

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

**OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS**

**SOP Title: INTRODUCTION TO THE NIH HUMAN RESEARCH PROTECTION  
PROGRAM**

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**INTRODUCTION TO THE NIH HUMAN RESEARCH PROTECTION PROGRAM**

<b>TABLE OF CONTENTS</b>	<b>PAGE</b>
<b>A. THE NIH MISSION</b>	<b>1</b>
<b>B. THE NIH FEDERALWIDE ASSURANCE (FWA)</b>	<b>2</b>
<b>C. THE NIH INTRAMURAL RESEARCH PROGRAM (IRP)</b>	<b>2</b>
<b>D. THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)</b>	<b>3</b>
<b>1. Governance and Advisory Entities</b>	<b>4</b>
<b>2. The Regulatory/Compliance Arm</b>	<b>5</b>
<b>3. The Protocol Development/Operations Arm</b>	<b>8</b>
<b>E. THE CLINICAL CENTER</b>	<b>9</b>
<b>F. OTHER NIH COMMITTEES</b>	<b>10</b>
<b>G. AUTHORITY AND RESPONSIBILITY FOR THE DEVELOPMENT,     MAINTENANCE AND REVISION OF POLICIES FOR THE NIH HRPP</b>	<b>11</b>
<b>REFERENCES</b>	<b>13</b>
<b>ATTACHMENT: HRPP ORGANIZATIONAL CHART</b>	<b>14</b>

## **INTRODUCTION TO THE NIH HUMAN RESEARCH PROTECTION PROGRAM**

### **A. THE NIH MISSION**

The mission of the National Institutes of Health (NIH) is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life and reduce the burden of illness and disability. The NIH's Intramural Research Program (IRP) established the Human Research Protection Program (HRPP) to protect the rights and safeguard the welfare of human subjects who participate in its research studies. The NIH HRPP endorses the following goals:

1. NIH performs clinical research according to the highest scientific and ethical standards and in a manner that promotes and respects the rights and welfare of all human subjects, consistent with applicable laws, regulations and policies including but not limited to The Belmont Report and, when applicable, the Food and Drug Administration's (FDA) Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (1996).
2. NIH ensures that the performance of all research involving human subjects conducted in the IRP complies with applicable federal laws, Department of Human and Health Services (DHHS) and FDA regulations; the Standard Operating Procedures (SOP) of the NIH HRPP; NIH Manual Chapters; The Standards for Clinical Research Within the NIH Intramural Research Program\* , Guidelines for the Conduct of Research in the Intramural Research Program at NIH\*, and a Guide to Training and Mentoring in the Intramural Research Program at NIH\*.
3. NIH complies with the HRPP standards listed in the NIH Policy Manual 3014 - NIH HRPP which provides a detailed description of the clinical research infrastructure and resources each Institute and Center is expected to provide in the areas of clinical informatics, data management, protocol tracking, biostatistics, quality assurance and quality control, protocol review, human resources, physical plant, training and education.
4. NIH requires its investigators to understand the regulatory definition of research with human subjects, to know when they are conducting research with human subjects, and provides appropriate training for investigators and Institutional Review Boards (IRBs).
5. NIH establishes and maintains IRBs. These IRBs are responsible for the prospective and continuing review and approval of research activities involving

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\* see: REFERENCES, page 12

human subjects. Their primary mandate is to protect the rights and safeguard the welfare of human research subjects.

6. The composition and operation of each NIH IRB conforms to the terms and conditions of federal regulations.
7. NIH IRBs review research protocols only after they have been reviewed by the applicable Institutes and Centers (ICs) and found to be scientifically meritorious.
8. NIH ensures that the IRBs exercise independent authority and decision-making with respect to the review and approval of research with human subjects.

## **B. THE NIH FEDERALWIDE ASSURANCE (FWA)**

The NIH has a FWA (#00005897) on file with the DHHS Office for Human Research Protections (OHRP). Through this document NIH commits to DHHS that it will comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR 46.

## **C. THE NIH INTRAMURAL RESEARCH PROGRAM (IRP)**

The IRP consists of separately funded programs within the ICs of the NIH:

1. National Institute on Alcohol Abuse and Alcoholism (NIAAA).
2. National Institute of Allergy and Infectious Diseases (NIAID), including the Vaccine Research Center and the Rocky Mountain Laboratory, Hamilton, Montana.
3. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).
4. National Institute of Biomedical Imaging and Bioengineering (NIBIB).
5. National Cancer Institute (NCI), including the Frederick Cancer Research and Development Center, Frederick, Maryland.
6. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), including the Perinatology Research Branch, Wayne State University, Hutzel Hospital, Detroit, Michigan.
7. National Institute of Deafness and other Communication Disorders (NIDCD).
8. National Institute of Dental and Craniofacial Research (NIDCR).
9. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including the Phoenix Epidemiology and Clinical Research Branch, Phoenix, Arizona.

10. National Institute on Drug Abuse (NIDA), Baltimore, Maryland.
11. National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.
12. National Eye Institute (NEI).
13. National Heart, Lung and Blood Institute (NHLBI).
14. National Human Genome Research Institute (NHGRI), including the Center for Inherited Disease Research in Baltimore, Maryland.
15. National Institute of Mental Health (NIMH).
16. National Institute of Neurological Disorders and Stroke (NINDS).
17. National Institute of Nursing Research (NINR).
18. National Center for Complementary and Alternative Medicine (NCCAM).
19. The Clinical Center research complex, including the Warren Grant Magnuson Clinical Center and the Mark O. Hatfield Clinical Research Center.
20. The National Institute on Aging (NIA).

Each IC is administered by the Institute Director, Scientific Director, and Clinical Director.

1. **Institute Directors** have overall responsibility for their Institutes' intramural activities, but generally delegate authority to the Institutes' Scientific and Clinical Directors.
2. **Institute Scientific Directors** are responsible for the overall direction of and allocation of resources for all the laboratory and clinical research programs carried out in their Institute's intramural laboratories and branches and in the Clinical Center research complex.
3. **Institute Clinical Directors** report to the Institute Directors or Scientific Directors and are responsible specifically for oversight and conduct of the clinical research programs carried out in the Institute's intramural clinical branches.

#### **D. THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)**

The NIH's HRPP is made up of NIH ICs, NIH officials, NIH IRBs, and researchers and staff who conduct and support research involving human subjects.

The HRPP is divided into three arms; Governance and Advisory Entities, Regulatory/Compliance Arm and Protocol Development/Operations Arm\*\*

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\*\* see: ATTACHMENT: HRPP ORGANIZATIONAL CHART, page 13

## 1. Governance and Advisory Entities

The governance arm oversees the NIH HRPP and consists of the Deputy Director for Intramural Research (DDIR) and the Deputy Director for Intramural Clinical Research (DDICR) who have overall responsibility for the NIH HRPP. Advising them are Scientific Directors, IC Directors, the Director of the Clinical Center, as well as advisory committees including: the Medical Executive Committee (MEC); the Human Subjects Research Advisory Committee (HSRAC); the IRB Professional Administrators Committee (IPAC); and the Intramural Clinical Research Steering Committee (ICRSC).

**DDIR** is the **NIH Institutional Official** responsible overall for the NIH HRPP. The DDIR, through written delegated authority from the Director, NIH, is the signatory official for the FWA, filed with the DHHS, OHRP, and is responsible for oversight of human subjects research at NIH. See section G, below, for authority and responsibility for the development, maintenance and revision of policies for the NIH HRPP.

**DDICR** oversees the IRP clinical research program and chairs the ICRSC.

The following committees serve in an advisory capacity to the Governance Arm of the HRPP:

**MEC** is advisory to the Director, Clinical Center, and is comprised of all the Clinical Directors and senior members of some Clinical Center medical Departments, services and branches (e.g., Critical Care Medicine, Pediatrics, Surgery). The MEC provides advice and guidance to the Director, Clinical Center and the NIH community about issues that relate directly to clinical care and research support within the IRP. It is chaired by a Clinical Director elected by the membership. It oversees the provision of safe care and protection to research participants. The MEC approves the Medical Administrative Series policies (MAS), which govern clinical care in the Clinical Center, NIH's research hospital.

**HSRAC** is Chaired by the DDIR, it advises the DDIR about the conduct of human subjects research in the NIH IRP. It is a forum for the dissemination of new information, policies and procedures, including those

of the OHRP and the FDA. Membership consists of the IRB Chairs, the Director, Clinical Care, the Chief of the Clinical Care Department of Clinical Bioethics, the Director, OHSRP (Executive Secretary), a representative of the NIH Fellows Committee, a member of the NIH Radiation Safety Committee, and a representative of the IPAC. IRB administrative staff and other interested HRPP staff attend as guests.

### **IPAC**

This Committee, composed of IRB administrative staff members, is dedicated to ensuring compliance with regulatory standards governing human subjects research by developing and promoting effective and consistent procedures and practices across the NIH Intramural Research Program.

### **ICRSC**

The NIH ICRSC was established as a forum for trans-NIH governance and policy development in the area of human subjects research. The DDICR serves as the Chair of the ICRSC and is appointed by the NIH DDIR. The ICRSC is advisory to the NIH DDIR and is specifically charged with providing guidance in the following areas:

- a. Standards and strategies for the development, review, and implementation of human subjects protocols, including IRB operations, support, and accountability, and ethical interactions with the pharmaceutical industry (including technology transfer).
- b. Standards and strategies for the development, review, and implementation of human subjects research more broadly, including the scientific review of protocols, and Boards of Scientific Counselors' review of clinical programs.

The Clinical Center Director and the Institute Scientific Directors and Clinical Directors also serve the Governance and Advisory Entities Arm of the HRPP in an advisory capacity.

## **2. The Regulatory/Compliance Arm**

The regulatory/compliance arm is the Office of Human Subjects Research Protections (OHSRP) which carries out the day-to-day operations of the HRPP. The IRB Chairs are accountable to and have a reporting responsibility to the OHSRP.

### **The NIH OHSRP**

The OHSRP reports directly to the DDIR. It helps IRP investigators, research staff, IRBs and others understand and comply with the ethical guidelines, regulatory requirements, and NIH policies and procedures for research involving human subjects. Specifically, OHSRP:

- a.** Assists various NIH intramural components in administering and managing human subjects research activities so as to promote the rights and welfare of human subjects and the NIH's research mandate.
- b.** Provides advice on the federal regulations for the protection of human subjects for the IRP and works with various NIH groups to formulate and develop NIH policies and procedures consistent with these regulations.
- c.** Plans, organizes and conducts educational activities for NIH intramural personnel about human subject protections, including a mandatory computer-based training program for research staff and a computer-based training program specifically for IRB members.
- d.** OHSRP professional staff members attend NIH IRB meetings on a regular basis as observers and consultants on human subject protection issues.
- e.** Assists investigators in identifying and resolving ethical and regulatory issues associated with the design and conduct of their protocols, including studies conducted at non-NIH sites in the U.S. and overseas.
- f.** Is the sole authority in the IRP for determining which research activities are exempt from the 45 CFR 46 regulations and maintains a database of such exemptions.
- g.** Assists IRP investigators in negotiating reliance (authorization) agreements with other institutions and maintains a database for such reliances. The OHSRP Director has signatory authorization from the DDIR for approval of authorization agreements (reliances) for single protocols.
- h.** Maintains current lists of all NIH IRB members and provides updates to the DHHS OHRP.
- i.** Keeps an updated copy of the NIH FWA.

- j. Notifies OHRP of unanticipated problems and serious unexpected adverse events that may occur on intramural protocols.
- k. Maintains a web site containing computerized training programs, forms, information sheets, etc.\*
- l. Initiates and/or assists in the conduct of inquiries and/or investigations concerning the conduct of human subjects research in the IRP.
- m. Acts as liaison with the OHRP on matters pertaining to the NIH HRPP.
- n. Develops and maintains SOPs for the HRPP.

**The Director, OHSRP** reports to the DDIR. The OHSRP Director is the designated Human Protections Administrator (HPA) for the NIH FWA. Through written delegated authority from the DDIR, the OHSRP Director coordinates and oversees the NIH HRPP on a day-to-day basis. This includes oversight of the NIH IRB system and IRB Chairs.

**IRBs:** NIH IRBs review and approve research involving human subjects conducted in the IRP (unless the research is exempt from IRB review, pursuant to 45 CFR 46.101 (b)) in accord with the regulatory mandates to protect subjects' rights and safeguard their welfare. NIH IRBs also sometimes review research activities of NIH staff who are involved in extramural research activities. The NIH IRP maintains 12 IRBs, in part because the NIH Institutes and Centers are administratively separate organizations with discrete missions and research portfolios. However, all IRB Chairs report to the OHSRP Director and follow the requirements of NIH's FWA, the HRPP Policies, the NIH SOPs for IRBs\*, and the Clinical Center Medical Administrative Series Policies\* (MAS Policies). The 12 NIH Institutional Review Boards are:

- a. NCI IRB
- b. National Cancer Institute Special Studies (NCISS IRB)
- c. NHLBI IRB
- d. NIAID IRB
- e. NIDDK IRB
- f. NIAMS IRB
- g. NICHD IRB
- h. NIEHS IRB

- i. NHGRI IRB
- j. Addictions (NIDA, NIAAA IRB)
- k. Combined Neurosciences Blue Panel (NINDS, NIDCD, NEI IRB)
- l. Combined Neurosciences White Panel (NIMH IRB)
- m. Combined Neurosciences Purple Panel (NIDCR IRB)

The Clinical Center, The National Institute on Aging (NIA), NINR, NIBIB, and NCCAM may rely on any NIH IRB listed above, depending on the nature of the protocol and the expertise needed for its review.

Each IRB has a Chair and Administrative Support Staff.

### **3. The Protocol Development/Operations Arm**

Each IC Clinical Director conducting human subjects research in the IRP is responsible for:

- a. The development of a central clinical investigations database that maintains data specified to be collected in the clinical study (either intervention or natural history).
- b. The establishment of a quality assurance program with infrastructure that ensures that clinical trials are monitored adequately and centrally.
- c. Providing protocol development services for investigators, including a Protocol Services Center (PSC), PSC Managers; Protocol Navigators; administrative support; and biostatistics support. Providing these services may be done in cooperation with another Institute through a memorandum of understanding.
- d. The review of protocols involving human subjects to assess scientific quality, the importance of clinical practice and the appropriateness of the study to the IC.
- e. The provision of necessary personnel, office space proximal to patient care areas, and accompanying resources to support the clinical research infrastructure, including the IRBs; and;
- f. Education and training of clinical investigators on their roles and responsibilities, including Good Clinical Practice.

## E. THE CLINICAL CENTER

The Clinical Center, consisting of the Warren Grant Magnuson Clinical Center and the Mark O. Hatfield Clinical Research Center, provides inpatient and outpatient hospital facilities for the IRP's biomedical and behavioral research. The hospital's proximity to the IRP's research laboratories facilitates the rapid translation of research from the bench to the bedside. Each IC with a clinical research program participates in the usage and cost of the Clinical Center and provides its own infrastructure (laboratories, physical plant, space and personnel, e.g., physicians, nurses, support staff) to sustain its clinical research program.

Some Clinical Center programs and departments that contribute to the HRPP include, but are not limited to:

1. **The Office of the Deputy Director for Clinical Care** is responsible for clinical quality and clinical performance improvement.
2. **The Office of Protocol Services (OPS)** maintains a protocol data repository for the IRP and provides consultation services to investigators, IRBs, and Institutes and Centers. OPS works closely with the 12 IRB Offices to conduct a quality review of the IRB approved protocol application; maintain the repository of consent documents on the NIH Clinical Center Website for protocols conducted at the NIH Clinical Center; and facilitate the flow of data to update systems such as Clinicaltrials.gov and internal Clinical Center systems. OPS monitors protocols for compliance in conjunction with the IRB Offices and inactivates protocols in the hospital system when a lapse in continuing review occurs. In addition, OPS reports data to the Office of Research on Women's Health on behalf of the IRP, generates inclusion enrollment data for investigators from the Clinical Research Information Service (CRIS), and generates *ad hoc* reports from the repository as requested.
3. **The Medical Record Department** maintains medical records of all subjects registered as patients at the NIH Clinical Center.
4. **The Pharmacy Department** provides pharmaceutical services and research support to research participants and investigators, including: provision of drug information; development, formulation, distribution and dispensing of drugs; investigational drug information development and control; and assisting investigators with meeting FDA regulatory requirements for filing Investigational New Drug applications. Pharmacy staff members actively conduct and participate in pharmacokinetic studies and various research

- programs about optimal dosing and appropriate use of investigational and commercially available agents. The Medical Administrative Series policies include guidance for clinical research investigators about the safe management of investigational drugs and other medications used in clinical research in Clinical Care.\*
5. **The Clinical Bioethics Department** conducts research in bioethics and organizes Ethics Grand Rounds. It also provides consultants to help research subjects, their families, investigators and other Clinical Care staff in the resolution of clinical ethical issues. The Clinical Bioethics Department provides advice, upon request, to investigators in the development of protocols and informed consent documents.
  6. **The Patient Representative** serves as a link between the patient and the hospital. The Patient Representative makes every effort to assure that patients are informed of their rights and responsibilities and that they understand what the Clinical Center is, what it can offer, and how it operates.
  7. **The Nursing and Patient Care Services Department** provides nursing services in support of research protocols for all Institutes. Each Institute also employs its own specialized research nurses who participate in and coordinate research protocols.
  8. **The Patient Recruitment and Public Liaison Office** provides information to the public about participation in research being conducted at the Clinical Center.
  9. **The Clinical Research Volunteer Program** provides information to interested persons on protocols that enroll healthy volunteers. It also ensures that such volunteers are properly registered and, when appropriate, compensated.
  10. **The Patient Advisory Group**, consisting of patient representatives from the ICs using the Clinical Care, advises the Director, Clinical Care, on patient issues related to care and clinical research.
  11. See the Clinical Care Department's website for additional information.\*

## F. OTHER NIH COMMITTEES

1. **The Trans-NIH Bioethics Advisory Committee (TNBC)** coordinates policy development among the Institutes and the Office of the Director (OD), NIH, in the areas of ethical, legal and social implications of NIH-funded research,

including the research of the IRP. The Committee meets monthly, or as needed, and is chaired by the Associate Director for Science Policy, OD. It is composed of senior staff members designated by the IC Directors. Relevant OD offices, including the OHSRP, are also represented.

2. In addition to IRBs, there are several specialized NIH committees involved in ensuring the safety of IRP research subjects and NIH staff during the conduct of research protocols:
  - a. The Radiation Safety Committee (RSC)
  - b. The Radioactive Drug Research Committee (RDRC)
  - c. The Recombinant DNA Advisory Committee (RAC), Office of Biological Activities (OBA)
  - d. The Institutional Biosafety Committee (IBC), Office of Research Services (ORS).

## **G. AUTHORITY AND RESPONSIBILITY FOR THE DEVELOPMENT, MAINTENANCE AND REVISION OF POLICIES FOR THE NIH HRPP**

**Delegations of Authority:** Authority for day-to-day oversight of the NIH HRRP has been delegated by the NIH DDIR and through the DDIR to the NIH OHSRP.

**Background:** The DDIR is the signatory official for all policies that apply to the NIH HRPP.

**Policy Approval** for all policies that apply to NIH HRPP research. The signatory official for the NIH FWA, the DDIR, approves, prior to implementation, all NIH policies that apply to human subjects research conducted by NIH intramural and extramural scientists (termed “HRPP policies” below).

**Policy Development:** Proposals for new policies can be submitted by individuals, committees, or others within the IRP. The OHSRP and the HSRAC review the proposals and advise the DDIR on whether the policy should be developed, presented for review, and approved. NIH staff members or committees who plan to propose or revise an HRPP policy consult OHSRP as early as possible to determine if the proposed policy is consistent with the NIH HRPP, or if a similar policy currently exists. If OHSRP determines that the proposed policy is consistent with the NIH HRPP and addresses a need of the

HRPP program, OHSRP brings the proposal forward to NIH senior officials, including the DDIR. If they concur, the DDIR and OHSRP develop a plan for review and approval by all applicable NIH committees, to be followed by review and final approval by the DDIR.

**Publication of Policies:** The OHSRP posts all human subjects policies and SOPs on its website.\*

**Maintenance and Revision of HRPP Policies:** All HRPP policies are reviewed every three years by OHSRP. OHSRP recommends any proposed substantive changes to the DDIR. The DDIR may approve the proposed changes or route them for review by applicable NIH committees prior to approval. OHSRP may handle minor changes, such as changes to administrative procedures, checklists, or formatting, internally. OHSRP is responsible for notifying the ICs, the MEC, HSRAC and other affected groups of any approved changes.

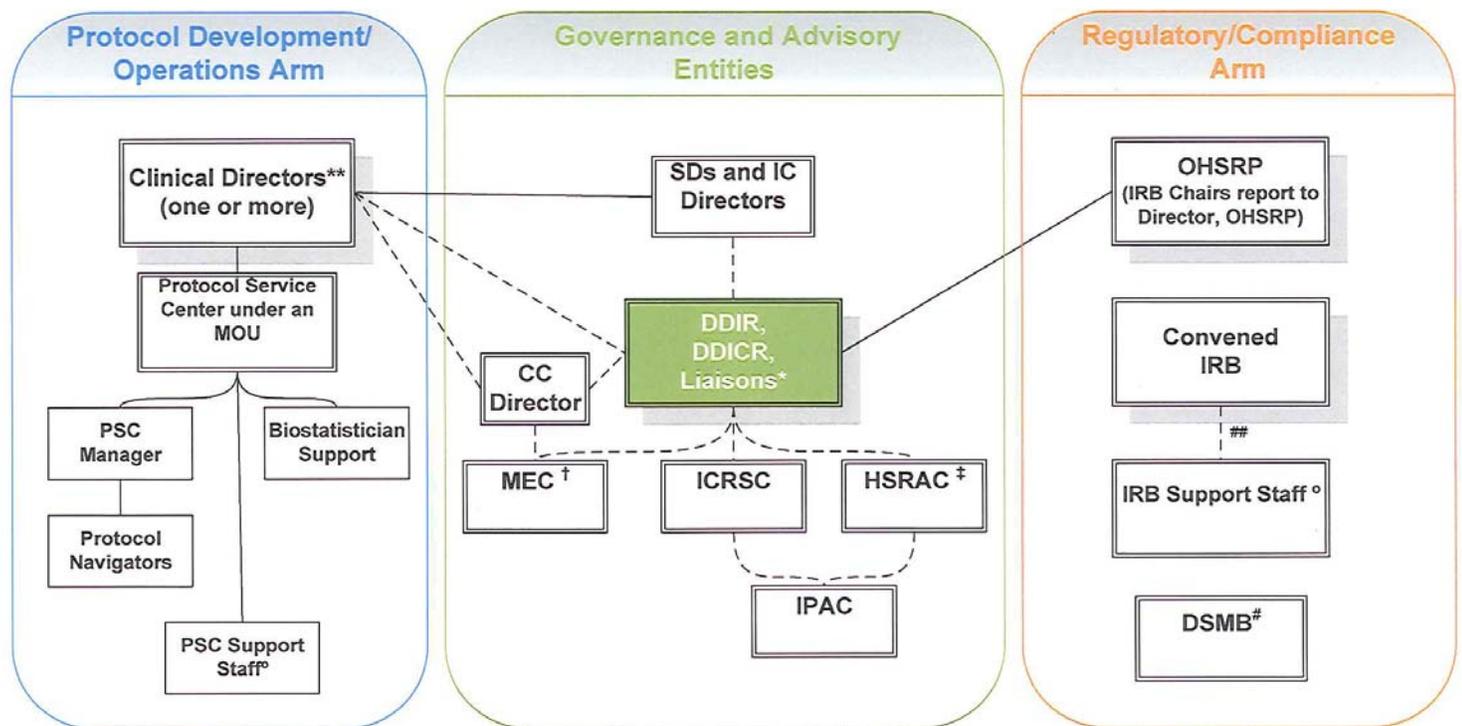
**Documentation of Policy Approval:** Each NIH-wide HRPP policy, when officially approved, contains the date of approval and the signature of the DDIR.

**REFERENCES**

1. The Standards for Clinical Research Within the NIH Intramural Research Program: <http://www.cc.nih.gov/ccc/clinicalresearch/index.html>
2. Guidelines for the Conduct of Research in the Intramural Research Program at NIH: <http://sourcebook.od.nih.gov/ethic-conduct/Conduct%20Research%206-11-07.pdf>
3. Guide to Training and Mentoring in the Intramural Research Program at NIH: <http://sourcebook.od.nih.gov/ethic-conduct/mentor-guide.htm>
4. NIH OHSRP: <http://ohsr.od.nih.gov/>
5. NIH SOPs for IRBs: <http://ohsr.od.nih.gov>
6. Clinical Center Medical Administrative Series Policies: <http://intranet.cc.nih.gov/mec/mas/>
7. Clinical research in the CC: <http://intranet.cc.nih.gov/mec/mas/>
8. Clinical Care Department's website: <http://intranet.cc.nih.gov>
9. The OHSRP SOP website: <http://ohsr.od.nih.gov/>

**ATTACHMENT: HRPP ORGANIZATIONAL CHART**

## Human Research Protection Program In the NIH Intramural Research Program



<sup>o</sup> Denotes possibility of shared responsibility at the discretion of the IC

\* Liaisons bridge the two arms and communicate with all individuals/components

\*\*Scientific Review is the responsibility of the ICs

<sup>†</sup> Comprised of Clinical Directors

<sup>‡</sup> Comprised of IRB Chairs

<sup>#</sup> Denotes independent outside review bodies responsible to IC Leadership and IRBs for reporting findings

<sup>##</sup> Denotes support but not supervisory relationship

3/10/2011

Figure 1: This chart shows the organization of the Human Research Protection Program as it relates to the NIH Intramural Research Program