



# Research Involving Human Subjects

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# Outline

- HHS Regulations: 45 CFR part 46: Protection of Human Subjects  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
- Definitions
- NIH Policies: Human Subjects/Clinical Research
- Applying for NIH funding for research involving human subjects
- Resources

# HHS Regulations

- 45 CFR part 46 – Protection of Human Research Subjects
  - **Subpart A** --Federal Policy for the Protection of Human Subjects
  - **Subpart B** --Additional Protections for Pregnant Women, Human Fetuses and Neonates
  - **Subpart C** --Additional Protections for Prisoners
  - **Subpart D** --Additional Protections for Children in Research

NIH follows all four subparts, A-D.

# Definition of *Risk*

...the **probability** of

- harm

or

- discomfort

Extracted from:

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#46.102>

# Definition of *Research*

- ... a systematic investigation
  - research development
  - testing, and
  - evaluation
- designed to develop or contribute to generalizable knowledge

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102>

# Definition of *Human Subject*

- ... a living individual
- about whom an investigator... conducting research obtains
  - 1) Data through intervention or interaction with the individual,  
or
  - 2) Identifiable private information

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102>

# Case Study #1: Research with autopsy specimens

- An application describes the following proposed research activities:
  - An investigator receives autopsy specimens from a pathologist.
  - The investigator will receive and record identifiable private information about the individuals from medical records.

## **Case #1:** Is the investigator conducting human subjects research?

- **No:** Research involving only specimens and data from deceased individuals is not human subjects research
  - Investigator is neither interacting nor intervening with living individuals for research;
    - Definition of “human subject” is not met

# Definition of *Investigator*

- Includes anyone involved in conducting research involving human subjects

Individuals who:

- Provide coded human data or specimens and collaborate on other activities related to conducting the research **are** involved in HS research
- Solely provide previously-collected coded human data or specimens **are not** involved in HS research

## Case #2: Collaborators

- An application describes the following proposed research activities:
  - An investigator receives coded data from a collaborator's ongoing clinical trial;
  - The investigator will perform analyses on the coded data;
  - The investigator and collaborator will co-author a publication

## Case #2: Is the investigator conducting human subjects research?

- **Yes:** Because the collaborator is conducting human subjects research, the investigator is also conducting research
  - Collaborator meets the definition of an “Investigator” for the proposed study;
  - Providing coded human data or specimens and collaborating on other activities related to conducting the research is human subjects research

# NIH Requirements

- NIH Policies
  - **Human Research Protections**
    - Data and Safety Monitoring
    - Human Subjects Education
  - **Clinical Research**
    - Inclusion of Women and Minorities
    - Inclusion of Children
    - Valid Analyses for NIH-defined Phase III Clinical Trials

# HHS Regulations: NIH v. IRB Responsibilities

- NIH Responsibilities

- Evaluation of proposed research involving human subjects for protections
  - Delegated to peer review process
- “On the basis of this evaluation [NIH] may approve or disapprove the application ... or enter into negotiations to develop an approvable one.”
- “Federal funds... may not be expended for research involving human subjects unless the requirements... have been satisfied.”

(46.120 & 122)

# HHS Regulations: NIH v. IRB Responsibilities

- IRB Responsibilities
  - Initial and continuing review of research involving human subjects
  - To “approve, require modifications in..., or disapprove research” (46.108)
    - Ensure rights & welfare of human subjects
    - Protection of institution

# Instructions for Preparing the Human Subjects Section

- Use SF 424 or PHS 398 Forms as appropriate.
- All proposed research will fall into one of six scenarios:
  - A:** No Human Subjects
  - B:** Human Subjects Research, Exemption 4
  - C:** Human Subjects Research, Exemptions 1,2,3,5,6
  - D:** Clinical Research
  - E:** Clinical Trial(s)
  - F:** NIH-defined Phase III Clinical Trial(s)

# Scenario A: No Human Subjects

- HUMAN SUBJECTS?
  - **NO**
- Human Subjects Section

## **PHS 398 Section E.**

“No Human Subjects research is proposed”

## **SF 424 Human Subjects**

No Human Subjects section is required

# Scenario B or C: Exempt Human Subjects Research

- HUMAN SUBJECTS RESEARCH?
  - YES
- Research Exempt
  - YES, Exemption No. \_\_\_\_\_
- Human Subjects Section
  - Exemption Category(ies)
  - Justification for exempt status
  - Population sample
    - Number
    - Age range
    - Health status
  - Sources of research materials or data
- For Scenario C: Exemptions 1, 2, 3, 5, 6
  - Address NIH Inclusion Policies

# Categories of exempt human subjects research

1. Research in educational settings on educational practices;
2. Tests, Surveys, Interviews...;
3. Tests, Surveys, Interviews with public officials, or if laws require confidentiality;
4. Collection/Study of existing data, specimens... publicly available or unidentifiable;
5. Research approved/conducted by Federal Agencies;
6. Evaluation of taste or food quality

# Determination of Exempt Human Subjects Research

- Investigators should not determine that their research involving human subjects is exempt
  - OHRP guidance: Exemptions should be **independently determined**  
<http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf>
- Institutions often designate IRB to make determination
- NIH Policy requires certification of IRB approval prior to award

<http://grants.nih.gov/grants/policy/policy.htm>

# Definition of *Clinical Research*

- Patient-oriented research
- Epidemiologic and behavioral studies
- Outcomes research and health services research
  - Exemption 4 research is not clinical research

# Scenario D: Clinical Research

- HUMAN SUBJECTS RESEARCH?
  - YES
- Research Exempt?
  - YES or NO
  - Inclusion information not required for Exemption 4 (Scenario B)

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## Human Subjects Section

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>● Risks</li><li>● Adequacy of protections against risks</li><li>● Potential benefits</li><li>● Importance of knowledge to be gained</li></ul> | <ul style="list-style-type: none"><li>● Identification of Exemption</li><li>● Justification for Exempt Status</li></ul> |
|---|---|

# Scientific Review of Human Research Protections

- “Acceptable” or “Unacceptable”
  - Human Subjects Concern:
    - Actual or potential unacceptable risks, or inadequate protections OR
    - Insufficient information
  - Summary Statement:
    - **PROTECTION OF HUMAN SUBJECTS (Resume): UNACCEPTABLE**

# Common Concerns (FY2005)

- Inadequate Human Subjects section (30%)
- Risks (24%)
- Issues related to Informed Consent (15%)
- Issues related to Confidentiality (10%)
- Missing/inadequate Data and Safety Monitoring (8%)
- Inequitable recruitment (7%)
- Other (5%)

# Scenario D: Clinical Research, Proposed Enrollment & Outreach

- Inclusion of Women/Minorities
  - W/M must be included in clinical research unless exclusion justified for health of subject or purpose of the research
- Subject Selection Criteria & Rationale
- Rationale for Any Exclusions
- Plans for Outreach and Recruitment
- Proposed Composition of Study Population Using Targeted/Planned Enrollment Tables

# Inclusion of Children

NIH policy requires that children must be included in Clinical Research unless there are clear and compelling reasons not to include them

➤ “Children” are defined as individuals <21 years

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

# Point of clarification: Protections for Children against risks

**Subpart D of HHS regulations** defines “Children”

- Less than legal age of consent for treatment/procedures involved in the research;
- According to local law where research will be conducted
  - “Children” must provide “Assent”
  - Parents must provide “Permission”

# NIH uses TWO definitions for *Children*

- Children: protections from risks in research are defined as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” ([46.402](#))
- Children for the purposes of the requirement to address inclusion are defined as individuals under the age of 21.

([NIH Policy and Guidelines on the Inclusion of Children as participants in Research Involving Human Subjects](#))

➤ Try not to get confused!

# Scientific Review of Inclusion Plans

- **Inclusion** -
  - If proposed inclusion is appropriate for scientific objectives
  - Rationale for selection of subjects and composition of study population
- **Exclusion** -
  - Justification for exclusion when representation is limited or absent
    - Based on risks to health of participants &/or inclusion inappropriate with respect to the research topic
- **Assessment:** “Acceptable” or “Unacceptable”

# Scenario E: Clinical Trial & Definition

**Prospective biomedical or behavioral research study designed to answer questions about biomedical or behavioral interventions**

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Applicants should:

- Provide information required for Scenario D: Clinical Research

PLUS:

- Data and Safety Monitoring Plan
  - General Description in Grant Applications
    - Monitoring Entity
    - Process for Adverse Event Reporting

# Scenario F: NIH-Defined Phase III Clinical Trial

Definition:

A broadly-based, prospective Phase III clinical investigation

- Purpose
  - Evaluate an experimental intervention in comparison with standard or control intervention or to compare existing treatments
  - For disease prevention, prophylaxis, diagnosis, or therapy
- Often provides evidence for change in health policy or standard of care.

# Requirements for NIH-defined Phase III Clinical Trials

- All information required for Scenario E: Clinical Trial

PLUS:

- Research plan must include consideration of one of the following:
  1. Prior Studies support significant differences between subgroups; OR
  2. Prior studies support no significant differences between subgroups; OR
  3. Prior studies neither support nor negate significant differences in intervention effect between subgroups

# Requirements for NIH-Defined Phase III Clinical Trials (con't)

1. If prior studies support significant differences between subgroups:
  - Need plans to conduct valid analyses to detect significant differences between sex/gender and/or racial/ethnic subgroups
  - For the purpose of this policy, **Significant Difference** is a difference that is of clinical or public health importance based on substantial scientific data. This is not the same as “statistically significant difference.”
  - For the purpose of this policy, **Valid Analysis** means an unbiased assessment that does not require high statistical power and should be conducted for both large and small studies.

# Requirements for NIH-Defined Phase III Clinical Trials (con't)

OR:

2. If prior studies support no significant differences between subgroups:
  - Representation as subject selection criterion is not required; however, inclusion and analyses are encouraged

OR:

3. If prior studies neither support nor negate significant differences in intervention effect between subgroups:
  - Need plans to conduct **valid analyses** of the intervention effect in sex/gender and/or racial/ethnic subgroups

# Before Award

## **Human Research Protections Issues:**

- OHRP Federal-Wide Assurance (FWA) Number for grantee institution
- Certification of IRB review and approval from IRB registered under grantee's FWA number
- Acceptable/Resolved Human Subjects Protections
- Certification of Human Subjects Education for Key Personnel

## **Inclusion Issues:**

- Acceptable/Resolved Inclusion of Women/Minorities/Children
- Plans for Valid Analyses for NIH-defined Phase III Clinical Trials

# Before Award

## **Inclusion Issues:**

- Targeted/Planned Enrollment Table – Totals by
  - Ethnic Category (Hispanic or Latino)
  - Racial Categories
- Separate tables for each study
- Separate tables for domestic and foreign populations
- Plans for Outreach and Recruitment

# After Award

## **Human Research Protections Issues:**

- Annual Progress reports from the grantee to the NIH and certification of continuing IRB review for non-exempt human subjects research
- Adverse Event Reports

# After Award

## **Inclusion Issues:** Annual Report

- Inclusion Enrollment Tables
  - Part A: All Human Subjects
  - Part B: Hispanics or Latinos by Racial Categories
- Separate tables for each study
- Separate tables for domestic and foreign populations

# Definitions covered

- Risk
- Research
- Human Subject
- Investigator
- Clinical Research
- Clinical Trial
- NIH Defined Phase III Clinical Trial
- NIH Inclusion policies

# Resources and Getting Help

- NIH Guide for Grants and Contracts  
<http://grants.nih.gov/grants/guide/index.html>
- NIH Grants Policy Statement  
[http://grants.nih.gov/grants/policy/nihgps\\_2003/index.htm](http://grants.nih.gov/grants/policy/nihgps_2003/index.htm)
- SF 424 (Research & Related) & Electronic Submission Page  
<http://grants.nih.gov/grants/funding/424/index.htm>  
<http://era.nih.gov/ElectronicReceipt/>
- PHS 398 Instructions  
<http://grants.nih.gov/grants/funding/phs398/phs398.html>
- PHS 2590 Instructions  
<http://grants.nih.gov/grants/funding/2590/2590.htm>