When The Regs Come A Knockin': Nuts and Bolts of 45 CFR part 46

OHRP Webinar

June 7, 2012

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Poll #1

Can you hear me?

Yes

No

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Poll #2

Are You Experienced?

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Outline

- Ethical Principles
- Regulated Human Subject Research
- Applicability of HHS Regulations
- Regulatory Protections for Research Subjects

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Ethical Principles

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Ethical Principles

- Nuremberg Code
- Declaration of Helsinki
- The Belmont Report

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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)

- 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

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

Beecher Article

"Ethics and clinical research"

Henry K. Beecher
New Engl J Med 274 (1966):1354-60

- 22 published medical studies presenting risk to subjects without their knowledge or approval
- Published in some of the most prestigious journals and conducted at some of the most prestigious institutions

Public Health Service Policy

- NIH Director and Surgeon General requested that the National Advisory Health Council review human subject protections
- Council recommended prior institutional review for PHS supported research to:
  - Protect the rights and welfare of the subjects
  - Assure appropriate methods of informed consent
  - Determine acceptable balance of risks and benefits
- Adopted as Public Health Service policy in 1966
- Beginnings of the Institutional Review Board (IRB)

Tuskegee Syphilis Study

Unethical American medical research project conducted by the U.S. Public Health Service from 1932 to 1972, examined the "natural" course of untreated syphilis in African American men.

- *"The United States government did something that was wrong -- deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens."*
- *President William Jefferson Clinton, May 16, 1997 – apology to Tuskegee survivors and families*

National Research Act

- 1973 Kennedy Hearings "Quality of Health Care - Human Experimentation"
- 1974 National Research Act
  - Established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research"
  - Required IRBs at institutions receiving HEW support for human subjects research

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

Basic Ethical Principles:

- Respect for Persons
- Beneficence
- Justice

Poll #3:

Developments in human subjects' protections

Oversight of Human Subject Research

- Federal departments & agencies that are signatories to "The Common Rule" (including HHS)
- FDA
- State and local
- Institutions

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Federal Regulation and Policy

HHS regulations: Title 45 CFR part 46

- Subpart A – basic HHS Policy
  - IRB & informed consent requirements "The Common Rule" - Federal Policy
  - Other Federal Departments & Agencies have adopted

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

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Additional HHS Protections

- Subpart B - Pregnant Women, Human Fetuses, and Neonates
- Subpart C - Prisoners
- Subpart D – Children
- Subpart E – IRB Registration

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Food and Drug Administration

Regulations:

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

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HHS vs. FDA Regulations

- **Basic requirements for IRBs and for informed consent are congruent**
- **Differences in applicability**
  - **HHS regulations based on HHS funding of research**
  - **FDA regulations based on use of FDA regulated product: drugs, devices, or biologics**

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Applicability of HHS Regulations

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Determining Applicability of Regulations

Prerequisite:

- Research involving human subjects **conducted or supported by HHS** (or other Federal Departments or Agencies) that is not otherwise exempt

OR

- Non-exempt human subject research covered by **Assurance of Compliance**

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Determining Applicability, cont'd

- Does activity involve **research**?
- Does research involve **human subjects**?
- Is the human subject research **exempt**?
- Is your institution **engaged**?

Human Subject Regulations Decision Chart:

http://www.hhs.gov/ohrp/policy/decisionchart.html

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Does the Activity Involve Research?

- Research – a systematic investigation designed to develop or contribute to generalizable knowledge
  - includes research development, testing, evaluation, pilot studies

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Does the Research Involve Human Subjects?

- Human subject – a living individual about whom an investigator conducting research obtains
  - data through intervention or interaction with the individual, or
  - identifiable private information

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Is the Human Subject Research Exempt? Categories of Exempt Research*

1. Normal educational practices in established educational settings
2. Educational tests, surveys, interviews, or observation of public behavior -unless identified & sensitive**
3. Research on elected or appointed public officials or candidates for public office
4. Research using existing data, if publicly available or recorded without identifiers
5. Evaluation of public benefit service programs
6. Taste and food quality evaluation and consumer acceptance studies

46.101(b)(1-6)

* Exception for prisoners

** Exception for children

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Is your Institution Engaged?

Institution is Generally Engaged in Human Subjects Research:

- When employees or agents obtain, for research purposes:
  - data about the subjects of the research through intervention or interaction with them;
  - identifiable private information about them; or
  - the informed consent of the subjects

§46.102(d) & (f)

Guidance at:

http://www.hhs.gov/ohrp/policy/engage08.html

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Regulatory Protections for Research Subjects

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Basic Protections

The regulations contain three basic protections for human subjects:

- Institutional Assurance (FWA)
- IRB Membership & Review
- Informed Consent

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Institutional Assurance

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Institutional Assurance

- Required when engaged in non-exempt human subject research
- Documentation of institution's commitment to comply with applicable regulations - §46.103(b) & (f)
- Method of compliance oversight
- Federalwide Assurance (FWA) - only option
- Designate only registered IRB(s)

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IRB Membership

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Membership Requirements

- Number of Members
  - minimum of 5 members - §46.107(a)
- Experience and Expertise - §46.107(a)
- Diversity of Members - §46.107(a) & (b)
- At least one:
  - scientist - §46.107(c)
  - nonscientist - §46.107(c)
  - nonaffiliated - §46.107(d)
- Prisoner Representative - §46.304(b)

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Scientist & Nonscientist

- Minimum one nonscientist and one scientist
- Nonscientist must be present
- Considerations
  - training
  - background
  - occupation

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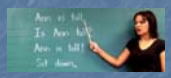
Scientist or Nonscientist?

- Registered Nurse

- Middle school English teacher



- Clergy

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Nonaffiliated Member

- Minimum one nonaffiliated member
- Only association with institution, if any:
  - patient
  - subject
  - service on the IRB

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Flexibility & Efficiency

- Expert Consultant - §46.107(f)
  - provides supplement review
  - does not vote
- Alternate members
  - appropriate expertise
  - substitute for entire meeting or any portion of meeting

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IRB Member Conflict of Interest - §46.107(e)

- May provide information requested by the IRB
- Recusal from IRB's deliberations and voting
- Conflicted members do not contribute to the quorum

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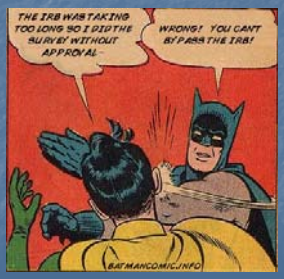
IRB Review



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Types of IRB Review

- Convened meeting of IRB – §46.109
- Expedited review – §46.110
  - minor changes to approved research
  - no greater than minimal risk and on "list" at:

http://www.hhs.gov/ohrp/policy/expedited98.html

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IRB Review

- Initial – prior to initiating human subjects research
- Continuing review – at least annually
- Prior to initiating changes to approved research
- Sufficient information to make required findings at §46.111 and any relevant subpart(s)

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Criteria for IRB Approval

Findings under §46.111

- Risks minimized
- Risk/benefit ratio reasonable
- Subject selection equitable
- Informed consent – obtained & documented (unless waived)

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Criteria for IRB Approval, cont'd

Findings under §46.111

- Data monitored
- Privacy and confidentiality
- Safeguards for vulnerable subjects

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Additional Findings under Applicable Subparts

- Categories of permissible research
- Informed consent, assent, permission
- Other considerations

-- e.g., IRB composition, Secretarial panel process, expert consultants

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Poll #4

Frequency of IRB review

Informed Consent

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Informed Consent

Key principles of the informed consent process:

- Full disclosure of the nature of the research and the subject's participation
- Adequate comprehension on the part of the potential subjects or legally authorized representative (LAR)
- The subject's voluntary choice to participate or not

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Basic Elements of Informed Consent

- Research
  - purpose
  - duration
  - procedures
- Risks, discomforts
- Benefits
- Alternatives
- Confidentiality
- Compensation for injury
- Whom to contact
- Right to refuse, withdraw without penalty

§46.116(a)

Note: Additional elements, when appropriate

§46.116(b)

Waiver or Alteration of Informed Consent

Consistent with §46.116(c) or (d), §46.408, or §46.101(i)

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Informed Consent - Waiver or Alteration, cont'd

IF IRB finds and documents that

- no greater than minimal risk,
- will not adversely affect rights & welfare of subjects,
- research could not practicably be carried out without the waiver or alteration, AND
- when appropriate, subjects will be "debriefed" after participation

§46.116(d)

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Documentation of Informed Consent
45 CFR 46.117

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Documentation of Informed Consent – § 46.117(b)

- Long form document, embodying elements
- Short form, oral presentation of elements

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Waiver of Written Documentation – Informed Consent

IRB may waive documentation if it finds either:

- consent form only record linking subject and research; *AND*
- principal risk from breach of confidentiality.

OR

- minimal risk research; *AND*
- research procedures do not require written IC if done outside research context

§46.117(c)

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The Consent Process

Informed consent is not a single event or just a form to be signed -- rather, it is an on-going process that takes place between the investigator and the prospective subject.

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Poll #5

The HHS regulations at 45 CFR part 46

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Key Points

- **Belmont Report**
- **Who regulates human subjects research**
- **How and when do the HHS regulations apply**
- **Basic protections afforded by HHS regulations**

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OHRP Contact Information

- **Website:** www.hhs.gov/ohrp
- **Email:** OHRP@HHS.GOV
- **Toll-free phone #: 1-866-447-4777**
- **Main phone #: 240-453-6900**
- **Join Listserv:**

http://www.hhs.gov/ohrp/newsroom

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