2011 Ethics Update
Ethical Considerations of the Past & Present

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Syphilis Study in Tuskegee Begins

Monster Study

Nuremberg Trials Conclude

Inoculation Studies in Guatemala End

Jewish Chronic Disease Hospital Study

Millgram Experiments Begin

Syphilis Study in Tuskegee Ends

Declaration of Helsinki

Willowbrook State School Study Finish

Belmont Report

Common Rule Adopted

ICH E6

Common Rule Changes Proposed

National Research Act

Guatemala Study Discovered

Havasupai Settlement

Presidential Commission for the Study of Bioethical Issues Created


Research Ethics: Historical Events
Nuremburg Trials: 1946 - 1947

- Trials at Nuremburg – series of military tribunals in response to WWII atrocities in the concentration camps
- Many defendants argued that the experiments were morally justified
- 15 of the 25 defendants (20 MDs) were found guilty and 7 were sentenced to death
Developed as a direct result of the Nazi medical experiment atrocities committed during World War II that were revealed during the Nuremberg Trials

Adapted from a section of the August 1947 verdict called “Permissible Medical Experiments”

Makes clear that
- The welfare and rights of human subjects must be protected
- The research conducted must be sound and beneficial
- The freedom of human subjects to participate or not is inviolable
22 elderly patients who were hospitalized in Brooklyn, New York injected with live cancer cells.

Researchers claimed oral consent was given but not documented.

- Patients were not told that they would receive cancer cells because the investigators believed this would frighten the patients unnecessarily.

Investigators defended the conduct of the study on the basis that they had good cause to predict that the cancer cells were going to be rejected.
Designed to gain an understanding of the natural history of infectious hepatitis
- Test the effects of gamma globulin in preventing or ameliorating the disease

Children subjects were deliberately infected with the hepatitis virus
- Early subjects fed extracts of stools from infected individuals
- Later subjects received injections of more purified virus preparations

Investigators stated that the vast majority acquired hepatitis while at Willowbrook
- It would be better for them to be infected under carefully controlled research conditions
Obedience to Authority Study
- Measured willingness of subjects to obey an authority figure who instructed them to complete a task that conflicted with their conscience
- Subjects believed actual shocks were being given for incorrect responses

Many subjects realized they were capable of committing acts of extreme violence against others

Ethical questions raised due to the associated extreme emotional stress and insight into personal flaws inflicted upon the subjects
Declaration of Helsinki: 1964

- Developed by the World Medical Association (WMA)
  - Statement of the ethical principles that should be followed in the conduct of human subject research
  - Originally developed in 1964, and later amended 8 times, most recently in 2008
- Addresses ethical review, risk/benefit considerations, research with vulnerable populations and other issues related to protecting the autonomy, rights and welfare of participants
- Discusses use of placebos when effective treatments are available


- Subjects were disadvantaged, rural African-American men
  - 399 chosen who were infected and 201 who were not
  - Provided with free medical exams, free meals, and burial insurance, but were not told about their disease

- Men denied treatment
  - Penicillin was accepted treatment in 1943
  - PCN was available for syphilis treatment in 1952
National Research Act of 1974

- Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Charge to the Commission:
  - Identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects
  - Develop guidelines to assure that such research is conducted in accordance with those principles
The Belmont Report: 1979

- Issued April 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Distinguished between medical practice (treatment) and research
- Established the responsibility of the investigator to submit research activity for review by an Institutional Review Board
- Provided three pillars of ethical research
The Three Pillars of Belmont

Respect for Persons

Beneficence

Justice
Common Rule: 1991

- 45CFR46, Subpart A
  - The Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance

- Published in 1991

- Codified in the regulations of 15 separate agencies (hence the name, “Common Rule”)
  - Human subject research conducted or supported by each federal department/agency is governed by the regulations of that department/agency
Established the ICH E6 Guidelines on Good Clinical Practice (GCP)

- Designed as, “an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects”
- Generally agree with the Common Rule, but sometimes go farther

ICH E6 contains 8 parts
- Glossary, Principles of ICH E6, IRBs, Investigator, Sponsor, Protocol & Amendments, Investigators Brochure, Essential Documents
The Havasupai: 2010

- Specimens collected for diabetes research

- Informed consent obtained, but subsequent research outside the scope

- Havasupai v. Arizona State University
  - 2010 Settlement:
    - $700,000
    - Medical care & educational services
    - Return of known remaining specimens
Guatemala Inoculation Studies: 1946-1948

- US Public Health Service Sexually Transmitted Diseases Study of 1946-1948
  - Conducted by the same PI as the syphilis studies in Tuskegee

- Intent was to discover new ways to prevent STDs, including gonorrhea, chancroid & syphilis
  - Involved intentional infection of soldiers, prisoners and mental health patients

- ~1500 subjects involved
  - Governmental & Institutional officials were aware, but no subject consent obtained
  - Most, but not all, were treated for their infections
Presidential Commission for the Study of Bioethical Issues

- Established in light of the 2010 discovery of the Inoculation Studies in Guatemala

- Charge to the commission: To conduct a full review of the currently established HSP regulations and companion international standards to determine whether they sufficiently protect the health and well-being of participants
  - The Commission proceedings are ongoing

- May 2011 the Commission Chair stated that once its review of the currently established Human Subjects Protections is complete, the Commission would address the issues raised by the emergence of genome sequencing in the context of genetics research
Advanced Notice of Proposed Rulemaking

- Issued July 21, 2011

- Result of the work done by the Presidential Commission for the Study of Bioethical Issues

- The federal government is considering enhancements to the Common Rule
  - Data Security
  - Research classification
  - Modifications to informed consent documents & process

- Public comments are due by September 26, 2011
Resources

- CITI Program: www.citiprogram.org
- US Public Health Service Syphilis Study at Tuskegee (Timeline from CDC): http://www.cdc.gov/tuskegee/timeline.htm#
- Presidential Commission for the Study of Bioethical Issues: www.bioethics.gov