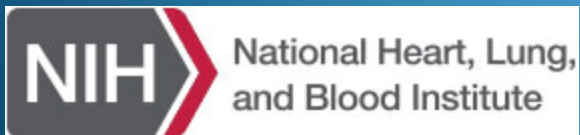


Purpose and Function of IRBs

Successes and Current Challenges

Richard Cannon, MD
Chair, NHLBI IRB



Why do we need IRBs?

- **Born from scandal....**

- **Nazi doctor's trial 1946- Nuremberg Code**

- 1) Voluntary consent
- 2) Experiment for the good of society
- 3) Experiment based on animal experimentation and natural history of the disease.
- 4) Avoid all unnecessary physical and mental suffering and injury.
- 5) No experiment if reason to believe that death or disabling injury will occur
- 6) The degree of risk should never exceed humanitarian importance of experiment
- 7) Protect the experimental subject against injury, disability, or death
- 8) The experiment should be conducted by scientifically qualified persons
- 9) Human subject should be at liberty to bring the experiment to an end
- 10) Scientist in charge should terminate the experiment at any stage, continuation of the experiment is likely to result in injury, disability, or death

Declaration of Helsinki

2nd revision 1975

Research Ethics Committees

The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Evolution of IRBs in the US

- **Mid-1950's- research on healthy volunteers at Clinical Center required approval by research review committee**
- **1966- PHS Policy on Protection of Human Subjects for research supported by HEW- required independent review of clinical research protocols to assure rights and welfare of research subjects**
- **1973- Congressional hearings on ethical problems in human subjects research following disclosure of the federally-funded Tuskegee syphilis study**
- **1974- National Research Act- required IRB approval of most human subjects research and established National Commission for the Protection of Biomedical and Behavioral Research-- Belmont Report 1979**

1981- HHS approval of Title 45, Part 46 of the Code of Federal Regulations

- **Defined role of IRB: “Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB.” 45 CFR 46.103 (Subpart A)**
- **1991- 45 CFR 46 subpart A (IRBs, consent) extended to 15 federal departments and agencies- the Common Rule**

FDA requirements for IRB Review

“Unless exemption or waiver is approved, any clinical investigation which must meet the requirements for prior submission to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved, and remains subject to continuing review, by an IRB meeting the requirements of this part.”

21 CFR 56.103

Organization of IRBs

45 CFR 46.107

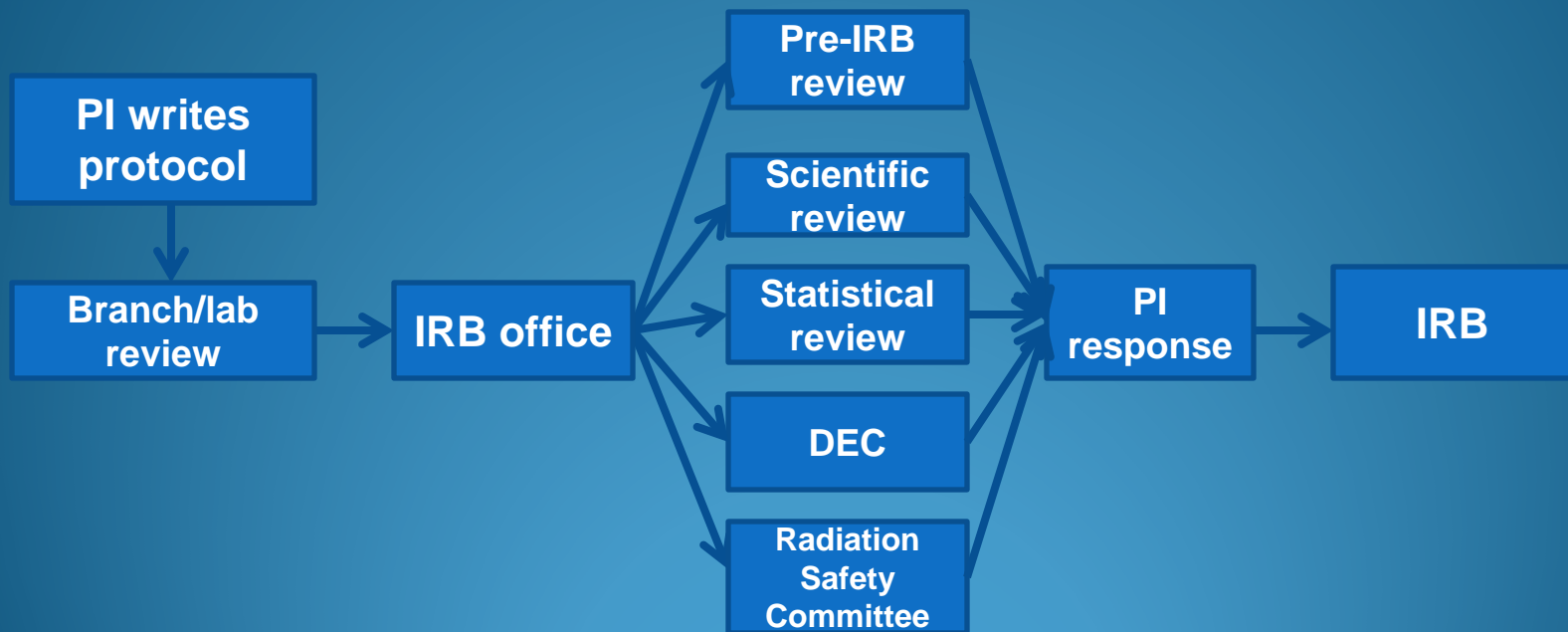
21 CFR 56.107

- **Must have at least 5 members with varying backgrounds to promote thorough review of protocols**
 - At least 1 scientist
 - At least 1 non-scientist
 - At least 1 not affiliated with institution
 - May need member expert in vulnerable populations
- **May not be all men or women, or members from 1 profession**
- **Meetings are regularly scheduled; quorum of members must be present**
- **Conflicts of interest must be identified at beginning of meeting**
- **May invite non-voting ad hoc individuals for subject matter expertise or vulnerable populations**

IRBs in the Intramural Research Program

- 12 IRBs operate under the Federal Wide Assurance, with Dr. Gottesman, DDIR as signatory for IRP
- NIH IRBs have chair, vice-chair and representatives from nursing, pharmacy, biostatistics, bioethics; at least 1 member not affiliated with Institute hosting the IRB
- IRBs typically review research from its Institute's members, but may review protocols from Clinical Center and from other Institutes for subject matter expertise or COI

IRB submission and review process



Criteria for IRB Review and Approval

45 CFR 46.111

21 CFR 56.111

- Research design scientifically sound and will not unnecessarily expose subjects to risks
- Risks are reasonable in relation to anticipated benefits, if any, to subjects and importance of generalizable knowledge
- Selection of subjects is equitable
- Safeguards to protect vulnerable subjects
- Informed consent will be obtained from subject or LAR
- Adequate monitoring of data to ensure safety and minimize risks
- Privacy of subjects and confidentiality of data

Risk/benefit assessment for adults

- **Risk categories**

- Not greater than minimal risk
- Greater than minimal risk

- **Benefit categories**

- Prospect of direct benefit to individual subjects
- No prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition
- No prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the disorder or condition under study

Risk/benefit assessment for children

45 CFR 46.404,405,406

21 CFR 50.51,52,53

- **Not greater than minimal risk**
- **Greater than minimal risk but prospect of direct benefit to individual subjects**
- **Greater than minimal risk with no prospect of direct benefit but likely to yield generalizable knowledge about subject's disorder or condition**
 - **Minor increase over minimal risk**
 - **Intervention commensurate with medical treatment**
 - **Importance of generalizable knowledge**
 - **Assent of child, consent of both parents**

Additional responsibilities for FDA-regulated research

- Accountability, storage and use of investigational products (including education of research subject)
- Reporting requirements (adverse events, amendments, continuing review, annual report to FDA)
- Record keeping (regulatory binder, CRF), protection and retention of data (2 years after marketing approval or 2 years after final shipment of drug product if application not approved [or N/A] and FDA notified)
- Sample storage
- CRADA/MTA with sponsor, collaborators
- Monitoring (QA/QC, medical monitor, DSMB)
- FDA inspections and audit— *including IRBs!*
- Final report to FDA and IRB

Requirements for informed consent

45 CFR 46.116

21 CFR 50.25

- **Research nature and purpose of study; duration of participation; required procedures**
- **Risks and discomforts**
- **Benefits to subject or others**
- **Options to participation that may provide benefit**
- **Protection of privacy and confidentiality**
- **Compensation or treatment of research-related injury**
- **Who to contact for answers to questions or address concerns**
- **Participation is voluntary; subject may discontinue participation at any time**

Subject withdrawal from an FDA-regulated study

- If subject withdraws (or is withdrawn) from an FDE-regulated study, **data collected to the time of withdrawal remains part of the study database and may not be removed** (state in consent)
- Subject may be asked to provide follow-up data collection (state in consent or will be required to provide additional consent)

Continuing Review

45 CFR 46.109

21 CFR 56.109

- **Must be conducted at least annually**
- **Summary of progress to date**
- **Reason to continue study, including literature review**
- **Summary of adverse events and relation to research**
- **Accrual table with sex/ethnic breakdown**
- **New risks or benefits?**

IRBs also review:

- **Amendments**
- **Problem reports (may result in suspension of enrollment until CAPA plan, amendment or termination of protocol)**
 - **Unanticipated problems**
 - Unexpected
 - Related or possibly related to participation in research
 - Places subjects or others at greater risk of harm
 - **Protocol deviations**
 - Change, divergence or departure from IRB-approved protocol
 - **Non-compliance**
 - Failure to comply with NIH, IRB or regulatory requirements for protection of human research
- **Advertisements**
- **Termination of protocol**

What happens at meetings?

- Agenda set at planning meeting and materials sent to IRB members 1 week before meeting
- Must have quorum for meeting that includes 1 non-NIH member
- May have primary reviewer system, but all members expected to read all materials
- All members have 1 vote in executive session
- PI expected to attend meeting for initial reviews, may be invited to attend amendments, problem reports
- Review standards must be addressed and documented in minutes



Allowable IRB Actions

45 CFR 46.109

21 CFR 56.109

- IRBs have authority to approve, require modifications (through stipulations) or disapprove research
 - IRB decision may not be overruled by NIH official or another IRB
- May suspend or terminate research if not conducted in accordance with IRB's requirements or if associated with unexpected serious harms to subjects
- May require third party to observe consent

Expedited Review

45 CFR 46.110

21 CFR 56.110

- Research activities may be eligible for expedited review by the IRB chair or designee from IRB if considered no more than minimal risk and included in the following categories:
 - Administrative changes
 - Retrospective data analysis
 - CR of protocols closed to enrollment
 - Minor changes to protocols (does not affect risk/benefit profile of study or scientific validity of design)
 - Certain categories of minimal risk research

Special situations for use of investigational drugs: Emphasis on treatment, not research

- **Expanded access to investigational drug:** 1) subject has serious or life-threatening disease or condition, and 2) no comparable or satisfactory alternative therapy. Requires IRB approval of protocol and consent, and FDA approval

21 CFR 312.300-320

- **Emergency use of test article:** life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. Requires FDA notification, clinical director and IRB chair approval, and submission of notification form to IRB within 5 days 21 CFR 56.104, 312.305-310

Have IRBs been a success? Yes!

- IRB serves as research subject advocate with emphasis on risk-benefit analysis and protections for rights and welfare
- Vulnerable subjects protections
- Better science of protocols because of multiple reviews
- Better monitoring and data management
- Understandable consent documents
- Community perspective to human subjects research
- PIs held accountable for actions

Room for improvement....

- Harm to research subjects
- Researcher--and institutional--conflicts of interest
- Lost records or specimens
- Data, specimens sent to outside parties without subjects' permission or institutional approval
- Poor oversight of clinical trials
- Ethical concerns regarding foreign site research
- Fraudulent IRB

Back to: [Clinical Center Home Page](#) >



Standards For Clinical Research Within The NIH Intramural Research Program

- [Preface](#)
- [Introduction / Standards](#)

Drawing at left of Louis Pasteur, colleague, and patient, courtesy of the New York Academy of Medicine.

Preface

The Standards for Clinical Research set forth some essential principles and processes for the conduct of clinical research in the intramural research programs of the National Institutes of Health. To achieve patient safety, efficient protocol implementation, and effective quality assurance and improvement requires adequate training of clinical investigators and sufficient infrastructure to support their endeavors. Consequently, the Standards should assist both new and experienced investigators as they apply good clinical practice in their research to achieve high-quality results.

The Standards were developed in January 2000 by the Clinical Center Medical Executive Committee, on which all the NIH institutes are represented by their clinical directors. They were endorsed by the scientific directors of the intramural research programs and the institute directors. Based on feedback from intramural clinical research programs and evolving standards within the human subjects research community, the MEC has reviewed and updated the Standards.

Standards for Clinical Research

- **Clinical informatics, data management and protocol tracking**
- **Biostatistics support**
- **Quality assurance and quality control**
 - **Protocol monitoring**
 - **Independent DSMB for clinical trials, high risk studies**
- **Protocol review**
 - **Independent scientific review**
 - **Infrastructure to support IRB**
- **Human resources and physical plant**
 - **Case managers, protocol coordinators, protocol navigators, data managers**
- **Training and education**
 - **PIs and IRBs**



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The Value of Accreditation

AAHRPP accreditation indicates that your organization follows rigorous standards for ethics, quality, and protections for human research. When you earn the AAHRPP seal, you earn a place among the world's most respected, trustworthy research organizations. [Learn More>>](#)

[Get Started >](#)

Tip Sheets

- [Tip Sheet 26 Reviewing Research Involving Adult Participants with Diminished Functional Abilities](#)
- [Tip Sheet 27 Guidance on Equivalent Protections](#)

[View more >](#)

Advance Newsletter

Advance Summer 2014: Streamlined Process, CEO Update, and More

Advance, Spring Edition: New Accreditations Signal AAHRPP's Value, Influence

What's New

Upcoming Webinar: Reportable Events, Developing Policies and Procedures

AAHRPP Clarifies Standard on Conflict of Interest in Tip Sheet 10: Does Not Exceed Federal Regulation
[More Flexibility for](#)

FEATURED Accreditation Guidance

As your Organization begins to consider applying for accreditation, take a look at the documents listed below for an overview of the procedures involved and the standards Organizations meet:

[Evaluation Instrument for](#)

CASE STUDY

Using AAHRPP Accreditation to Guide Expansion

Schulman Associates Institutional Review Board (IRB) had built a reputation as one of the nation's leading independent IRBs. For decades, the Ohio-based company was known primarily as a reviewer of

Department of Health and Human Services | National Institutes of Health

OHSRP OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

Human Research Protection Program

SEARCH

Home



Human Research Protection Program

NIH Federalwide Assurance
FWA#: 00005897
Expires: 8/28/2018
Go to the OHRP [search page](#) for additional information

The Human Research Protection Program promotes the rights and welfare of human subjects who participate in research conducted by the Intramural Research Program (IRP) of the NIH

[About the HRPP](#)

Office of Human Subjects Research Protections

This office sets the policy and provides regulatory oversight for the HRPP

[Policies and NIH Standard Operating Procedures](#)

[HRPP FAQs](#)



NIH Intramural IRBs

Click the link below to contact each NIH Intramural Institutional Review Board (IRB) Office

[NIH IRB Offices](#)

Committees

[IRB Professional Administrators Committee \(IPAC\)](#)

[Human Subjects Research Advisory Committee \(HSRAC\)](#)

NIH IRB Members

[NIH IRB Member Tools](#)

[NIH IRB Member Training](#)



Investigator Resources

Information and resources for investigators and research staff conducting research in the NIH Intramural Research Program (IRP)

[Guidelines for Research Involving Humans](#)

[Forms, Templates and Tools](#)

NIH Resources

[NIH Resource Links](#)

Regulations and Ethical Guidance

Office of Human Research Protections (OHRP)

[45 CFR 46- The Common Rule](#)

[The Belmont Report](#)

[Search for Federalwide Assurances](#)

[Guidance](#)

LATEST NEWS:

3/18/14: The NIH HRPP has received AAHRPP Full Accreditation. Thank you for assisting us to make this possible.

HRPP Policies: see "Policies and NIH Standard Operating Procedures"

Contact OHSRP

Office of Human Subjects Research Protections (OHSRP)
Building 10, (The Warren G. Magnuson Clinical Center)
Room 2C146, Bethesda, MD 20892-1154

Phone: 301-402-3444
Fax: 301-402-3443

External Resources

[ClinicalTrials.gov](#)

[FDA](#)

[OHRP](#)

OHSRP OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

Human Research Protection Program

Home

Home > Policy and Procedures

Policy and Procedures

- List of NIH HRPP Policies and Procedures by Topic Public
- NIH HRPP SOP Listing by Topic (Internal links)
- test
- IC AAHRPP Contact List
- Introduction to the NIH Human Research Protection Program
- Revised! SOP 1- HSR and the NIH IRB System
- SOP 2 - IRB Membership and Structures
- SOP 2 Attachment - IRB Roster Template v1-19-2013
- SOP 2 Attachment - NIH IRB Protocol Review Standards
- SOP 3 - Management and Administrative Operations of the IRB
- Revised! SOP 4 - Human Research Protection Program (HRPP) Documentation and Records
- SOP 5 - NIH Research Activities with Human Data/Specimens
- SOP 6 - Determinations, Including Exemptions Made by the Office of Human Subjects Research Protections (OHSRP)
- SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)
- SOP 7A - Requirements for Expedited Review of Research by NIH Institutional Review Boards
- SOP 7B - Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting
- Revised! SOP 8 - Procedures and Required Documentation for Submission and Initial Review of Protocols
- SOP 9 - Continuing Review by the Convened IRB
- SOP 10 - Amendments to IRB-approved Research
- SOP 11- Suspensions and Terminations of IRB Approval and Administrative Holds
- SOP 11A - Closure of an IRB-approved protocol
- SOP 12-Requirements for Informed Consent
- SOP 13 - Recruitment, Selection and Compensation of Research Subjects
- SOP 14A - Research Involving Vulnerable Subjects (General Considerations)
- SOP 14B- Research Involving Pregnant Women, Human Fetuses and Neonates
- SOP 14C- Research Involving Prisoners
- SOP 14D- Research Involving Children
- SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent
- SOP 14F - Research Involving NIH Staff as Subjects
- Revised! SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications
- Revised! SOP 15A - Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)
- HRPP SOP 15A - NIH Fillable Emergency-use IND NIH Approval Form
- Revised! SOP 15B - Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications

SOP 26 Evaluation of IRB Staff

- Evaluation of IRB chairs, vice-chairs and members
- Evaluation of IRB administrative staff
- Evaluation of meetings
- Researchers' assessment of IRB performance
- IRB member training and educational opportunities

Current Challenge for IRBs

Should researchers be responsible for--and report--incidental findings from whole genome/exome sequencing?

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Green.....Biesecker *Genetics in Medicine*, 2013

- Experts selected by ACMG chose mutations in 56 genes associated 24 disorders
- More common of the monogenic disorders
- Preventative measures and/or treatments available
- Patients with pathogenic mutations might be asymptomatic for long periods of time
- Recommendation: “Laboratories performing clinical sequencing seek and report mutations of the specific classes or types in the genes listed here.”

Partial list of monogenic disorders with preventative measures or treatments available:

- Hereditary breast and ovarian cancer (BRCA)
- Familial adenomatous polyposis
- Familial medullary thyroid cancer
- Familial aneurysms/dissections (Marfan syndrome)
- Arrhythmogenic RVC
- Long QT syndromes
- Familial hypercholesterolemia
- Malignant hyperthermia
- Li-Fraumeni Syndrome
- Hypertrophic/dilated Cardiomyopathies
- Von Hippel Lindau Syndrome
- Peutz-Jeghers Syndrome
- Lynch Syndrome
- Retinoblastoma
- Multiple endocrine neoplasia
- Neurofibromatosis
- Ehlers Danlos Syndrome

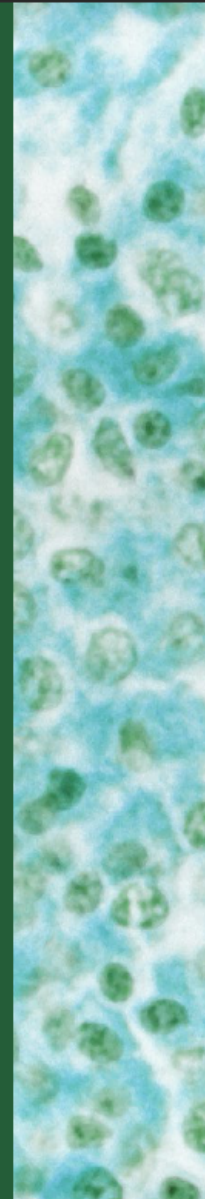


ANTICIPATE and COMMUNICATE

Ethical Management of
Incidental and Secondary Findings
in the Clinical, Research, and
Direct-to-Consumer Contexts

Presidential Commission
for the Study of Bioethical Issues

December 2013



Recommendation 14

- **Researchers should consider carefully the decision to actively look for secondary findings. In certain circumstances, with approval from an IRB, researchers can justifiably adopt a plan that includes looking for selected clinically significant and actionable secondary findings. Approved plans should be disclosed to prospective participants during the informed consent process.**

Incidental Findings Working Group

Les Biesecker, NHGRI, Chair

Howard Austin, NIDDK

David Bluemke, CC DRD

Richard Cannon, NHLBI

Ken Fischbeck, NINDS

Bill Gahl, NHGRI

David Goldman, NIAAA

Christine Grady, CC BEP

Mark Greene, NCI

Steve Holland, NIAID

Sara Hull, NHGRI

Forbes Porter, NICHD

David Resnick, NIEHS

Wendy Rubinstein, NLM/NCBR

Incidental Findings Working Group

Charge: Develop intramural-wide policy for management of incidental and secondary findings from whole exome and genome sequencing

Concerns raised at meetings....

- Who will screen sequencing data for actionable gene variants?
- Who will be responsible for maintaining list of actionable gene variants?
- What about costs of screening, bioinformatics, verification in CLIA lab and reporting to subjects in a responsible manner (genetic counselors)?
- What if samples are received from subjects who have never been to Clinical Center, have no relationship with research team?
- Will findings be of relevance to subjects with life-threatening diseases?
- Can a research subject “opt out” for reporting of secondary findings?
- Is there a time limit for screening samples for the latest medically important and actionable mutation, whether determined by ACMG or some other group?
- What is the role of the IRB?

Thanks to our IRB members!

NHLBI IRB.JPG - Windows Picture and Fax Viewer

