



Human Subjects Research Primer for Investigators

Ann M. Hardy, DrPH

NIH Extramural Human Subjects Protections Officer

Office of Extramural Research (OER), NIH

NIH Regional Seminar on Program Funding and Grants Administration

Las Vegas, Nevada; June 25-26, 2009





- HHS Regulations
- Am I Doing Human Subjects Research?
- NIH Grant Application Requirements for Research Involving Human Subjects
 - Instructions for Human Subjects Section
 - Inclusion Policies
- Review, Pre- and Post-Award Activities
- Resources





- 45 CFR part 46: Protection of Human Research Subjects
 - [Subpart A](#) –Basic Requirements for Protection
 - [Subpart B](#) --Pregnant Women, Human Fetuses and Neonates
 - [Subpart C](#) --Prisoners
 - [Subpart D](#) --Children



Office for Human Research Protections (**OHRP**)
is responsible for ensuring compliance



NIH Grant Application Requirements

- NIH follows all four subparts of the HHS regulations, A-D
- The Office of Extramural Programs provides policy guidance to grantees on the inclusion of human subjects in research.

Most Frequently Asked Question...





Am I Doing Human Subjects Research?





Definition of Human Subject

- ... a living individual
- about whom an investigator (whether professional or student) conducting research obtains
 - Data through intervention or interaction with the individual,
 - Or
 - Identifiable private information





Applying the Regulations: Example 1

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

You Decide...

Is this Human Subjects Research?





- **No**, this is not Human Subjects Research
- Research involving only specimens and data from deceased individuals is not human subjects research



Research Involving Coded Data or Specimens

- OHRP Policy Guidance 2004, 2008
 - If research involves only secondary analysis of data/specimens collected for another reason, it is NOT human subjects research if:
 - Subjects are not living
- OR
- None of investigators can readily ascertain the identity of subjects (provider has no other role in research and does not release key)





Applying the Regulations: Example 2

- An application describes the following proposed research activities:
 - Investigator receives coded data from another researcher's ongoing clinical trial;
 - Provider has access to patient identifiers
 - Investigator will perform analyses on the coded data
 - The Provider will provide clinical expertise to guide analyses, help interpret the results and will be co-author on research publications

You Decide...

Is this Human Subjects Research?





- **Yes**, this is Human Subjects Research
- Providing coded human data or specimens and collaborating on other activities related to the research is human subjects research



Is My Human Subjects Research Exempt?





- Exempt Research is Human Subjects Research
- Six categories designated as being exempt from regulations (very low risk)
- 45 CFR 46.101





Categories of Exempt Human Subjects Research

- (1) Research in educational settings on educational practices
- (2) Educational Tests, Surveys, Interviews... (not if ID and info disclosure put subject at risk; parts not applicable to research w/ children)
- (3) Tests, Surveys, Interviews with public officials, or if laws require confidentiality
- (4) Collection/Study of existing data, specimens if recorded by investigator in way subjects cannot be identified
- (5) Research approved/conducted by Federal Agencies on public benefit programs
- (6) Evaluation of taste or food quality





Sponsoring Agency Responsibilities

- 45 CFR 46 requires that Agencies evaluate all applications and proposals involving human subjects for protections including risks, adequacy of protections, benefits, and importance of knowledge to be gained
- NIH has delegated evaluation of human subjects in applications to peer review process





Sponsoring Agency Responsibilities

- On the basis of this evaluation [NIH] may approve or disapprove the application ... or enter into negotiations to develop an approvable one (45 CFR 46.120).
 - Human Subjects evaluation can affect grant application score
- Federal funds... may not be expended for research involving human subjects unless the requirements of this policy have been satisfied (45 CFR 46.122)
 - Grant may not be funded if there are human subjects problems





Human Subjects Section of Grant Application

- **Risks to Human Subjects**

- Human subjects involvement and characteristics

- Demographic and health characteristics
 - Inclusion and exclusion criteria
 - Rational for involvement of vulnerable populations

- Sources of materials

- What materials (specimens, records, data)
 - How will materials be collected
 - Who has access to information

- Potential Risks

- Physical, psychological, financial, legal or other risks
 - Alternative treatments/procedures





Human Subjects Section (con't)

- Adequacy of Protection Against Risks
 - Recruitment
 - Informed consent
 - Children – assent; parental permission
 - How consent will be obtained; info provided
 - Protections against risk
 - Procedures to minimize risk; protect privacy and confidentiality
 - Additional protections for vulnerable populations
 - Ensure necessary medical/professional intervention
 - Data and safety monitoring





Human Subjects Section (con't)

- Potential Benefits of Research to Human Subjects and Others
 - May not be direct benefit to subjects
 - Compensation is not a benefit
 - Discuss risks in relation to anticipated benefits
- Importance of Knowledge to be Gained
 - Discuss in relation to risks





Additional NIH Requirements

- For Clinical Trials:
 - Data and Safety Monitoring Plan or Board
- For Clinical Research
 - Inclusion of Women and Minorities
 - Valid analyses for NIH-defined phase III clinical trials
 - Inclusion of Children
- Targeted/planned Enrollment Tables
- Justification if NO human subjects but are using human specimens and/or data





Definition of Clinical Research

- Patient-oriented research
- Epidemiologic and behavioral studies
- Outcomes research and health services research



- Does not include in vitro studies that only use human specimens that are not linked to a living person



Not Required for Application

- After peer review, for grants likely to be funded, NIH requests (just-in-time):
 - OHRP Assurance Number
 - Certification of IRB review and approval
 - Certification that Key Personnel have completed appropriate human subjects research education





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. Non-Exempt Human Subjects Research
 - C. Exempt Human Subjects Research
 - D. Delayed-Onset of Human Subjects Research
 - E. Clinical Trial
 - F. NIH-defined Phase III Clinical Trial





Scenario A: No Human Subjects

Are Human Subjects Involved? ___ Yes ___ X No

PHS 398

Heading “Protection of Human Subjects”

“No Human Subjects research is proposed in this application”

SF 424 Human Subjects

No Human Subjects section is required



Provide justification if using human specimens/data





Scenario B: Non-Exempt Research

Are Human Subjects Involved?	<u> X </u> Yes	___ No
Research Exempt?	___ Yes	<u> X </u> No
Clinical Trial?	___ Yes	<u> X </u> No
NIH-Defined Phase III CT?	___ Yes	<u> X </u> No

- Human Subjects Section- no page limitations
 - Address 4 required points (risk, protections, benefits, knowledge)
- Inclusion of Women and Minorities
- Targeted/Planned Enrollment Tables
- Inclusion of Children





Scenario C: Exempt Research

Are Human Subjects Involved? X Yes No
Research Exempt X Yes No
 Exemption Number 1 2 3 4 5 6
Clinical Trial? Yes X No
NIH-Defined Phase III CT? Yes X No

- Human Subjects Section
 - Justify selection of exemption(s)
 - Sources of research materials
- Inclusion of Women and Minorities*
- Targeted/Planned Enrollment Tables*
- Inclusion of Children*

* Not required for Exemption 4





Scenario D: Delayed Onset HS Research

Are Human Subjects Involved? Yes No
Research Exempt? Yes No
Clinical Trial? Yes No
NIH-Defined Phase III CT ? Yes No

- Definition of Delayed Onset: Human subjects research is anticipated but plans for involvement of human subjects cannot be described in the application (45 CFR 46.118)
- Human Subjects Section – explain why delayed onset
- If funded, you will have to describe human subjects protections and provide assurance and IRB approval before involving human subjects





Scenarios E & F: Clinical Trial

- Definition of Clinical Trial: Prospective research study designed to answer questions about biomedical or behavioral interventions
- NIH Defined Phase III Trial - broad-based, prospective trial, often to provide scientific basis for change in health policy or standard of care (Scenario F)
- All other Phases (Scenario E)





Scenario E: Clinical Trial (not Phase III)

Are Human Subjects Involved? X Yes ___ No
Research Exempt? ___ Yes X No
Clinical Trial? X Yes ___ No
NIH-Defined Phase III CT? ___ Yes X No

- Provide information required for Scenario B (Non-Exempt Human Subjects Research)
- Must have a Data and Safety Monitoring Plan





Data and Safety Monitoring Plan

Data and Safety Monitoring Plan includes:

- Overall framework for data and safety monitoring
- Responsible party for monitoring
- Procedures for reporting Adverse Events

Data and Safety Monitoring Board (DSMB)
required for multi-site trials > minimum risk and
generally for Phase III trials

IRB and funding IC approval before enrollment
begins





Scenario F: NIH-def. Phase III Clinical Trial

Are Human Subjects Involved? Yes No
Research Exempt? Yes No
Clinical Trial? Yes No
NIH-Defined Phase III CT? Yes No

- Provide information required for Scenario E
- Generally requires DSMB





Analytic Requirement for Phase III CT

- Research Plan must consider whether significant gender and/or race/ethnic differences in the intervention effect is expected based on prior studies
 - Yes: plan to conduct analysis to detect significant differences in intervention effect for relevant subgroups
 - No: gender and/or racial/ethnic selection criteria not required but inclusion and analysis of subgroups is encouraged
 - Unknown: include sufficient subjects to conduct valid subgroup analysis





Peer Review of Human Research Protections

- Each reviewer will assess human subjects protections
 - Human subjects concern: actual or potential unacceptable risks, or inadequate protections or insufficient information
- Peer review group will determine overall rating of “acceptable” or “unacceptable”
- Summary Statement:
 - **PROTECTION OF HUMAN SUBJECTS: UNACCEPTABLE (Code 44)**
 - Code 44 is bar to award





- Inclusion of Women and Minorities
 - Women and Minorities must be included in clinical research unless exclusion is clearly justified for scientific reasons
 - Subject Selection Criteria
 - Rationale for Any Exclusions
 - Plans for Outreach and Recruitment
 - Proposed Composition of Study Population Using Targeted/Planned Enrollment Tables





Targeted Enrollment Tables

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





- Inclusion of Children
 - Children must be included in clinical research unless there are scientific or ethical reasons not to include them
 - “Children” are defined as individuals <21 years





Protection of Children Against Research 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





NIH Uses Two Definitions for Children

- **For purposes of human subjects protection:** Children are persons who have not attained the legal age where research will be conducted.
- **For the purposes of inclusion:** Children are individuals under the age of 21.





Peer Review of Inclusion Plans

- Each reviewer will assess inclusion plans
- Peer review group will determine overall rating of “acceptable” or “unacceptable” for each inclusion category
- Summary Statement:
 - **INCLUSION OF (WOMEN, MINORITIES, CHILDREN) PLAN: UNACCEPTABLE**
 - Unacceptable Inclusion is bar to award





Just-in-Time Requirements

- After peer review, for grants likely to be funded, NIH requests (just-in-time):
 - OHRP Assurance Number
 - Certification of IRB review and approval
 - Certification that Key Personnel have completed appropriate human subjects research education
 - Resolution of unacceptable HS or inclusion





Resolving Unacceptable Applications

- Human Subjects: Work with Program Officer
 - Written resolution
 - IC approval
 - NIH Office of Extramural Programs (OER) concurrence
- Inclusion: Work with Program Officer
 - IC approval





- Human Research Protections Issues:
 - Adverse Event Reports – within 3 days
- Inclusion Issues:
 - Annual Inclusion Enrollment report
 - Table A – total enrollment
 - Table B – Hispanic subjects by racial categories
 - Separate tables for domestic and foreign populations
 - For Phase III CT – progress in data analysis for sub-groups





Getting Help

- NIH Office of Extramural Research Human Subjects Website: <http://grants.nih.gov/grants/policy/hs/>
- Decision Chart for Research with Data/Specimens: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102>
- OHRP Website: <http://www.hhs.gov/ohrp/>
- 45 CFR 46: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
- SF 424 (Research & Related) & Electronic Submission Page
- <http://grants.nih.gov/grants/funding/424/index.htm>
- PHS 398 Instructions: <http://grants1.nih.gov/grants/funding/phs398/phs398.html>
- NIH Human Subjects Protection Education <http://phrp.nihtraining.com/users/login.php>
- Inclusion: http://grants.nih.gov/grants/funding/women_min/women_min.htm



Research Involving Human Subjects: Home Page - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address http://grants.nih.gov/grants/policy/hs/index.htm Go Links

Web Search Bookmarks Settings Mail My Yahoo! Answers Games Anti-Spy

Research Involving Human Subj... Add Tab

Grants Policy	<h2>Research Involving Human Subjects</h2>
Policy & Guidance	
Compliance & Oversight	<i>This site provides, in one place, HHS and NIH requirements and resources for the extramural community involved in human subjects research in their roles as: Applicants/Grantees, Offerors/Contractors, Peer Reviewers, Institutional Officials</i>
Research Involving Human Subjects	
Regulations, Policies & Guidance	News Flash:
Research w/Vulnerable Populations	On October 16, 2008 the Office for Human Research Protections (OHRP) released two updated Guidance documents:
Research Using Human Specimens, Cell Lines or Data	<ul style="list-style-type: none">• Guidance on Engagement of Institutions in Human Subjects Research [PDF - 66KB]• Guidance on Research Involving Coded Private Information or Biological Specimens [PDF - 41KB]
Human Subjects Protections Training	
Frequently Asked Questions	Regulations, Policies & Guidance
Additional Resources	<ul style="list-style-type: none">• Ethical Guidelines & Regulations• NIH Human Subjects Policies and Guidance• OHRP & FDA
Office of Laboratory Animal Welfare (OLAW)	Human Subjects Protections Training
Animals in Research	<ul style="list-style-type: none">• Training Resources
Peer Review Policies & Practices	Frequently Asked Questions ←
Intellectual Property Policy	<ul style="list-style-type: none">• From Applicants• About Research Using Human Specimens, Cell Lines or Data
Invention Reporting (iEdison)	Additional Resources
Global OER Resources	<ul style="list-style-type: none">• NIH Process for Applications that Propose Research Involving Human Subjects (MS Word - 36 KB)• Resources• NIH Reports on Human Subjects Research• Glossary• NIH Forms and Applications
Glossary & Acronyms	
Frequently Used Links	
Frequent Questions	
	Research with Vulnerable Populations
	<ul style="list-style-type: none">• Pregnant Women, Human Fetuses and Neonates• Prisoners• Children• Persons at Risk for Suicidality• Persons with Impaired Decisional Capacity
	Research Using Human Specimens, Cell Lines, or Data
	<ul style="list-style-type: none">• Flowchart: Research Involving Private Information or Biological Specimens (PDF - 27 KB)• Implementation Instructions and Definitions• FAQ
	For questions or comments regarding this site, contact Human Subjects Mailbox . ←



Contact Information

Ann Hardy

Email: hardyan@od.nih.gov

Thank You

