Ethics of Human Subject Research

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Acknowledgement

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Objectives
• Know the basic ethical principles of research involving human subjects
• Understand the ethical basis of the Federal regulations
Why Study History?

• History places ethics in perspective
• Ethics help explain what historical problems people were trying to solve

Why Study History?

• Those who fail to study history are condemned to repeat it
• Those who fail to study this course are condemned to repeat it

Ethical Decision Making
### Ethics and Morality

- **Ethics:**
  - The disciplined study of morality
- **Morality:**
  - What should one’s behavior and character be?

#### Descriptive Ethics

- What are the moral beliefs and practices of
  - An individual
  - Groups of individuals
  - Institutions
  - Society

#### Normative/Prescriptive Ethics

- What ought morality be?
- How should researchers behave?
- How should researchers not behave?
- What character traits should researchers cultivate as virtues?
- What character traits should researchers avoid as vices?
**Benefits of Research Ethics**

- Provide a structure for analysis and decision making
- Avoid snap decisions
- Make better decisions

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**Types of Ethical Decisions**

- Deductive - Principle based reasoning
- Inductive - Case based reasoning

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**Deductive Reasoning**

```
Ethical Theory ▼ Ethical Theory
  ▼ Principles ▼ Peace
    ▼ Rules ▼ Violence never solves anything
      ▼ Particular judgments ▼ Refuse to join the army
```
Case Based Reasoning

Ethical Theory

- Principles
- Rules
- Particular Judgments

Ethical Theory

- Family
- I must protect my children
- Join the army

Definition

- Conservative:
  A liberal who has been mugged
- Liberal:
  A conservative who has been indicted

Ethical Conflict

Ethical Theory

- Peace
- Violence never solves anything
- Refuse to join the army

Ethical Theory

- Family
- I must defend my children
- Join the army
Ethical Decision Making Summary

• Ethical decision making is both principle based and case based
• Conflict will always exist in ethical reasoning
• Strive for coherence between our principles and individual judgements

The Belmont Principles

The National Commission

• 1974: Identify the basic ethical principles that underlie the conduct of human research
• Develop guidelines to assure that human research is conducted in accordance with those principles

The Belmont Report (1979)
Belmont Principles

• Respect for Persons
• Beneficence
• Justice

Respect for Persons

• Treat individuals as autonomous agents
• Do not use people as a means to an end
• Allow people to choose for themselves
• Give extra protection to those with limited autonomy

Beneficence

• Acts of kindness or charity that go beyond duty
• Obligations derived from beneficence
  Do no harm
  Prevent harm
  Prevent evil
  Promote good
Justice

- Treat people fairly
- Fair sharing of burdens and benefits of research
- Distinguish procedural justice from distributive justice

Derived Rules

- Beneficence
  - Good research design
  - Competent investigators
  - Favorable risk-benefit analysis
- Respect for Persons
  - Informed consent
  - Respect for privacy
- Justice
  - Equitable selection of subjects

Conflict in Belmont Principles

- Respect for Persons
- Protect those with limited autonomy
- Limit research in children
- Fairly share research benefits
- Promote research in children
History of Research
Ethics

Nuremberg Code

• Nazi Doctors' Trial
• Supplement to Nuremberg Trials
• Written as part of the judgement
• Doctors convicted of murder, not for being unethical researchers

Nuremberg Code

• Voluntary informed consent essential
• Research should yield useful results
• Base research on prior work
• Avoid physical and mental suffering
• No expectation of death or disabling injury
• Risk must be outweighed by importance
• Subjects must be protected from injury
• Qualified scientists must conduct research
• Subject may withdraw
• Investigator must be ready to withdraw subject
Effect of the Nuremberg Code

- No effect on research
- Medical profession thought it was: Implicit to US researchers
  Description of criminal research
  Created after the fact to convict Nazis
- Missed many aspects of research

Declaration of Helsinki

- 1964: World Medical Assoc.
- Reinterpretation of Nuremberg
- Provoked a reaction by medical profession
- Journal editors required that research be performed in accordance with the Declaration

Public Health Service Policy

- 1966: All PHS supported research must undergo prior review to:
  Protect rights and welfare of subjects
  Assure appropriate informed consent
  Determine acceptable risk/benefit balance
- Beginnings of the IRB
The Era of Standards

- Standards accepted by researchers
- Standards accepted by media

JUDGEMENT

Beecher Article

- 22 studies performed unethically
  - Major journals
  - Respected researchers
  - Questionable study design
  - No informed consent

Beecher Article Studies

- Placebo trial of penicillin for strep throat
- Cyclopropane/CO$_2$ and ventricular arrhythmia
- Transplantation of melanoma
Impact of Beecher Article

“Until this article we assumed that unethical research could only occur in a depraved regime like the Nazis”
Robert J. Levine, MD

Media Exposés

- Thalidomide
- Jewish Chronic Disease Study
- Willowbrook Hepatitis Study
- San Antonio Contraception Study
- Tea Room Trade
- Milgram Study
- Study of Untreated Syphilis in Black Males

Study of Untreated Syphilis

- Purpose: Identify natural history of untreated syphilis

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Ethics of Human Subject Research for Investigators

Syphilis Study: History

• 1932: 300 black syphilitic males
• 1933: 300 controls added
• 1943: Penicillin for military
• 1949: Nuremberg Code
• 1951: Penicillin widely available
• 1966: Local ethics committee review

Syphilis Study: Results

• 28 deaths
• 100 cases of disability
• 19 cases of congenital syphilis

Syphilis Study: Problems

• Respect for persons
  No informed consent
  Deception
  Coercion
• Beneficence
  Withholding effective treatment
  Lack of effective continuing review
• Justice
  Vulnerable population
Syphilis Study Ad Hoc Panel

- Study be stopped immediately
- Inadequate oversight of human research
- Recommended Federal regulation of human research

Response to Research Abuses

- National Research Act
- May 1974 - 45 CFR 46
- June 1974 - National Commission
- April 1979 - Belmont Report
- 1981 - 45 CFR 46 revised

Applying Research Ethics
Protections of Federal Regulations

• IRB review
• Informed consent
• Institutional assurances

What Makes Research Ethical?

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<tr>
<th>BENEFICENCE</th>
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<tr>
<td>Social or scientific value</td>
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<tr>
<td>Scientific validity</td>
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<td>Favorable risk/benefit ratio</td>
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<table>
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<th>JUSTICE</th>
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<td>Fair subject selection</td>
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<td>Inclusion/Exclusion</td>
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<td>Recruitment</td>
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<th>RESPECT FOR PERSONS</th>
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<td>Initial and continuing informed consent</td>
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<td>Withdrawal from research</td>
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<td>Maintaining welfare of subject</td>
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Protocol Design: Beneficence

• Can the research design be improved?
• What are the risks? How can they be minimized?
• What are the benefits? How can they be maximized?
Ethics of Human Subject Research for Investigators

Protocol Design: Respect for Persons

• How can the consent process maximize autonomy?
• How can the protocol maximize autonomy?
• What additional protections can be in place for vulnerable populations?
• How can this study maximally protect subject privacy?

Protocol Design: Justice

• How can you ensure that recruitment targets the population that will benefit from the research?
• How can you ensure that recruitment will not unfairly target a population?
• How can the inclusion/exclusion criteria be made fair?

Key Issues in Research Ethics

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Some Key Issues

- Understanding the term “risk”
- Understanding the term “benefit”
- Ethics of placebo controlled trials
- Investigator-staff relationship
- Investigator-subject relationship

Definition of “Risk”

- Probability of harm occurring as a result of participation in research

Evaluation of Risks

- Quantitate by: Probability Magnitude
- Types: Social Physical Legal Economic Psychological
- May apply to: Individual Society
Definition of “Benefit”

• A valued or desired outcome; an advantage.
• Examine the probability of benefit occurring as a result of participation in a research study
• Payment for participation is not a benefit

Evaluation of Benefits

• Quantitate by: Probability Magnitude
• Types: Medical Psychosocial Kinship
• May apply to: Individual Society

When Is a Placebo Trial Ethical?

• Outcomes of placebo do not include death/disability
• Failsafe rescue from all bad outcomes of placebo
• When there is clinical equipoise between the active arm and placebo and the trial is designed to disturb the current state of clinical equipoise
Clinical Equipoise Defined

• Genuine uncertainty by experts about the merits of treatment arm versus placebo
• Clinicians disagree, but respect differences

Placebos and Respect for Persons

• When a placebo controlled trial is justified on the basis of clinical equipoise:
• Only include subjects in placebo controlled trials who also have equipoise.

Robert Veatch, PhD

PIs’ Relationship with Staff

• Many noncompliance investigations include a staff member who told the investigator there was something wrong …but was brushed off
Milgram Study: Purpose

- Determine response to authority
- Recruited volunteers to study learning and memory

Milgram Study: Methods

- Subject told to teach a “student”
- Punish errors with electric shocks
- “Student” was a confederate
- “Student” faked being a bad learner
- “Student” faked pain, unconsciousness

Milgram Study: Results

- 63% of subjects administered lethal shocks
- 65% after “student” revealed heart disease
**Milgram Study: Ethical Problems**

- Respect for persons - Deception
- Beneficence - Psychological harm

“I observed a mature and initially poised businessman enter the laboratory smiling and confident. Within twenty minutes he was reduced to a twitching, stuttering wreck, who was rapidly approaching a point of nervous collapse.”

Stanley Milgram

**Milgram Study: Lessons**

- People can readily perform unethical acts in the presence of an authority figure
- Authority relationships include:
  - PI over staff
  - Sponsor over PI
  - PI over subject
  - Protocol over PI

**Milgram Study**

- Learn team management (CRM)
- Encourage questions
- Listen
- Build consensus
- Eliminate intimidation
### Investigator-Subject Relationship

- The investigator must place the subject's rights, welfare and safety above all other personal and scientific concerns.
- Moral fiduciary relationship

### Moral Fiduciary Relationship

- Protecting research subjects is the investigator's primary concern.
- Investigator's self-interest is blunted by the obligation to protect the subject.
- Scientific knowledge, remuneration and prestige are side effects of being a fiduciary.

### Moral Fiduciary Relationship

- Similar to physician-patient relationship.
- But different:
  - Informed consent
  - Withdrawal from procedures
Moral Fiduciary Relationship

- Allows researchers to deal with conflict of interest
- Allows researchers to also be subject’s physician
- Basis of societal trust in researchers
- **ESSENTIAL**

Death of Normal Volunteer

- March 31, 1996 - Univ. of Rochester
- 19 year old Asian American student
- Responded to ad for bronchoscopy to harvest alveolar macrophages
- Had a very difficult bronchoscopy and required numerous doses of topical lidocaine

Death of a Normal Volunteer

- Investigators repeatedly asked subject if she wanted to continue and patient shook her head yes
- Returned in cardiac arrest with lidocaine overdose and died April 2, 1996
Investigation into Rochester Death

• Protocol did not limit lidocaine dose
• Lidocaine dose not documented
• No patient observation after bronchoscopy
• Lidocaine concentrations increased without IRB approval

Cause of Rochester Death

• Breach of moral fiduciary relationship
• Investigators should have withdrawn subject

Lessons from Rochester Death

• Acceptable risk for a patient may not be acceptable for a subject
• Informed consent does not equalize your knowledge and the subject's
• Use knowledge to protect subjects
• Withdraw subjects from trials who are not tolerating research procedures