Research Involving Human Subjects

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Outline

• HHS Regulations: 45 CFR part 46
  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

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

Extracted from:
http://ohrp.osophs.dhhs.gov/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

Extracted from:
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#46.102
**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


**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)

- 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**

- 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

<table>
<thead>
<tr>
<th>PHS 398 Section E.</th>
<th>SF 424 Human Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;No Human Subjects research is proposed&quot;</td>
<td>No Human Subjects section is required</td>
</tr>
</tbody>
</table>
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

Scenario D: Clinical Research

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

Definition of Clinical Research

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

Scientific Review of Human Research Protections

- “Acceptable” or “Unacceptable”
- Human Subjects Concern:
  - Actual or potential unacceptable risks, or inadequately protected 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**

- Inclusion of Women/Minorities
- Subject Selection Criteria & Rationale
- Rationale for Any Exclusions
- Plans for Outreach
- Proposed Composition of Study Population Using Targeted/Planned Enrollment Tables

**Inclusion of Children**

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

- “Children” are defined as individuals <21 years
- [Link](http://grants.nih.gov/grants/guide/notice-files/not98-024.html)

**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 & inclusion inappropriate with respect to the research topic
- **Assessment:** “Acceptable” or “Unacceptable”

**Scenario E: Clinical Trial**

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

Applicants should:

- Provide information required for Scenario D: Clinical Research
- 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**

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
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.

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

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 Assurance Number for grantee institution
  - Certification of IRB review and approval from IRB registered under grantee’s Assurance 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

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

- Inclusion Issues:
  - Inclusion Enrollment Tables
    - Part A: All Human Subjects
    - Part B: Hispanics and Latinos
  - Separate tables for each study
  - Separate tables for domestic and foreign populations
Resources and Getting Help

- NIH Guide for Grants and Contracts
- NIH Grants Policy Statement
- PHS 398 Instructions
- PHS 2590 Instructions
  [http://grants.nih.gov/grants/funding/2590/2590.htm](http://grants.nih.gov/grants/funding/2590/2590.htm)
- SF 424 (Research & Related)