Human Subjects’ Research

Learning Objectives

• Discuss key ethical concerns
• The role of the IRB
• Principles and origin of Belmont Report
• Principle of informed consent & considerations surrounding this
• Responsibilities to participants before, during and after study
A Little History

• It is important to look at history
  – We learn from our mistakes
  – History repeats itself!

• The Nuremberg Doctors Trial of 1946
• The Milgram Obedience Experiments
• Thalidomide Tragedy
• Untreated Syphilis Study – Tuskegee experiments
• Human Radiation Experiments

The Nuremberg doctors Trial
(Dec 1946-Aug 1947)

Twenty-three Nazi physicians charged with conducting inhuman experiments on German civilians and prisoners.

Examples:
• High altitude experiments
  – 40% of the 200 participants died
• Parachuting into cold water experiments
  – 300 prisoner-participants suffered a mortality rate of 30%
• Wound, burns, amputation, chemical and biological agent exposure experiments
• Mortality of 25% typical, many disabled or scarred for life
**The Nuremberg Code**

16 of 23 defendants found guilty of war crimes and crimes against humanity; 7 sentenced to death

Code of ethics developed in aftermath
1. Informed consent of volunteers essential
2. Anticipated results should justify experiment
3. Human experiments should be based on prior animal experimentation
4. Physical and mental suffering and injury should be avoided
5. There should be no expectation of death or disabling injury (*)
6. Degree of risk should be weighed by potential benefit
7. Proper preparation & precautions should be taken
8. Only qualified scientists should conduct medical research
9. Subjects has right to end experiment at any time
10. Scientist must be prepared to end experiment if subject at risk

**Nuremberg Aftermath**

While the Nuremberg Code and subsequent ethical guidelines represented the most enlightened thinking of the time, many well-intentioned researchers did not know about them or did not apply this guidance to their research activities.
**Tuskegee Syphilis Experiments (1932-1972)**

- Study of the evolution of syphilis
  - 600 impoverished African-Americans selected for study, 399 with syphilis, 201 without
  - Subjects never informed they were sick, and never treated for disease
  - Penicillin was by 1947 known as an effective cure for syphilis, yet subjects continued untreated
  - By 1972; 38 had died of syphilis, 100 of related complications, 40 wife's had been infected, and 19 children born with congenital syphilis

**Thalidomide Tragedy (1957-1961)**

- Wonder drug
  - Cure for insomnia, coughs, colds, headaches, morning sickness
- Doctors assumed drugs could not pass through placental barrier
  - Therefore drugs safe for non-pregnant women were considered safe for pregnant women
- Drug never approved for distribution in the US, but given out freely as part of medical trials
- More than 10,000 children in 46 countries born with severe birth defects
- Led to drug companies identifying vulnerable populations, and the need for special protections and testing
Human radiation experiments

• Large collection of experiments
  – 1949-1962 radioactive iodine given to newborns and pregnant women without consent to determine mortality and transmission
  – 1946-1957 injecting patients with uranium to determine how much the body could absorb
  – 1945-1946 plutonium injections
  – 1960-1973 irradiation experiments

• For more unethical human research in the US: http://en.wikipedia.org/wiki/Human_experimentation_in_the_United_States

The Milgram Obedience to Authority study (Yale 1961)

Designed to answer the question "Could it be that Eichmann and his million accomplices in the Holocaust were just following orders? Could we call them all accomplices?" (Milgram, 1974)

Subject was “teacher,” learner actor paid by researcher, followed script.

Subject asked to administer “electric shocks” when subject answered wrong

Deception used, causing psychological stress, no informed consent

http://www.youtube.com/watch?v=BcvSNg0HZwk
The Milgram Experiments

Milgram polled 40 psychologists asking them at what point the subject-teacher would break off, stop giving shocks and defy the experimenter.

Psychologists believed that less than 1% of subjects would administer the maximum 450 volts shock. They gave a figure of one subject in a thousand.

80 subjects, 30 levels

- 10th level (150V) – Subject asks to be released from experiment
  - 87.5% reach this stage
- 21st level (315V) – Screams in agony, begs to be released
  - 67.5% reach this stage
- 23rd level (345V) – Subject stops responding
  - 65% reach this stage
- 30th level (450V) – Max level
  - 63.75% reach this stage
The Milgram Experiments

“I observed a mature and initially poised businessman enter the lab smiling and confident. Within 20 minutes he was reduced to a twitching, stuttering wreck, who was rapidly approaching a point of nervous collapse.”

S. Milgram in *Obedience to Authority*

The Belmont report (1979)

*The Basic Principles:*

- **Respect for Persons**
  - individuals should be treated as autonomous agents
  - persons with diminished autonomy are entitled to increased protection
- **Beneficence**
  - persons treated ethically and their decisions respected
  - maximize possible benefits and minimize risks
- **Justice**
  - fairness in distribution

Federal Regulations derived from the Belmont Report (aka. “Common Rule”)

- Review of research by an IRB
- Informed consent of participants
- Institutional assurances of compliance
Institutional Review Board (IRB)

Purpose:
– Review research and determine if the rights and welfare of human participants involved in research are adequately protected

The IRB has authority to approve, require modification, or disapprove all research activities

Informed Consent

• Information:
  – Informed consent is a process of information exchange that takes place between the prospective investigator, before, during, and sometimes

• Comprehension:
  – Investigators are responsible for ascertaining that the participant has comprehended the information

• Voluntariness:
  – Agreement to participate in the research constitutes a valid consent only if voluntarily given
Investigator’s Responsibilities

Investigators bear the ultimate ethical responsibility for their work with human participants

Other responsibilities include:
- compliance with federal/state laws and regulations
- assuming fiscal management
- supervising and training of students, post docs, and residents
- complying with the terms and conditions of the sponsor’s award
- submission of all technical, progress, invention, and financial reports on a timely basis

Violations may result in loss of funding or debarment