The Protection of Human Research Subjects

History of Research Ethics

Prior to 1906, when the Pure Food and Drug Act was passed, there were –
- No regulations regarding the ethical use of human subjects in research,
- No consumer regulations,
- No Food and Drug Administration (FDA),
- No Common Rule, and
- No Institutional Review Board (IRB).

Development of Research Ethics

The history that follows is a brief discussion of why federal rules and regulations were established and why the IRB became a necessity.

1948: The Nuremberg Code

On December 9, 1946, criminal proceedings began against 23 leading German physicians and administrators for war crimes and crimes against humanity. Among the charges were:
- German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent and
- Most of the subjects of these experiments died or were permanently crippled as a result.

Direct results…

The Nuremberg Code was established 1948 as the first international document stating that:
- The benefits of research must outweigh the risks and
- Subjects should give informed voluntary consent.
1950: Thalidomide Tragedy

In the late 1950s, thalidomide was approved as a sedative in Europe but not approved in the United States by the FDA.
Issues included:
- Taking this drug during pregnancy caused severe deformities in the fetus and
- Many patients did not know they were taking a drug not approved for use by the FDA, nor did they give informed consent.

1950: Thalidomide Tragedy

1964: Declaration of Helsinki

The World Medical Association established recommendations for doctors in biomedical research with human subjects:
- Governs international research ethics
- Defines rules for "research combined with clinical care" and "non-therapeutic research"
- Basis for good clinical practices used today

1972: Tuskegee Syphilis Study

Research project conducted and monitored for 40 years by the U.S. Public Health Service with 600 low-income African-American males, 400 of whom were infected with syphilis.

Direct results…

- "Kefauver Amendments" to the Food, Drug and Cosmetic Act became law
- Ensured drug efficacy and greater drug safety
- Drug manufacturers required to prove to FDA the effectiveness of their products before marketing them

Direct results…

Direct results…

- Research with humans should be based on the results from laboratory and animal experimentation.
- Research protocols should be reviewed by an independent committee prior to initiation.
- Informed consent from participants is necessary.
- Research should be conducted by medically/scientifically qualified individuals.
- Risks should not exceed benefits.

Direct results…

- The study used disadvantaged, rural black men to study the untreated course of a disease that was not confined to that population.
- All of the burden of risk placed on that population when a much broader population benefits from the findings.
- The study did not minimize risks to human subjects. In fact, it increased their risks.
- These issues heightened awareness of the need to protect human subjects and to assure their informed voluntary consent.
1974: National Research Act

Due to the publicity from the Tuskegee Syphilis Study, the National Research Act of 1974 was passed. The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Direct results…

◆ The National Research Act codified the requirement that human subjects in research must be protected
◆ Set the stage for the issuance of the Belmont Report

1978: Belmont Report

This report prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research summarizes:

◆ The basic ethical principles identified by the Commission in its deliberations and
◆ Serves as a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

Direct results…

The Belmont Report established three basic ethical principles which are the cornerstone for regulations involving human subjects:

■ Respect = People are autonomous agents who should be given information such that they can make voluntary decisions for themselves
■ Beneficence = Maximize the benefits and minimize the harms.
■ Justice = No members of society should receive all the benefits of the study nor shoulder all the risks

Current Regulations

In 1981, the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report:

◆ DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects)
◆ FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards)

Common Rule

In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects, or "Common Rule." Also in 1991, the Department of Veterans Affairs promulgated this same rule at 38 CFR Part 16. Today, the 1991 Federal Policy is shared by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.
Common Rule and FDA Regulations Protect Human Subjects

- Obtaining and documenting informed consent
- Institutional review board (IRB) membership, function, operations, review of research, and record keeping
- Additional protections for certain vulnerable research subjects –
  - Pregnant women
  - Prisoners
  - Children
- Assuring compliance by research institutions

Federal Wide Assurances

- The DHHS Office for Human Research Protections requires a policy statement "Assurance", that sets forth the procedures used to protect human subjects.
- OHRP has authority for approving an Assurance at DHHS-funded institutions. Institutions may be granted a Federal Wide Assurance (FWA).

Federal Wide Assurances (Cont.)

- Indiana University, through the FWA, has pledged to protect human subjects and comply with all relevant federal regulations.
- The requirements of the Assurance apply to ALL research, regardless of funding source. Failure by an investigator to adhere to the requirements of the Assurance may cause the institution to have its Assurance suspended or revoked.

What do Regulations and Assurance Apply to?

- Research?
- Human Subjects?
- Student Research?

What do Regulations and Assurance Apply to? (Cont.)

- Research - If you are planning to publish the results of a project, it is almost always regarded as "research." Research can involve a variety of methods and materials.
- Human Subject - A Human Subject is defined as 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.

What do Regulations and Assurance Apply to? (Cont.)

- Student Research - The IRB does not normally include classroom assignment projects under its operational definition of research. HOWEVER, regardless of whether any student research is conducted as part of a course assignment or not, student research projects that:
  - Place subjects at risk;
  - Are undertaken with the intent of adding to generalizable knowledge;
  - Involve special populations including pregnant women, fetuses, prisoners, minors, or human in vitro fertilization are subject to IRB review.
INSTITUTIONAL REVIEW BOARD

How to Contact the IRB

- IUB has one IRB, the Committee for the Protection of Human Subjects, or the Human Subjects Committee (HSC). Research projects involving human subjects must be submitted to the HSC to obtain approval.

IRB Review of Study

Research projects are reviewed at one of three levels, depending on the level of risk to the human subjects. The federal guidelines that define the categories of review, which are:

- Exemption from full IRB review,
- Expedited IRB review, and
- Full IRB review.

Exemption from IRB Review

- Investigators do not have the authority to determine whether research involving human subjects is exempt from full review.
- Even if an investigator believes that a project is exempt, an application must be submitted to the HSC for a final determination.
- If the project does not qualify as exempt, it is referred back to the investigator with the appropriate application forms.

Expedited IRB Review

If your research is considered "minimal risk", it could qualify for the expedited review process and is not required to be reviewed at a meeting of the full IRB board:

- Research activities that present no more than minimal risk to human subjects, and
- Involve only procedures listed in the federal regulations, may be reviewed by the IRB through the expedited review procedure.
**Full IRB Review**

Research that involves greater than minimal risk requires review and approval by a full IRB including, but not limited to, research with:
- Children, prisoners, pregnant women, fetuses and other vulnerable populations;
- Experimental drugs or devices;
- Most invasive procedures; and
- Sensitive questions or is likely to be stressful for the subject.

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**IRB Review Process**

Why Review Research?

To protect research subjects against undue or unnecessary invasion of privacy, disregard for human dignity, and physical, psychological, or social harm.

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**IRB Actions**

What can the IRB do?

- Final approval
- Provisional approval
- Table
- Disapprove

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**Continuing IRB Responsibilities**

- Conducting continuing reviews
- Observing the consent and research process
- Receiving prompt reports
- Suspending or terminating IRB approval of research, when appropriate
Informed Consent Process

An ongoing process that assures that research subjects are fully informed and are voluntarily participating in the research. The process must explain:

- Research
- Risks versus Benefits
- Voluntary

Informed Consent Process (Cont.)

Considerations for the Investigator:

- Subject population
- Information to be conveyed
- Circumstances under which the consent process will take place

Basic Informed Consent Requirements

- Written in a language understandable to the subject population
- Provide sufficient information to fully inform the subject
- Contain NO exculpatory language

Basic Informed Consent Elements

Explain:

- Research
- Purpose
- Procedures
- Risks and benefits
- Compensation
- Alternative procedures
- Confidentiality
- Costs
- Contacts

Additional Informed Consent Elements

- Unforeseeable risks
- Termination/Withdraw
- Significant new findings
- Number of subjects

Waiving or Modifying Informed Consent Requirements

- No more than minimal risk
- Will not adversely affect the subject
- Could not otherwise be carried out
Waiving _Written Informed Consent_

- Consent is the only link
- No more than minimal risk

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Only the full IRB can waive or alter the consent process.

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Other Necessary Approvals

- Radiation Safety
- Biosafety
- Other IU campus

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Principal Investigator Responsibilities

- Management and completion of project
- Hiring and assigning employees
- Ensuring integrity and safeguard of data
- Ensuring consent process
- Adherence to protocols and policies

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Principal Investigator Responsibilities (Cont.)

- Notification of protocol and consent changes
- Meeting continuing review requirements
- Adherence to drug and devices
- Reporting serious and unexpected adverse events
- Assuring compliance with IRB policies

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SPECIAL PROTECTIONS FOR VULNERABLE POPULATIONS
### Special Protections for Vulnerable Populations

- Fetuses
- Pregnant Women
- Prisoners
- Children
- Cognitively Impaired

### Fetuses

- Research directed toward the fetus in utero
- Research involving the fetus ex utero
- Research with dead fetuses, fetal material and placenta

### Pregnant Women

- Studies in which pregnancy is coincidental to subject selection
- Studies directed primarily toward the mother’s health
- Studies directed toward pregnancy

### Prisoners

- Study of the possible causes, effects, and processes of incarceration and of criminal behavior
- Study of prisons as institutional structures or of prisoners as incarcerated persons
- Research on conditions particularly affecting prisoners as a class
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the subject

### Children

- Research not involving greater than minimal risk
- Research involving greater than minimal risk, but presenting the prospect of direct benefit to the subject
- Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield knowledge about the subject’s disorder or condition
- Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

### Children (Cont.)

Consent Procedures (Children):
- Parental Consent
  - One or both parents
  - Waiver of parental consent
- Child Assent
Cognitively Impaired

- Do such individuals comprise the only appropriate subject population?
- Are there sufficient protections for privacy and confidentiality of information gathered?
- How are issues of consent and competence addressed?

After Approval: Amendments

ANY change to a research protocol by the principal investigator or the sponsor.
- Minor
- Major

After Approval: Continuing Reviews

Review of research at least on an annual basis:
- Expedited
- Full
IRB can require:
- New information be communicated to research participants (via the informed consent document)
- The study be modified in some way
- The research be stopped entirely

After Approval: Adverse Event Reporting

Report only serious and unexpected adverse events related to the study intervention.

Good intentions are not enough

A few examples of the importance of oversight in research involving human subjects

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Stuttering (1/4)

- University of Iowa speech pathologist Wendell Johnson was a severe stutterer who called the affliction “crippling.”
- The dominant theory at the time (the 1930s) held that stuttering was caused by organic or genetic defects.

Stuttering (2/4)

- Johnson’s hypothesis: When parents or teachers draw attention to ordinary pauses in children’s speech, the children become self-conscious and begin to stutter.
- “The affliction is caused by the diagnosis.”

Stuttering (3/4)

- Johnson set up a controlled study at the Iowa Soldiers’ Orphans’ Home in Davenport.
- The subjects were 10 stutterers and 12 normal speakers.
- Subjects were randomly assigned to a control group that received positive therapy and an experimental group that received negative therapy, inducing stuttering.

Stuttering (4/4)

- The intervention worked.
- Most of the experimental subjects became stutters – for life.

Consumer complaints (1/3)

- Columbia Business School professor Francis J. Flynn wanted to know how restaurants respond to customer complaints.
- He wrote a polite letter claiming his romantic anniversary dinner had been ruined when he had contracted food poisoning after eating at a restaurant.

Consumer complaints (2/3)

- He sent the letter to 240 New York restaurants.
- Restaurant owners and staff were devastated.
- Cooks were berated, procedures were double-checked, restaurants spent hours trying to find out when Flynn had dined there.
- At least one restaurant responded to Columbia with a complaint about the fraudulent letter.
- The story made the front page of the New York Times.
Consumer complaints (3/3)

- Columbia’s business school decided to revise its ethics rules
- Columbia and/or Professor Flynn will likely be sued


TEST

Human Subjects Protection Test –

A self-administered test designed to complement the Protection of Human Subjects in Research course. The test is available online. Go directly to the test at: https://www.indiana.edu/~rcr/index.php

Useful Web Sites

- Office for Human Research Protections – http://www.hhs.gov/ohrp/

Thank You!

For Questions and Information Please Contact…

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