




## 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

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## 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

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## Definition of *Risk*

...the **probability of**

- harm
- or
- discomfort

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

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## 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>

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## 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>

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## 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

7 <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

## 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

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## 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)

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## 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

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## 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)

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## Scenario A: No Human Subjects

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

PHS 398 Section E.	SF 424 Human Subjects
"No Human Subjects research is proposed"	No Human Subjects section is required

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## 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

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## 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

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## 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: Certification of IRB approval prior to award  
<http://grants.nih.gov/grants/policy/policy.htm>

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## Scenario D: Clinical Research

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

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>

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## Definition of *Clinical Research*

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

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## 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

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## 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%)

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## 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

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## 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

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

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## 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"

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## 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

PLUS:

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

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## 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

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## 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

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## 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.

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## 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

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## 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

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## 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

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## After Award

### 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

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## 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)
- PHS 398 Instructions  
<http://grants.nih.gov/grants/funding/phs398/phs398.html>
- PHS 2590 Instructions  
<http://grants.nih.gov/grants/funding/2590/2590.htm>
- SF 424 (Research & Related)  
<http://grants.nih.gov/grants/funding/424/index.htm>

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