes to exclude women, minorities, or other groups, a statement of the reason(s) for such exclusion must be included in the protocol.

THE HUMAN SUBJECTS RESEARCH ADVISORY COMMITTEE

Responsibility

The primary responsibility of the HSRAC is to advise the DDIR, NIH, on policies and procedures regarding the conduct of human subjects research at NIH.

Membership

The membership of the HSRAC includes the DDIR; the Director, CC; the Director, OHSR (who serves as Executive Secretary); the Chairs of the Institutes' IRBs; and the Chief, Bioethics Program, CC. Members are appointed by virtue of their NIH positions, and shall serve as long as they hold those positions.

Chair

The DDIR shall serve as the Chair of the HSRAC. The Chair will vote only in case of a tie.

Meetings

Meetings of the HSRAC will be held regularly and are open to the public, except for discussions dealing with confidential information. A majority of the membership of the HSRAC constitutes a quorum. In the absence of a committee member, an alternate may attend and vote, subject to approval by the Chair. HSRAC membership lists and meeting minutes will be maintained by the OHSR.

Actions

The HSRAC shall consider and make recommendations to the DDIR concerning research review policies and procedures.

At the discretion of the DDIR, the HSRAC may serve as the IRB of record for the review, approval, and oversight of any research activity involving human subjects covered by the MPA. In the event that the HSRAC serves as an IRB, its membership shall be appropriately augmented to meet the requirements prescribed in 45 CFR 46, and a list of the members will be provided to the Office for Protection from Research Risks for approval.

INSTITUTIONAL REVIEW BOARDS

General

IRBs have the responsibility and authority to review and approve, require modification in, or disapprove all activities or proposed changes in previously approved activities that are covered by DHHS regulations and the MPA. IRBs shall approve research based on their determination that the following requirements are satisfied: (1) risks to subjects are minimized, (2) the risks are reasonable in relation to anticipated benefits, if any, to subjects, and to the importance of knowledge that may reasonably be expected to result, (3) the selection of subjects is equitable, and that (4) informed consent will be sought from the subjects or their authorized representatives.

Each Institute will organize an IRB to review and approve protocols by researchers in that Institute, except that (a) smaller Institutes may combine to produce one IRB that will serve them, or (b) investigators from the CC and other NIH ICDs that generate an insufficient quantity of research protocols to warrant their own IRB shall submit their protocols to the IRB most closely related to the subject matter of the proposed study.

An IRB will review all proposals submitted by members of the Institute's intramural staff and such other studies as may be referred by Institute Directors and/or the Director, CC. If a protocol involves, as principal (PI) or associate (AI) investigator(s), staff of more than one Institute, the study must be approved by the IRB of the PI and by the Clinical Directors of *all* involved Institutes before it is submitted to the Director, CC, for final approval.

Membership

The IRB shall be constituted in such a way that the experience and expertise of its members, and the diversity of the members' backgrounds, shall enable it to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable laws, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

Each IRB at NIH shall have at least five members whose varying backgrounds will promote complete and adequate review of the research activities commonly carried out by that Institute. No IRB shall consist entirely of men, entirely of women, or entirely of members of a single profession. Each IRB shall include one member whose primary concerns are in nonscientific areas (such as a lawyer, ethicist, or cleric), at least one member who is not otherwise affiliated with the PHS and who is not an immediate family member of an affiliated person, one member of the NIH scientific or professional staff not affiliated with the IRB's ICD, and a biostatistician.

In addition, a representative of the CC's Bioethics Program shall serve as a voting member on each IRB. The IRB may seek advice from other experts, when needed for the proper review of a protocol; these individuals shall serve as *ad hoc*, non-voting members of the committee.

Members of an IRB shall be recommended by that ICD's Clinical Director in consultation with the ICD's Scientific Director, and shall be appointed by the DDIR to serve renewable one- to three-year terms. Members shall be identified by earned degree, affiliation, and area of specialty. The DDIR shall be notified of proposed changes of membership, via a memorandum detailing the changes sent to the Director, OHSR.

Chair

The IRB's Chair shall be recommended by the ICD Clinical Director in consultation with the ICD Scientific Director, and shall ordinarily be appointed by the DDIR for a renewable two-year term. ICD Directors, Scientific Directors, and Clinical Directors may not serve as Chairs of their Institute's IRB. The Chair votes only in case of a tie.

Meetings

Meetings are called by the Chair as often as required to accomplish the business of the IRB. The meetings are open to the public except when discussions are held that in the judgment of the Chair deal with confidential information.

A majority of the membership of an IRB shall constitute a quorum, except that no action of the committee shall be legally voted upon unless a member whose primary interests are non-scientific is present and voting.

The IRB Chair may request that the PI of a protocol be present at a portion of the meeting to provide information and answer questions. Generally, the investigator is excused before the IRB resumes deliberations concerning the protocol. PIs or AIs who are IRB members shall leave the room during deliberations and voting.

Records

The IRB shall prepare and maintain adequate documentation of its activities, to include:

- copies of all protocols reviewed; scientific evaluations, if any, that accompany the proposals; approved sample consent documents; progress reports submitted by investigators; and reports of injuries to subjects,

- minutes of IRB meetings in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controversial issues and their resolution,

- records of continuing review activities,

- copies of all correspondence between the IRB and the investigators,

- a list of IRB members,

- written procedures that the IRB will follow for the conduct of its initial and continuing reviews, and

- statements of significant new findings that have been provided to subjects.

Required records shall be retained for at least three years after termination of the protocol.

Actions

The IRB shall have the responsibility and authority to review and approve, require modifications to, or disapprove protocols submitted by investigators. Protocols become effective only when they have been approved by the IRB, the Protocol Implementation Review Committee (see below), and the Director or Deputy Director, CC.

Approval is by a majority of those members present at the meeting. If the vote is not unanimous, the minority opinion shall be recorded in or attached to the minutes of the meeting. In those cases in which the vote is not unanimous and the disagreement is substantial, or if the Director or Deputy Director, CC, disagree substantially with the IRB's decision, the Director, CC, may refer the protocol to the HSRAC or to the DDIR, NIH, for an opinion.

The Director, CC, or the DDIR may not approve a protocol that has been disapproved by the IRB.

An atmosphere free of pressure — real or implied — from IRB members' superiors must be maintained when reviewing protocols in which an Institute's Director, Scientific Director, or Clinical Director is the PI. Therefore, it shall be the prerogative of an IRB either to review such protocols, with *ad hoc* representation from appropriate investigators from other Institutes, or to refer them to another Institute's IRB. Protocols in which an Institute Director, Scientific Director, or Clinical Director is an AI need not be referred to an outside IRB.

PROTOCOL IMPLEMENTATION REVIEW COMMITTEES

While review and approval of a protocol by the IRB is required by regulation, another level of review of a protocol takes place before it is forwarded to the Director, CC.

Each Institute will have a Protocol Implementation Review Committee (PIRC), generally composed of the Scientific Director, Clinical Director, and a member chosen from the staff of the Institute's extramural program, which reviews new protocols approved by the Institute's IRB to bring to the attention of the DDIR and/or the Director, NIH, any protocols that might benefit from further consideration from the NIH's perspective. Specifically, in determining whether an

IRB-approved protocol should be implemented, PIRCs are charged with the responsibility for ensuring that (1) IRB minutes are fully reflective of the IRB's deliberations and document review and approval in accordance with 45 CFR 46; (2) where appropriate, additional safeguards have been provided for human subjects, as set forth in 45 CFR 46, subparts A through D; (3) the protocol is consistent with the Institute's research objectives and is likely to yield knowledge of importance to the mission of the NIH; and (4) all collaborative, cooperative, or multi-site arrangements, including Cooperative Research and Development Agreements, are fully documented and are deemed to be free of conflict of interest.

THE OFFICE OF HUMAN SUBJECTS RESEARCH

The OHSR, an office within the Office of the Deputy Director for Intramural Research, NIH, was established to help investigators understand and comply with regulatory requirements for the ethical involvement of human subjects in biomedical research. Investigators are urged to consult with OHSR staff members to help identify and resolve ethical and regulatory issues associated with the design and conduct of their human subjects research activities.

THE BIOETHICS PROGRAM

The Bioethics Program, a unit of the Office of the Director, Clinical Center, helps investigators and others answer questions regarding ethical matters in the development and performance of biomedical research.

The highest standards of ethical conduct are sought in the Clinical Center. Therefore, research and clinical staff are urged to consult with the Bioethics Program to help identify and resolve issues associated with the design and conduct of research and treatment.

APPROVAL BY DIRECTOR, CLINICAL CENTER

A protocol approved by an Institute's IRB and PIRC is forwarded to the Clinical Center where it is reviewed primarily from the standpoint of its impact on the hospital's resources. If difficulties are forseen, the Director will contact the PI to work out an appropriate compromise. The protocol is then approved by the Director or Deputy Director, CC, and is returned to the PI — with an accession number — so that accrual of subjects can begin.

III. PROCESS

APPROVAL PATH OF NEW PROTOCOLS

Sequence of Events

The sequence of events by which a protocol receives approval at the CC is shown in Figure 1.

After the protocol has been written and reviewed for scientific merit by the Laboratory and Branch Chief through which the protocol is being generated, the PI will initiate the completion of form NIH-1195, Clinical Research Study Initial Review Application (Attachment 1). Approval (as signified by initials) of each of the AIs (and of their Clinical Directors [or CC Department Head, as appropriate] if any of the AIs are from Institutes other than that of the PI) and the PI's Branch Chief and Clinical Director will be obtained. The protocol is then sent to the IRB Chair who will schedule it for review by the full IRB.

The IRB's review may result in any of the following actions:

- Approval of the protocol, which requires the approval of a majority of those members present at the meeting. If the vote of the IRB is not unanimous, the minority opinion must be recorded in, or attached to, the minutes and accompany the majority decision when forwarded for final institutional review and approval. A copy of each approved new protocol together with all the correspondence and approval cover sheet will be forwarded to the PIRC, and following review and approval by the PIRC, to the Director, CC, for review and approval.

IRB approval may also be granted with recommendations for modifications in the protocol. Recommendations do not have the force of stipulations, and their acceptance by the investigator is not a requirement for approval of the protocol.

- Approval with stipulations, i.e., specific conditions that must be met by the PI before IRB approval of the research. Upon receipt of a written, acceptable response to the stipulations requested during the IRB review, the IRB authorizes the Chair to approve the study and forward it as described above.

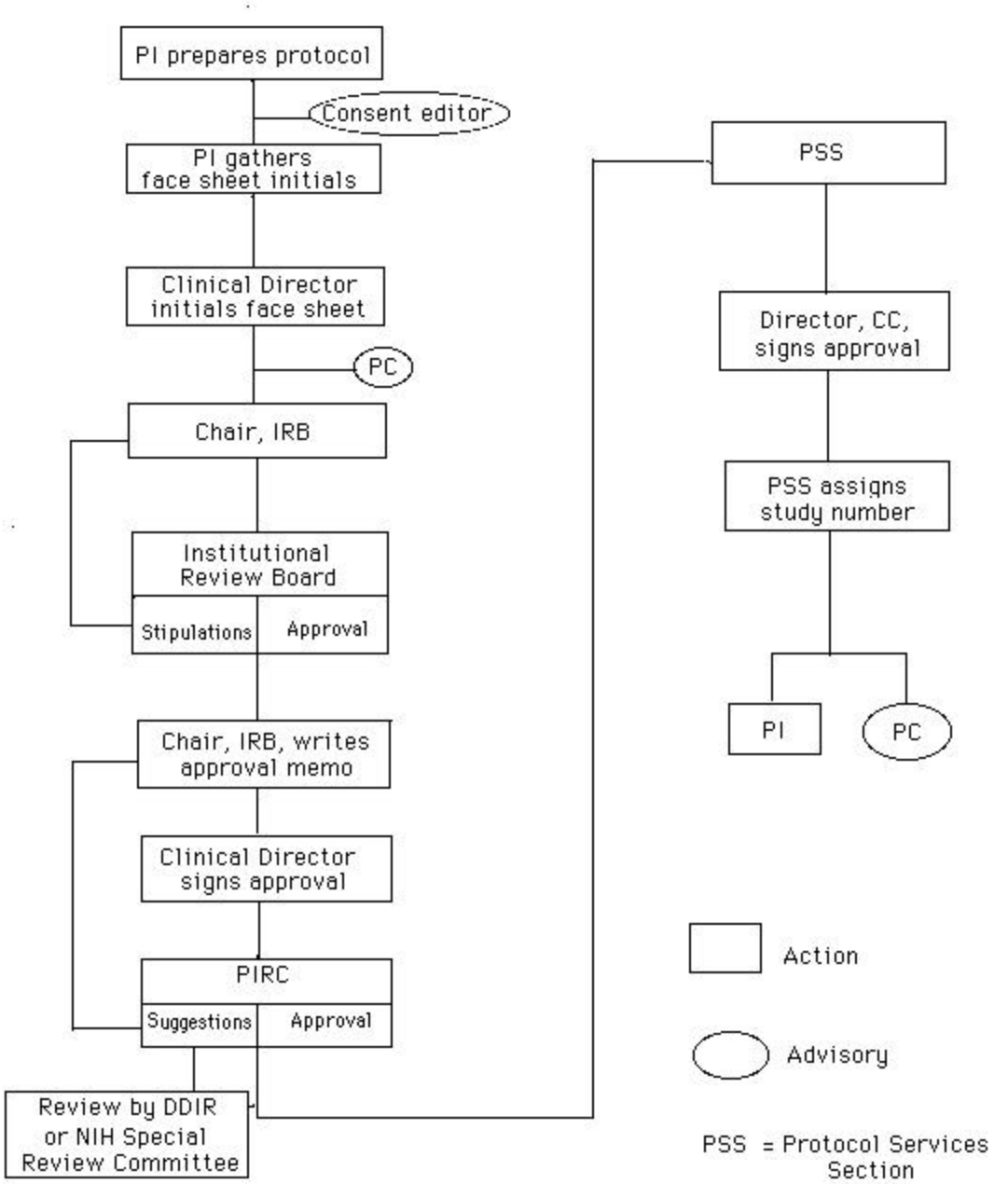

FIGURE 1. The Protocol Track

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- Tabling, when the IRB agrees that approval cannot be granted until further information is provided or specific changes are made. When the new information is submitted, the protocol is reviewed again by the IRB.

- Disapproval, in which case notice is sent to the PI with the reasons for the disapproval and information about reconsideration.

When a new protocol is approved by the IRB, it is forwarded to the PIRC as described above. Following review and approval by the PIRC, the protocol is sent to the Protocol Services Section, Medical Record Department, CC, for accession and transmittal to the Director, CC, for approval. The PIRC may send protocols to the DDIR for review by that individual or by the NIH Special Review Committee prior to transmittal to the Director, CC.

Following all approvals, the protocol is returned to the Protocol Services Section where it is assigned a unique number. The PI is notified of the approval, and research subjects may then begin to be accrued. Throughout the approval process, the Institute's Protocol Coordinator (PC) tracks the protocol and can advise the PI of its status at any given time.

IRB-approved protocols for research not conducted in the CC are forwarded to OHSR where a unique number is assigned and the PI is notified.

Changes, Additions, and Amendments to Protocols

The PI must submit a memo to the IRB to request (1) desired modifications in protocols that materially affect risk to subjects, or (2) approval for continuation of a protocol when anticipated risks to subjects have changed substantively as a result of adverse reactions or new information reported in the literature. Requests for approval in changes of PI must also be submitted in this fashion.

If amendments or additions will materially change the procedures and/or risks to subjects, revised consent forms (see below) must accompany the request.

PROTOCOLS INVOLVING IONIZING RADIATION

If ionizing radiation will be used as a part of the protocol, the PI will indicate on the NIH-1195 whether the radiation is *medically indicated*, i.e., involving the use of radiation or radioactive materials for diagnosis or treatment when such use is considered to be standard medical procedure for the clinical management of the patient, or *indicated for research*, where uses of radiation or radioactive materials for research do not meet the criteria of "medically indicated," including procedures for diagnosis or treatment that are considered experimental. Any radiation exposure in normal control subjects falls in the latter category. If there is any question about the category in which a protocol's radiation may fall, the PI should confer with the Chairman or Executive Secretary of the Radiation Safety Committee (RSC).

If the radiation is medically indicated, the protocol can be reviewed and acted upon by the IRB with no further consideration by the RSC.

Procedures for Applying to the RSC

• New protocols: If the radiation is indicated for research, new protocols must be reviewed by the NIH's RSC and, if appropriate, the Radioactive Drug Research Committee (RDRC). A physician who is authorized by the RSC to use radiation in clinical applications must complete NIH Form 88-23(a), "Application for Authorization to Administer Radioactive Material for Research to Human Subjects," (Attachment 2) and submit 13 copies each of the NIH 88-23(a) (including the original), the protocol, and the informed consent statement.

• Amendments to existing protocols: Radiation Authorizations shall be reviewed and approved by the Committee before work commences. (Proposed changes must also be presented for approval by the IRB.) If there are changes with respect to radiation (i.e., in the administration of radiation, experimental design, or the number of subjects studied), approval by the RSC is required. If changes are substantive, a new NIH Form 88-23(a) should be completed and submitted; if amendments have resulted in the protocol being materially different from the original, the RSC may require that a protocol be rewritten to reflect the changes and/or consolidate amendments. Contact the Executive Secretary of the RSC for guidance.

• Continuing protocols:

  • Annual reviews: Radiation Authorizations will be reviewed on an annual basis. If there are major changes (e.g., change in radiation usage, experimental design, etc.) the changes constitute an amendment; therefore, procedures for amendments should be applied. If there are no changes or if changes are minor (e.g., change in PI, number of subjects), submit one copy of the material being submitted to the IRB for administrative review by the RSB staff.

  • Triennial reviews: The RSC requires a full review of all continuing Radiation Authorizations on a triennial basis. The protocol should be revised to include all amendments, and 13 copies of NIH Form 88-23(a), the protocol, and informed

consent should be submitted to the RSC. When triennial reviews are required by the IRB, applications should be submitted for concurrent review by the RSC.

• Applications to the RSC must be signed by a clinician authorized by the RSC, and the PI, with the exception that the signature of the PI is sufficient for studies that involve only radiographic procedures indicated for research.

Concurrent Reviews by RSC and IRB

The IRB and the RSC will evaluate the applications concurrently, communicating with each other by means of memos and advising of any changes or stipulations required of the PI. When stipulations are met, the Chair, RSC, signs off the approval memo; a copy of this approval is then sent to: the Chair, IRB; the Applicant; the PI; Protocol Services; and Radiopharmacy. A copy is kept in the RSC files.

It is the responsibility of the PI to ensure that approval of the RSC and IRB have been obtained before seeking final approval by the Director of the Clinical Center. Protocol Services will check to determine that approvals have been obtained.

FIGURE 2 - LEGEND:
Procedures for Concurrent Review and Approval
of Research Protocols Using Ionizing Radiation

1. The IRB and RSC shall conduct concurrent reviews and exchange information as needed about stipulations required of the Applicant/PI. Copies of minutes in which the protocol is considered and memoranda to the Applicant/PI should be exchanged promptly to document any stipulations.

   The IRB and RSC Chairs have executive authority to approve a protocol after the PI has satisfied any stipulations required as a result of group review.

   The IRB Protocol Coordinator sends the following to the RSC:

   a) Thirteen copies of the protocol,
   b) Thirteen copies of the NIH Form 88-23(a),
   c) Thirteen copies of the informed consent, and
   d) The IRB minutes approving the protocol and signed approval memorandum (when they become available).

2. Following approval by the RSC Chair, the RSC staff support person assigns a Radiation Authorization Number and forwards a copy of the RSC's approval to the Protocol Services Section, Medical Record Department, CC. The RSC retains a copy of the complete application in its files.

3. The Protocol Services Section compiles the following material for review by the Director, Clinical Center:

   a) The finalized protocol with IRB approval memo,
   b) The signed NIH 88-23(a),
   c) The IRB minutes.

4. After the Director, CC, approves the protocol, the Protocol Services Section shall enter the CC protocol control number at the appropriate place on the face sheet of NIH 88-23(a) and notify the RSC of this number.

5. The Protocol Services Section shall transmit the approved protocol, with the CC protocol control number, to the PI. Note that all applications (NIH Form 88-23(1)) must be signed as discussed under "Procedures for Applying to the RSC" above.

It should be noted that the PI, as described in the application, may not be the Authorized User unless he/she has been authorized by the Radiation Safety Committee to use radioactive materials in clinical research. If the PI is not so authorized, an AI who is so authorized must be included in the authorship of the protocol.

Details regarding the concurrent review and sequential approval of protocols utilizing ionizing radiation for research purposes are shown in Figure 2.

EXPEDITED REVIEW

An IRB may use expedited review to review (1) research activities appearing on the list shown as Attachment 3 and found to involve no more than minimal risk as defined on page 4 of this issuance or (2) minor changes in previously approved research during the period (of up to one year) for which approval has been authorized.

Regulations (45 CFR 46.110) provide a list of categories of research that may be reviewed by the IRB through an expedited review procedure. Examples of such activities have been published, and appear as Attachment 3.

Under the expedited review procedure, the review may be carried out by the IRB Chair (or by one or more reviewers designated by the Chair from among IRB members). Through expedited review, the reviewer(s) may exercise all of the authorities of the IRB except that the reviewer(s) may not disapprove the research.

Each instance of expedited review shall be reported to the full IRB at its next scheduled meeting.

MONITORING OF APPROVED PROTOCOLS

Continuous Surveillance of Protocols

The Institute's Clinical Director may terminate or suspend a protocol at any time in the interest of the health or welfare of the subject. Further, the Clinical Director may request that the IRB review an ongoing protocol at any time.

The Director of the Clinical Center, being responsible for the quality of care and treatment of all patients at the Clinical Center, may terminate or suspend a protocol at any time should such action be deemed necessary. Generally, the Director will consult with Institute personnel before any termination takes place.

Submission of Reports of Unanticipated Problems and/or Unexpected Harm

Principal Investigators shall promptly report (1) any unanticipated problems involving risks to subjects or others, or (2) unexpected serious harm to subjects. Written reports shall be submitted for evaluation to the appropriate IRB Chair; the Institute Clinical Director; and the Director, CC (the latter only if the protocol is conducted in the CC).

If, in the opinion of the IRB, the Clinical Director, or the Director, CC, the effects or information are of sufficient impact, the protocol may be suspended or terminated. Alternatively, an amendment may be prepared for review by the IRB requesting (a) continued approval, or (b) approval of an amended procedure or of subject populations.

If the problem involves an FDA-approved IND drug, the IND sponsor and the CC Pharmacy Department must also be notified.

Continuing IRB Review and Approval

Each protocol at the CC will be reviewed at least annually by the IRB. Depending on the degree of risk to subjects, the IRB may choose to review the protocol more frequently. The timely, scheduled IRB review of active protocols is required by regulation and is an important mechanism by which IRBs fulfill their responsibility to protect the rights and welfare of human subjects.

In its continuing review, the IRB will examine the progress made in the conduct of the project, the occurrence of any unexpected reactions in the subjects studied, and the rate of accrual of subjects. The protocol's consent form(s) will be examined to ascertain that the information therein contained remains accurate.

PIs shall keep records of all persons entered in the protocol, their unit numbers, and their date of entry. These data should be kept available, to be provided on request with the narrative indicating the experience with the protocol that accomplanies the annual review form. All records and documents pertaining to the protocol should be retained by the PI for at least three years after the termination of the protocol.

The PI and the Institute PC will be informed by memo from the Protocol Services Section when the protocol is due for review. The PI will complete Part 1 of NIH form 1195-1 (Attachment 4) and forward the form and the protocol's consent form, with an accompanying memorandum providing requested information, to the individuals listed on the form's lower half.

Via this form, the PI can request that the project be terminated. If continuation is preferred, the PI must provide information, on the form and in an accompanying narrative, to the IRB on the progress of the project. Any scientific developments that bear on the protocol — especially those that affect the risks or hazards to participants — must be mentioned.

Proposed changes must be presented for approval by the IRB. If there are changes with respect to radiation (i.e., in the administration of radiation, experimental design, or the number of subjects studied), these proposed changes must be presented for approval by the RSC. If changes are substantive, a new NIH 88-23(a) should be completed and submitted; contact the Executive Secretary of the RSC for guidance.

If changes requested by the PI are substantive, or if amendments have resulted in the protocol being materially different from the original, the IRB may require that a protocol be rewritten to reflect the changes and/or consolidate the amendments.

Triennial Review

Although preparation of a completely rewritten protocol at the time of the three-year review, formerly required at the CC, is no longer mandated by the MPA, individual Institutes may elect to retain this review. PIs are advised to consult with their IRB Chairs regarding this review activity.

Suspension of a Protocol

In addition to the authorities of the Clinical Director or Director, Clinical Center, to terminate or suspend a protocol as mentioned above, an IRB has the authority to modify, suspend, or terminate approval of research that has been associated with unexpected serious harm to subjects or is not being conducted in accordance with 45 CFR 46, the NIH MPA, or the IRB's decisions, conditions, and requirements.

When an IRB suspends or terminates approval of a research project, the Chair shall report the decision to the PI, to the Institute Clinical Director, and to the OHSR for further reporting to the OPRR. If the research is conducted in or by an employee of the CC, the Director, CC, will also be notified.

Termination

Termination of the protocol means that no human subjects are further involved with the study.

A project may be terminated in any of the following ways:

- The PI may request that the project be terminated by checking the appropriate box on the NIH 1195-1.

- The PI may request termination at any time via a memo to the Clinical Director and Protocol Services Section (or, in the case of an off-site protocol, to OHSR).

- An IRB may terminate a project at any time in the interest of patient welfare, or because of the failure of a PI to submit a protocol for annual review.

- The Institute Clinical Director and/or the Director, CC, may also terminate a project at any time in the interest of patient welfare.

A PI may request that a protocol be kept active, without further accrual, for follow-up studies of subjects.

Exceptions

Certain situations may occur in which patients who do not meet the eligibility criteria for a protocol may be entered in the study. They are:

Single patient exception. This mechanism is used to enter a patient in a study even though the patient does not quite meet the specified entry criteria. Drug companies sponsoring such studies generally discourage this mechanism because such deviation from careful selection criteria potentially damages the study and may reduce its value.

Compassionate exception. An investigational drug may be given to a patient to treat a serious illness when there is no comparable or satisfactory alternative available. These exceptions may involve IND agents under trial at the CC or elsewhere; the physician ordering the drug must have the approval of the sponsor of the IND. This form of exception has no effect on the validity of the ongoing trials.

Emergency use IND. This category permits the use of a test substance in a life-threatening situation in which no standard, acceptable treatment is available and in which there is not sufficient time to obtain a regular IND. A temporary IND is granted by the FDA, usually by telephone, with the understanding that a proper IND submission will be made by the sponsor. Such use is to be reported promptly to the IRB Chair, and any further use of the article in the CC is to be subject to IRB review.

Premature entry exception. This exception, used when a protocol has received all necessary approvals save that of the Director, CC, will be granted only in those exceptional circumstances when there is an eligible patient waiting to be enrolled and the delay before final approval would cause unwarranted hardship.

Requests for special exceptions must be submitted on NIH form 2702 (Attachment 5) and must be accompanied by a consent document, NIH-2514-1, signed by the patient, or, in the case of a minor, a copy of NIH-2514-1 signed by the parent or guardian and a copy of NIH-2514-2 signed by the patient (if applicable). These consent/assent forms are shown as Attachment 6.

FILES

Copies of approved Clinical Center protocols will be kept in the Protocol Services Section office. Copies of off-site protocols will be kept in the OHSR. Copies of all correspondence relative to protocols should be sent to these offices for inclusion with the file.

CLINICAL RESEARCH PROTOCOL: INITIAL REVIEW APPLICATION

PRINCIPAL INVESTIGATOR (Name, Institute/Branch, Address, Telephone):

PROTOCOL TITLE: _____ PROTOCOL NO.

PROPOSED START DATE: _____ END DATE: _____ TOTAL SUBJECTS TO BE ACCRUED: _____

MULTI-SITE COLLABORATION:
- ☐ None
- ☐ Domestic site(s) only*
- ☐ Foreign site(s) only*
- ☐ Foreign & domestic sites*

*Include the full name and address of each site and identify whether each holds a Multiple Project or Single Project Assurance. For more information, contact the Office of Human Subjects Research (402-3444).

REQUESTED ACCRUAL EXCLUSION (Check all that apply):
- ☐ None
- ☐ Male*
- ☐ Female*
- ☐ American Indian or Alaskan Native*
- ☐ Asian or Pacific Islander*
- ☐ Black* (Not of Hispanic origin)
- ☐ White* (Not of Hispanic origin)
- ☐ Hispanic*

*Complete and attach a detailed statement describing the rationale for the exclusion(s).

ACCRUAL CHARACTERISTICS:

Median Subject Age		☐ 0-17 Yrs.	☐ 18-65 Yrs.	☐ 66> Yrs.
Pediatric Subjects	☐ None	☐ <1 Yr.	☐ 1-3 Yrs.	☐ 4-17 Yrs.
Impaired Subjects	☐ None	☐ Physically	☐ Cognitively	☐ Both
Volunteer Subjects	☐ None	☐ Normal Control	☐ NIH Employee	☐ NIH Patient

SPECIAL RESOURCE REQUIREMENTS (Check all that apply):
- ☐ Intensive care
- ☐ Pediatric intensive care
- ☐ Positron Emission Tomography (PET)
- ☐ Surgery
- ☐ Transfusion
- ☐ Bone marrow transplantation
- ☐ Isolation
- ☐ Gene therapy
- ☐ Controlled substance(s)
- ☐ Prosthetics
- ☐ Gynecologic services
- ☐ Other: _____

KEY WORDS (Enter 5 words, not contained in the protocol title, particularly salient in describing the protocol):
1. _____
2. _____
3. _____
4. _____
5. _____

IONIZING RADIATION USE (X-rays, radioisotopes, etc.):
- ☐ None
- ☐ Medically indicated only
- ☐ Research indicated (Complete NIH-88-23a, and attach to this application. Send a copy of entire protocol and of NIH-88-23a to Chair, Radiation Safety for concurrent review.)

INVESTIGATIONAL NEW DRUG/INVESTIGATIONAL DEVICE EXEMPTIONS USAGE:
- ☐ None
- ☐ IND: FDA No. _____
  - Drug Name: _____
  - Drug Sponsor: _____
  - Holder: _____
- ☐ IDE: FDA No. _____
  - Device Name: _____
  - Device Sponsor: _____
  - Holder: _____

MEDICALLY RESPONSIBLE INVESTIGATOR (If necessary):

_____
(Name) (Institute/Branch) (Telephone)

ASSOCIATE INVESTIGATOR(S):
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
(Name) (Institute/Branch) (Telephone)

(Principal Investigator: Be sure to include PRECIS <=400 words as first section of protocol)

SIGNATURE	_____ Principal Investigator	DATE _____	Send to Branch or Department Chief
RECOMMENDATION	_____ Branch Chief or Clinical Center Department Head of Principal Investigator	DATE _____	Send to Clinical Director
APPROVALS	_____ Clinical Director	DATE _____	Send to Chair, Institutional Review Board
	_____ Chair, Institutional Review Board	DATE _____	Send to Protocol Implementation Review Committee
	_____ Protocol Implementation Review Committee	DATE _____	Send to Protocol Services, MRD (10/1N204) through IRB Protocol Coordinator
	_____ Director, Clinical Center	DATE _____	Send to Protocol Services, MRD (10/1N204)
COMPLETION	_____ Credentials & Protocol Specialist	DATE _____	

Date Received (PS/10/1N204)

Clinical Research Protocol Initial Review Application NIH-1195 (11-92)

Copy: Protocol Services Section

APPLICATION FOR AUTHORIZATION
TO USE RADIATION IN RESEARCH
INVOLVING HUMAN SUBJECTS
Form NIH 88-23(a)

Attached is a Form 88-23(a) for your use. The NIH's policy on who may submit an application the Radiation Safety Committee is reproduced below.

APPLICATION POLICIES FOR AUTHORIZATION TO USE RADIATION IN RESEARCH INVOLVING HUMAN SUBJECTS

Studies that require x rays, radionuclides, or both, with the resulting exposure to ionizing radiation indicated solely for research, should be considered at two levels: 1) Complex high dose procedures central to the protocol involved and 2) Standard procedures often used in the practice of medicine.

The following table specifies the background required of an applicant PI or AI submitting a protocol using those modalities at the levels indicated.

	Level #1 Procedures that are complex or high dose is central to the protocol	Level #2 Standard procedures often used in medical practice
Radiological examination	RSC Authorized credentialed clinician[1] or a credentialed clinician with a relevant specialty board certification[2]	Credentialed clinician
Radionuclide use	RSC Authorized clinician	Credentialed clinician with the actual procedure under super-vision of an RSC Authorized clinician

[1] The RSC authorizes clinicians based upon the "Applications for Authorization To Administer Radioactive Material for Research With Human Subjects"

[2] Such as cardiology, gastroenterology, or nuclear medicine

All studies involving research irradiation, whether at Level 1 or Level 2, must be reviewed by the RSC with a single exception: radiotherapy protocols involving external beam radiation from non-NRC licensed sources need only be reviewed by the RSC when requested by the PI.

Reminders for completion of application:

1. Fill out all parts of form completely.

2. Applications must be signed by applicant consistent with the above guidelines of the Committee as well as the PI.

3. Be sure to include literature citations and other information sufficient to support dosimetry calculations.

Revised November 1990
Minor Revision September, 1992

Action Requested:

___ New Application

___ Amend Existing Rad Authorization

___ Triennial Review of Rad Authorization

NIH 88-23(a)

APPLICATION FOR AUTHORIZATION TO USE RADIATION IN RESEARCH INVOLVING HUMAN SUBJECTS

PLEASE TYPE OR PRINT LEGIBLY

(Radiation Safety Committee Use Only)

Action Item No. ____-____

Rad Authorization No. _____

Clinical Project No. ____-____-____

Applicants*					
Name	Institute	Division/ Branch/Lab	Bldg./Room	SIGNATURE	Date
Principal Investigator(s) (If different than applicant)					

* Refer to current *Application Policies for Authorization to use Radiation in Research Involving Human Subjects.*

SAMPLE

TITLE OF RESEARCH PROJECT: _____

CLINICAL PROJECT NO. _____ RAD AUTHORIZATION NO. _____

Material to Be Administered									
Radionuclide		Compound	Maximum activity per single administration (mCi)	Maximum number of administrations per subject:		Method of administration			Maximum quantity of active drug or compound per single administration (μg or mg)
				Quarterly	Yearly	IV	Oral	Other	
1.									
2.									
3.									
4.									
5.									

ATTACHMENT 3

RESEARCH ACTIVITIES WHICH MAY BE REVIEWED THROUGH EXPEDITED REVIEW PROCEDURES

Research activities involving no more than minimal risk and in which the only involvement of human subjects will be in one or more of the following categories (carried out through standard methods) may be reviewed by the Institutional Review Board through the expedited review procedure authorized in 45 CFR 46.110.

(1) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, X-rays, microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not

manipulate subjects' behavior and the research will not involve stress to subjects.

(10) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

CLINICAL RESEARCH PROTOCOL: CONTINUING REVIEW APPLICATION

PROTOCOL NO.	PRINCIPAL INVESTIGATOR (Print or Type Name)

PROTOCOL TITLE: _____

ACTION REQUESTED:
- ☐ Renew-New subject accrual to continue
- ☐ Renew-Enrolled subject followup only
- ☐ Terminate-Protocol discontinued

HAVE THERE BEEN ANY AMENDMENTS SINCE THE LAST REVIEW?
- ☐ No
- ☐ Yes (Describe briefly in the attached narrative)

SUMMARY OF PROTOCOL SUBJECTS:
- _____ Accrual ceiling set by IRB
- _____ New subjects accrued since last review
- _____ Total subjects accrued since protocol began (If accrual has been less than expected, discuss in the attached narrative)

_____ Age Range

ACCRUAL EXCLUSIONS:
- ☐ None ☐ Male
- ☐ Female ☐ Other: _____

IMPAIRED SUBJECTS:
- ☐ None ☐ Physically ☐ Cognitively

HAVE THERE BEEN ANY CHANGES IN THE SUBJECT POPULATION, RECRUITMENT OR SELECTION CRITERIA FROM THOSE ORIGINALLY APPROVED BY THE IRB?
- ☐ No
- ☐ Yes (Explain changes in the attached narrative)

HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
- ☐ No
- ☐ Yes (Explain changes in the attached narrative)

HAS ANY INFORMATION APPEARED IN THE LITERATURE, OR EVOLVED FROM THIS OR SIMILAR RESEARCH, THAT MIGHT AFFECT THE IRB's EVALUATION OF THE RISK/BENEFIT ANALYSIS OF HUMAN SUBJECTS INVOLVED IN THIS PROTOCOL?
- ☐ No
- ☐ Yes (Discuss in the attached narrative)

HAVE ANY UNEXPECTED COMPLICATIONS OR SIDE EFFECTS BEEN NOTED SINCE LAST REVIEW?
- ☐ No
- ☐ Yes (Identify and explain in attached narrative)

HAVE ANY SUBJECTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
- ☐ No
- ☐ Yes (Discuss in the attached narrative)

CHANGE IN PRINCIPAL INVESTIGATOR:
- ☐ None
- ☐ Delete: _____
- ☐ Add: _____

HAVE ANY ASSOCIATE INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
- ☐ No
- ☐ Yes (Identify all changes in the attached narrative)

CHANGE IN MEDICALLY RESPONSIBLE INVESTIGATOR:
- ☐ None
- ☐ Delete: _____
- ☐ Add: _____

INVESTIGATIONAL NEW DRUG/INVESTIGATIONAL DEVICE EXEMPTIONS USAGE:
- ☐ None
- ☐ IND: FDA No. _____
  - Drug Name: _____
  - Drug Sponsor: _____
  - Holder: _____
- ☐ IDE: FDA No. _____
  - Device Name: _____
  - Device Sponsor: _____
  - Holder: _____

HAVE ANY NON-NIH INVESTIGATORS OR SITES BEEN ADDED SINCE THE LAST REVIEW?
- ☐ No
- ☐ Yes (Identify the persons or sites and describe the collaboration in the attached narrative))

IONIZING RADIATION USAGE (X-rays, radioisotopes, etc.):
- ☐ None
- ☐ Medically indicated only
- ☐ Research indicated:
  - ☐ Research usage HAS NOT changed since originally approved by the IRB and RSC
  - ☐ Research usage HAS changed since originally approved by the IRB and RSC (explain changes in the attached narrative)

HAVE ANY INVESTIGATORS DEVELOPED AN EQUITY OR CONSULTATIVE RELATIONSHIP WITH A NON-NIH SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
- ☐ No
- ☐ Yes (Append a statement of disclosure)

The Principal Investigator must attach to this application: (1) a copy of the current consent/assent document and (2) a memorandum to the IRB Chairperson that addresses any "yes" responses to the above questions, and that includes a concise statement regarding protocol progress to date and reason(s) for continuing the study.

SIGNATURE	_____ Principal Investigator	DATE _____	Send to Branch or Department Chief
RECOMMENDATION	_____ Branch Chief or Clinical Center Department Head of Principal Investigator	DATE _____	Send to Clinical Director
APPROVALS	_____ Clinical Director	DATE _____	Send to Chair, Institutional Review Board
	_____ Chair, Institutional Review Board	DATE _____	Send to Protocol Services, MRD (10/1N204) through IRB Protocol Coordinator
	_____ Director, Clinical Center	DATE _____	Send to Protocol Services, MRD (10/1N204)
COMPLETION	_____ Credentials & Protocol Specialist	DATE _____	

Date Received (PS/10/1N204)	34	Clinical Research Protocol: Continuing Review Application NIH-1195-1 (11-92) Copy: Protocol Services Section

MEDICAL RECORD	SPECIAL EXEMPTION FROM RESEARCH PROTOCOL	Protocol No. Initiating Office No. (NCI ONLY)

INSTRUCTIONS Principal Investigator

1. Obtain Branch Chief, Clinical Director and ICRS Chair approval signatures.
2. Forward the NIH-2702 Special Exemption from Research Protocol form to the Associate Director for Quality Assurance and Hospital Epidemiology, OD, CC (Building 10, Room 2C146) for final approval and signature.
3. If **APPROVED** for Inpatient: place original NIH-2702 form in the patient's chart. Otherwise, send form to Record Management Section, MRD, CC (Building 10, Room 1N211) for filing in the patient's Medical Record.
4. Submit a 30-day follow-up (for all approved exemptions except "Premature Entry") to your Institute Clinical Director.

Associate Director for Quality Assurance and Hospital Epidemiology, OD, CC

1. Return **APPROVED/DISAPPROVED** NIH-2702 form to Principal Investigator.
2. If **APPROVED**, forward one (1) copy to Documentation Analysis and Coding, MRD, CC (Building 10, Room 1N205).

DIAGNOSIS	SEX ☐ Male ☐ Female	DATE OF BIRTH Mo Day Yr
	NATURE OF REQUEST ☐ Single Patient ☐ Emergency Use IND ☐ Compassionate ☐ Premature Entry	

CLINICAL SUMMARY (To include a brief history, present status of patient, diagnosis, relevant lab data and *"reason for requesting special exemption")*

PRINCIPAL INVESTIGATOR

▶ _____ _____
Principal Investigator Date

Building_____ Room_____ Telephone_____ Institute_____

APPROVALS

▶ _____ _____
Branch Chief Date

▶ _____ _____
Institute Clinical Director Date

▶ _____ _____
ICRS Chair Date

▶ _____ _____
Associate Director for Quality Assurance and Hospital Epidemiology, CC Date

Patient Identification

SPECIAL EXEMPTION FROM RESEARCH PROTOCOL
NIH-2702 (4-92)
P.A. 09-25-0099
File in Section 4: Protocol Consent

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: _____

STUDY NUMBER _____ PRINCIPAL INVESTIGATOR: _____

STUDY TITLE: _____

_____

_____

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

STUDY NUMBER: _____

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of National Institutes of Health or Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the National Institutes of Health, Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

3. **Payments.** If you are a patient, you are not paid for taking part in National Institute of Health studies. Exceptions for volunteers will be guided by the National Institutes of Health or Clinical Center policies.

4. **Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, _____, or these other staff members also involved in this study: _____; _____; Building _____, Room _____. Telephone: (301) _____. National Institutes of Health Bethesda, Maryland 20205

5. **Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:

A. Adult Patient's Consent.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____
Signature of Adult Patient & Date Signed

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

_____
Signature of Parent(s) & Date Signed

_____
(If Other Than Parent, Specify Relationship)

_____
Signature of Investigator & Date Signed

_____
Signature of Witness & Date Signed

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)
• Adult Patient or • Parent, for Minor Patient
NIH-2514-1 (9-91)
P.A.:09-25-0099
File in Section 4: Protocol Consent

INSTITUTE: _____

STUDY NUMBER: _____ PRINCIPAL INVESTIGATOR: _____

STUDY TITLE: _____

_____

_____

MEDICAL RECORD	**CONTINUATION SHEET for either:** NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: _____ CONTINUATION: page ___ of ___ pages.