

NIH Regional Seminar

Human Subjects' Protections Update

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Office for Human Research Protections (OHRP)

(Formerly Office for Protection from Research
Risks)

Department of Health and
Human Services
Office of Public Health and Science

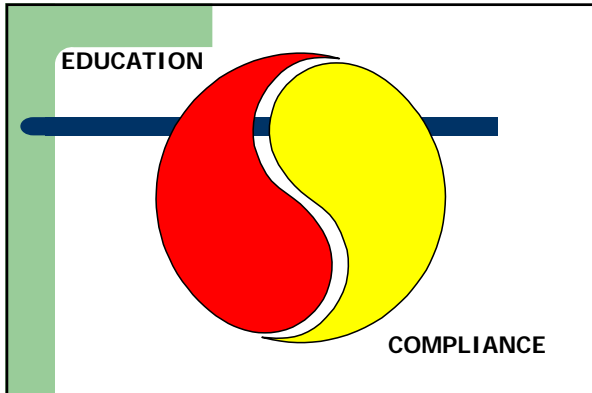
OHRP Responsibilities

- Policy and Assurances
- Education and Quality Improvement
- Compliance
- International research



NEGOTIATING ASSURANCES





Ethical Principles

- Nuremburg Code
- Declaration of Helsinki
- The Belmont Report

Nuremberg

During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for "performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts."

The Nuremberg Code (1947)

As part of the verdict, the Court enumerated some rules for "Permissible Medical Experiments", now known as the "Nuremberg Code". These rules include:

- **voluntary consent**
- **benefits outweigh risks**
- **ability of the subject to terminate participation**

Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

"Concern for the interests of the subject must always prevail over the interests of science and society."

Tuskegee Syphilis Study

American medical research project conducted by the U.S. Public Health Service from 1932 to 1972, examined the natural course of untreated syphilis in black American men. The subjects, all impoverished sharecroppers from Macon county, Alabama, were unknowing participants in the study; they were not told that they had syphilis, nor were they offered effective treatment.

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research



The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
April 18, 1979

The Belmont Report

Three Basic Ethical Principles:

- Respect for Persons
 - Individual autonomy
 - Protection of individuals with reduced autonomy
- Beneficence
 - Maximize benefits and minimize harms
- Justice
 - Equitable distribution of research costs and benefits

Federal Regulations and Policy

45 CFR 46 - Basic DHHS Policy for Protection of Human Research Subjects - Subpart A

Originally adopted January 13, 1981
Revised June 18, 1991

"The Common Rule" - Federal Policy for the Protection of Human Subjects June 18, 1991

Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS. NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission.

Federal Regulations and Policy

Additional Protections Included in 45 CFR 46:

- **Subpart B** - Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization
- **Subpart C** - Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- **Subpart D** - Additional DHHS Protections for Children Involved as Subjects in Research

Food and Drug Administration



Regulations:

- IRB - 21 CFR 56
- Informed Consent - 21 CFR 50

HHS vs. FDA Regulations

- Basic requirements for IRBs and Informed Consent are congruent
- Differences center on differences in applicability
 - HHS regulations based on federal funding of research
 - FDA regulations based on use of FDA regulated product: drugs, devices, or biologics

Definitions

- **Research** - a systematic investigation designed to develop or contribute to generalizable knowledge.
- **Human Subject** - a living individual about whom an investigator conducting research obtains
 - data through intervention or interaction with the individual, or
 - identifiable private information

Exempt from Regulations

- 45 CFR 46.101(b)(1)-(5) -- HHS categories; no FDA analog
- 45 CFR 46.101(b)(6) & 21 CFR 56.104(d) -- HHS & FDA -- pertaining to food testing (FDA exempt from "IRB review")

Basic Protections

The regulations contain three basic protections for human subjects:

- Institutional Assurances (FWA)
- IRB Review
- Informed Consent

Assurances

- "Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall provide written assurance ... that it will comply with the requirements set forth in this policy." [45 CFR 46.103(a)]
- Negotiated and approved by OHRP

Assurances

Information to be included in the assurance:

- **Statement of principles governing the institution**
- **IRB procedures**
- **Procedures for ensuring prompt reporting**

Sample assurances and procedures for submitting assurances can be found at the OHRP web site: www.hhs.gov/ohrp/assurances/

Assurance Applications – Extending FWA

- Individual Investigator Agreement
 - Independent investigators
 - Institutional investigators
- Assured institution responsible for oversight of research

Guidance: <http://www.hhs.gov/ohrp/humansubjects/assurance/guidanceonalternativetofwa.htm>
Sample Agreement: <http://www.hhs.gov/ohrp/humansubjects/assurance/unafsup.rf>

Assurance Applications - Relying on External IRB

- Institution responsibility
 - Written agreement
 - IRB authorization agreement
 - <http://www.hhs.gov/ohrp/humansubjects/assurance/protosup.rtf>
 - Ensure research conducted per IRB approved plan
 - Reporting to OHRP

Assurances

- The institution must certify that the research has been reviewed and approved by an IRB. [45 CFR 46.103(b)]
- Submitted to funding agency

IRB Registration

- Integral part of Assurance process
- FWA must cite to OHRP-registered IRB
- See, <http://www.hhs.gov/ohrp/assurances/index.html#registernew>

Institutional Responsibilities

- Institutions bear full responsibility for all research involving human subjects covered under their Assurance
- All requirements of 45 CFR 46 must be met for all *federally-sponsored* research
- OHRP strongly encourages institutions to embrace the HHS regulations regardless of sponsorship, and to commit to this standard in their Assurance.

IRB Responsibilities

- Review and approve, require modifications, or disapprove all covered research
- Require that informed consent is in accordance with regulations
- Require documentation of informed consent or may waive documentation in accordance with regulations
- Notify investigators in writing of decisions
- Conduct continuing review of research no less than once per year

Informed Consent

Beyond the Consent Form

GENERAL INFORMED CONSENT REQUIREMENTS (45 CFR 46.116)

CIRCUMSTANCES:

- MUST AFFORD POTENTIAL SUBJECT OPPORTUNITY TO WEIGH DECISION
- MUST MINIMIZE POSSIBILITY FOR COERCION OR UNDUE INFLUENCE

GENERAL INFORMED CONSENT REQUIREMENTS (45 CFR 46.116), CONT'D

LANGUAGE:

- INFORMATION PROVIDED MUST BE UNDERSTANDABLE TO SUBJECT OR REPRESENTATIVE
- EXCULPATORY LANGUAGE REGARDING LEGAL RIGHTS OR LIABILITY IS FORBIDDEN

Basic Elements of Informed Consent

- Research
 - Purpose
 - Duration
 - Procedures
- Risks
- Benefits
- Alternatives
- Confidentiality
- Compensation for Injury
- Whom to Contact
- Right to Refuse or Withdraw



COMPLIANCE

COMPLIANCE OVERSIGHT JURISDICTION

- 45 CFR 46
- OHRP APPROVED ASSURANCE

Not-For-Cause Compliance Investigations

- Since 2001, approximately 13 conducted (11 on-site, 2 "paper" visits)
- Not based on a complaint or problem

OHRP

- COMPLAINTS
- SELF-REPORTING
- MEDIA
- OTHER INCIDENT REPORTS

OHRP

HUMAN SUBJECTS COMPLIANCE OVERSIGHT PROCEDURES

www.hhs.gov/ohrp/compliance/ohrpcomp.pdf

OHRP COMPLIANCE PROCEDURES

- WRITTEN COMPLAINTS
- OHRP INITIATES INQUIRY
- OHRP EVALUATION

<http://www.hhs.gov/ohrp/compliance/ohrpcomp.pdf>

OHRP COMPLIANCE SITE VISIT

- SITE VISIT TEAM
 - 2-4 OHRP STAFF
 - 2-3 CONSULTANTS (e.g., IRB CHAIR, SCIENTIFIC SPECIALTY)
- SPECIFIC COMPLAINT
- SYSTEMIC PROTECTIONS

OHRP

"GREATEST HITS" COMMON FINDINGS AND GUIDANCE

NOW PLAYING AT:
www.hhs.gov/ohrp/compliance/findings/pdf

OHRP-GREATEST HITS

- DEFICIENCIES IN INFORMED CONSENT
 - PROCESS
 - DOCUMENT
- See,
www.hhs.gov/ohrp/ohrp/policy/index.html#informed

OHRP-GREATEST HITS, CONT'D

- DEFICIENT CONTINUING REVIEW
 - INADEQUATE REVIEW OF GAINED INFORMATION
 - UNTIMELY
- See,
<http://www.hhs.gov/ohrp/policy/index.html#continuing>

OHRP-GREATEST HITS, CONT'D

- INADEQUATE MINUTES
 - FAILURE TO DOCUMENT FINDINGS (e.g., CHILDREN, PRISONERS)

OHRP-GREATEST HITS, CONT'D

- FAILURE TO NOTIFY OHRP OF
 - UNANTICIPATED PROBLEMS
 - NONCOMPLIANCE
 - SUSPENSIONS
 - TERMINATIONS
- See,
<http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd702.htm>

OHRP-GREATEST HITS, CONT'D

- DEFICIENT IRB PROCEDURES
 - INADEQUATE WRITTEN IRB GUIDELINES
 - INADEQUATE FORMS/APPLICATIONS
 - FAILURE TO FOLLOW PROCEDURES IN EXISTENCE
 - INSUFFICIENT EDUCATION REGARDING PROCEDURES

OHRP

ACTIONS DESIGNED TO ENSURE PROTECTION OF HUMAN RESEARCH SUBJECTS

- TERMINATION
- SUSPENSION
- CORRECTIVE ACTIONS
 - REWRITE/INSTITUTE NEW PROCEDURES
 - EDUCATION
 - INCREASED IRB STAFFING, OTHER RESOURCES

New Guidance

New Guidance

- Use of Coded Private Information or Biological Specimens
- 407 Review Process
- International Compilation of Human Subject Research Protections

Other New Guidance

- Incident Reporting
- IRB Review of Clinical Trial Websites
- OHRP's Compliance Oversight Procedures for Evaluating Institutions

Guidance in the Pipeline

- Reporting Adverse Events & Unanticipated Problems (issued as draft on Oct. 13, 2005)
- Engagement of Institutions in Research
- What Is Research?
- Definition of Human Subject
- Informed Consent for Subjects Who Do Not Understand English

Frequently Asked Questions

New Web Resource - Frequently Asked Questions

- 45 CFR 46
- IRB Registration
- Federalwide Assurance
- Subpart D
- Informed Consent

Contact Information

- Main Phone Number: 240-453-6900
- Toll Free Phone Number: 1-866-447-4777
(1-866-HHS-HRPP)
- New Staff Phone Numbers – check website

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