

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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SOP Title: HUMAN SUBJECTS RESEARCH AND THE NIH IRB SYSTEM

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators**

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SOP 1 HUMAN SUBJECTS RESEARCH AND THE NIH IRB SYSTEM

1.1 PURPOSE

This Standard Operating Procedure (SOP) provides an overview of human subjects research and a description of the NIH Institutional Review Board (IRB) system.

1.2 POLICY

NIH IRBs will review research involving human subjects in accordance with the U.S. Department of Health and Human Services (DHHS) regulations at 45 CFR 46 (“Common Rule”) and the relevant NIH SOPs. This policy addresses human subjects research that is reviewed by IRBs. Research, that is exempt, or otherwise excluded, from IRB review under 45 CFR 46, is covered in SOP 5 - Required Review for NIH Research Activities with Human Subjects and Specimens/Data and SOP 6 - Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP).

1.3 INTRODUCTION

DHHS regulations apply to all research at NIH and to all NIH SOPs. NIH IRBs review and approve research involving human subjects conducted in the Intramural Research Program in accord with 45 CFR 46 and/or 21 CFR 50, 56, 312 and 812 to protect subjects' rights and safeguard their welfare, (see SOP 15 - Research Regulated by the Food and Drug Administration (FDA) General Procedures for Both IND and IDE Applications). In limited circumstances, NIH IRBs may be approved to apply other human subjects regulations and/or policies to the review of research.

1.4 DEFINITIONS

- A. **Research:** means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some

demonstration and service programs may include research activities, (45 CFR 46.102(d)).

B. **Human subject:** means a living individual about whom an investigator (whether professional or student) conducting research obtains:

1. Data through **intervention** or **interaction** with the individual, **or**
2. Identifiable **private information**

C. **Intervention:** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

D. **Interaction:** includes communication or interpersonal contact between investigator and subject.

E. **Private information:** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR.102 (f) (2)).

F. **Undue Influence:** Undue influence with regards to the IRB refers to any attempt to interfere with the standard procedures of the IRB or to inappropriately place pressure on an IRB member, IRB Chair or IRB staff member in order to obtain a specific outcome from the IRB or one of its members or staff.

1.5 ENGAGEMENT IN HUMAN SUBJECTS RESEARCH BY NIH

The NIH is engaged in human subjects research projects when its **staff** for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

Engagement of NIH staff in human subjects research may also occur during cooperative or collaborative research. See SOP 20 : NIH HRPP Requirements for Collaborative Research and the Office for Human Research Protections (OHRP) “Guidance on Engagement of Institutions in Human Subjects Research” (see References).

The assessment of whether an NIH activity is “engagement in human subjects research” can only be made by the Office of Human Subjects Research Protections (OHSRP) or by an NIH IRB.

1.6 DETERMINATIONS OF EXEMPT RESEARCH OR RESEARCH OTHERWISE EXCLUDED FROM IRB REVIEW

Certain activities that involve interacting with human subjects or specimens/data may be exempt, or otherwise excluded, from IRB review consistent with the Common Rule. At NIH, OHSRP has sole authority to make determinations to exempt, or otherwise exclude, research from IRB review under 45 CFR 46.101(b)(1)-(6) and 45 CFR 46.102. For further guidance, please see SOP 5 - Required Review for NIH Research Activities with Human Subjects and Specimens/Data and SOP 6 - Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP).

1.7 REQUIREMENT FOR REVIEW BY NIH’S IRBS

Except as otherwise provided in these SOPs, when NIH investigators become engaged in human subjects research, such research must be reviewed, prospectively approved, and subject to continuing review by an NIH IRB. Officials at the NIH may not approve the conduct of research unless it receives NIH IRB approval or is determined by OHSRP to be exempt, or otherwise excluded, from IRB review. The most common exceptions to the requirement for such NIH IRB review will be:

- A. Studies that meet the requirements for an exemption under 45 CFR 46.101(b), or are otherwise excluded, from IRB review (see SOP 5 - Required Review for NIH Research Activities with Human Subjects and Specimens/Data and SOP 6 - Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP)); and,
- B. Studies that would otherwise require review by an NIH IRB, but for which NIH enters into a reliance agreement to rely on IRB review by a non-NIH IRB (see

SOP 20 - NIH HRPP Requirements for Collaborative Research and SOP 20A - Obtaining a Reliance (Authorization) Agreement at the NIH).

1.8 DESCRIPTION OF THE NIH IRBS

The NIH IRB system is composed of 12 active IRBs with discrete missions and research portfolios. Except as otherwise stated in the HRPP SOPs, each of the NIH IRBs will follow the requirements of the NIH Federalwide Assurance (FWA) and SOPs. The NIH IRBs are:

Name	Primary Institute(s) Assigned	IRB Registration
National Cancer Institute	NCI	IRB 00000001
National Cancer Institute Special Studies	NCI	IRB 00000002
National Heart, Lung and Blood Institute	NHLBI	IRB 00000004
National Institute of Allergy and Infectious Diseases	NIAID	IRB 00000005
National Institute of Digestive and Kidney Diseases & National Institute of Arthritis and Musculoskeletal Diseases	NIDDK/NIAMS	IRB 00000006
Combined Neurosciences Purple Panel	NIDCR	IRB 00000007
National Institute of Child Health and Human Development	NICHD	IRB 00000008
Addictions IRB	NIDA, NIAAA	IRB 00008803
National Institute of Environmental Health Sciences	NIEHS	IRB 00000013
National Human Genome Research Institute	NHGRI	IRB 00000014
Combined Neurosciences Blue Panel	NEI, NINDS, NIDCD, NINR	IRB 00005894
Combined Neurosciences White Panel	NIMH	IRB 00005895

Unless otherwise stated in these SOPs, the use of the term IRB refers to any of these twelve IRBs.

1.9 JURISDICTION OF EACH IRB

Institutes with designated IRBs (single-Institute IRBs - see 1.12, below) generally review protocols from their own investigators. There are, however, exceptions to this rule, as follows:

- A. **PIs from other Institutes:** When the **PI** of a research protocol is an employee of an NIH **Institute/ Center (IC)** that is not assigned to an IRB in 1.7, above, (see **Appendix 1**, List of NIH Components Not Assigned to an IRB), that protocol will be reviewed by the IRB whose expertise is most closely related to the protocol's research topic. The PI initially contacts the administrative staff of the IRB that appears most appropriate. The appropriateness of that protocol for review is determined by the IRB's Chair. **If there is disagreement over the assignment of the protocol, the OHSRP Director will make the final decision.** A research study submitted to one NIH IRB for review may not be submitted to a different NIH IRB either at the same time or subsequently, **except for the situations outlined below** (see 1.9.**B-E**).
- B. **PI transfers or is detailed to another Institute:** If a PI transfers **or is detailed** to another Institute, the appropriateness of transferring the study to another **NIH** IRB will be **evaluated**. In the event that there is any uncertainty or dispute regarding which **NIH** IRB should review a protocol, the Deputy Director for Intramural Research (DDIR) will make the final determination, or delegate that authority to OHSRP. **If a protocol is transferred between NIH IRBs, please refer to SOP 27 – Transfer of Protocols between Institutional Review Boards (IRBs) for further guidance.**
- C. **IC Directors, Scientific Directors, and Clinical Directors:**
 1. The NIH *Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research* (see SOP 21 - Managing Conflict of Interest in Research) states that Institute Directors and Institute Scientific Directors **must have their protocols reviewed by an IRB not affiliated with their Institute when they are a PI or an AI on a protocol. The DDIR may waive this requirement.**

2. IRBs have the prerogative to review the protocols of their Institute's Clinical Director (CD) or refer them to another Institute's IRB. IRBs reviewing protocols in which their CD is the PI must have a majority of members who are not employed by the CD's Institute, otherwise any alternative plan must have prior approval by the DDIR.

D. **Other Circumstances:** Circumstances may justify having a protocol reviewed by an NIH IRB other than the one to which it would be assigned under the rules above. The DDIR has the authority to determine which IRB will have jurisdiction over such a protocol or may delegate the authority to OHSRP.

1.10 AUTHORITY OF THE IRBS

A. Each NIH IRB has the regulatory authority to:

1. Approve, modify or disapprove research (45 CFR 46.109(a))
2. Suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. (45 CFR 46.113)
3. Observe, or have a third party observe, the consent process (45 CFR 46.109(e))

B. The IRBs also have authorities associated with:

1. The consent process (45 CFR 46.109(b)-(c), 45 CFR 46.116).
2. Continuing review (45 CFR 46.109(e)).
3. Applicable authorities per the FDA.

1.11 FREQUENCY OF MEETINGS

Each of the NIH IRBs has regularly scheduled meetings. If necessary, IRBs may convene special meetings.

1.12 SCIENTIFIC DIRECTOR'S RESPONSIBILITY RELATING TO IC HRPP

A. **Single Institute IRBs:** The Scientific Director (SD) of the Institute has administrative responsibility for each of the IRBs assigned to a single Institute. Some of the responsibilities listed below may be delegated to the CD (for more information see the Introduction to the NIH Human Research Protection Program). Administrative responsibility includes:

1. Allocation of resources for the IRB, including budget, space, and staff.
2. In conjunction with the CD (or by delegation to the CD), nominating IRB Chairs, Vice Chairs and members for the DDIR's approval and appointment, see SOP 2 – IRB Membership and Structure for further information.
3. Providing resources for Data and Safety Monitoring Boards (see SOP 17 - Data and Safety Monitoring”).
4. Providing resources for pre-IRB Scientific Review Committees (see SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs”).
5. Ensuring the independence of the IRB, and upholding its decisions.

B. Multiple-Institute IRBs

1. As noted in 1.7, above, several IRBs (currently the Addictions IRB, NIDDK/NIAMS IRB, the CNS White IRB, and the CNS Blue IRB) are designated as the primary IRB for more than one NIH Institute.
2. Each of these multiple-institute IRBs must provide OHSRP with a written policy, signed by all the SDs for the Institutes assigned to that IRB, describing which SD and/or CD will assume, for that IRB, the administrative responsibilities assigned to SDs described in 1.11.A above.

1.13 REVIEW OF IRBS' PERFORMANCE

IRBs' performance is reviewed and evaluated as described in SOP 26 - Evaluation of NIH IRB Chairs, Vice Chairs and Members, IRB Administrative Staff and IRB Committee Activities.

1.14 INDEPENDENCE OF THE IRBS

- A. In exercising the authority provided to them under 1.9, above, the NIH IRBs will at all times maintain their independence. The DDIR, who serves as the Institutional Official, will oversee the NIH Human Research Protection Program (HRPP) in a manner that assures that the IRBs can exercise their authority independently.
- B. The SDs' and CDs' administrative responsibilities for providing resources for IRBs and nominating potential IRB members do not include authority to unduly influence IRB decisions. IC Directors, SDs and CDs must respect IRB decisions.
- C. An IRB member who is concerned about undue influence or inappropriate communications from any source should first report the occurrence to the Chair of that IRB, who will attempt to mediate or resolve the concern, in consultation with the applicable CD, OHSRP, or other NIH officials, as necessary or appropriate.
- D. An IRB Chair who is concerned about undue influence or inappropriate communications from any source should first report the occurrence to OHSRP, which will attempt to mediate or resolve the concern, in consultation with the DDIR or other NIH officials, as necessary or appropriate.
- E. Any individual who believes that inappropriate communications or undue influence have not been appropriately resolved in a timely manner, should report the matter to OHSRP or the DDIR.

1.15 NIH IRB INTERACTIONS WITH OTHER NIH COMMITTEES INVOLVED IN SAFETY AND MONITORING

In addition to the NIH IRBs, there are several specialized NIH committees involved in ensuring the safety of Intramural Research Program (IRP) research subjects and NIH staff during the conduct of research protocols. If applicable, the following specialized NIH committee(s) will review protocols, regardless of location (i.e., NIH CC and NIH off-site locations). Research cannot commence until all applicable approvals are in place (see SOP 8 - Procedures and Required Documentation for Submission and Initial Review of Protocols).

- A. **The NIH Radiation Safety Committee (RSC):** is responsible to the Director, NIH for oversight of the NIH Radiation Safety Program to ensure the safe use of radioactive materials and all sources of ionizing radiation throughout NIH and those NIH-occupied buildings included in the NIH Radiation Safety Program. The RSC is responsible for formulating policy with regard to radiation protection matters in the **IRP** that involve NIH employees and members of the general public, routine clinical and research programs, and protection of the environment to ensure compliance with Federal regulations, including those of the U.S. Nuclear Regulatory Commission.

PIs must obtain clearance from the RSC for protocols whose subjects may be exposed to radiation before the protocol can be approved (See SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)).

- B. **The Radioactive Drug Research Committee (RDRC):** functions as a subcommittee of the RSC and is mandated by the FDA Regulations, 21 CFR Part 361.1, "Radioactive Drugs for Certain Research Uses," to review and approve the use of radioactive drugs for research purposes in humans for which an approved New Drug Application (NDA) or an approved Investigational New Drug Application (INDA) does not exist.

- C. **The Office of Biological Activities (OBA), and the Recombinant DNA Advisory Committee (RAC):** is responsible for oversight and policy development regarding scientific, safety, and ethical issues associated with basic and clinical recombinant NIH research. This role includes implementation of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, which articulate principles of containment and biosafety review for this type of research. A key element of this system of oversight is the NIH **RAC**, which reviews human gene transfer protocols and makes recommendations to PIs and others on improving the science, safety and ethics of their trials. The RAC also advises the NIH on scientific, safety, and policy matters related to the use of recombinant DNA in research generally, including needed modifications of the *NIH Guidelines*. Most intramural trials involving human gene transfer need to be registered with OBA and reviewed by the RAC. Further, basic and clinical research involving recombinant DNA should be registered, and in many cases reviewed, by the NIH Institutional Biosafety Committee (IBC). More information on the RAC and IBC can be found at their website (see **References**).

D. The Institutional Biosafety Committee (IBC), Office of Research Services

(ORS): This committee, created pursuant to the *NIH Guidelines* reviews basic and clinical research involving recombinant DNA, including human gene transfer, to ensure that proper containment and biosafety practices are employed. When reviewing human gene transfer protocols, the IBC also oversees compliance with the *NIH Guidelines*, which details points to consider in the design of human gene transfer protocols and their submission to the NIH **OBA**.

REFERENCES

A. OHRP “Guidance on Engagement of Institutions in Human Subjects Research”: <http://www.hhs.gov/ohrp/policy/engage08.html>

B. OBA, RAC and IBC guidance: <http://oba.od.nih.gov/oba/>

C. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules: <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>

LIST OF APPENDICES

APPENDIX 1 - List of NIH Components Not Assigned to a Specific IRB

APPENDIX 1 - LIST OF NIH COMPONENTS NOT ASSIGNED TO A SPECIFIC IRB

- A. The National Institute on Aging
- B. The National Institute of Biomedical Imaging and Bioengineering
- C. The National Institute of General Medical Sciences
- D. The National Library of Medicine
- E. The NIH Clinical Center
- F. The Center for Information Technology
- G. The Center for Scientific Review
- H. **Fogarty International Center**
- I. **The National Center for Complementary and Integrative Health**
- J. The National Institute on Minority Health and Health Disparities
- K. National Center for Advancing Translational Science
- L. The NIH Office of the Director
- M. **The National Institute of Nursing Research**