Institutional Review Board and Protection of Human Subjects in Research

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Ethical Issues on Research Involving Human Participants

- What is the goal of all research involving human participants?
  - To improve well-being of all people
- Why is human participant research justifiable?
  - Seeks knowledge and benefits many individuals and society
- Benefit to participants is not the purpose of research although it can happen.
- Individuals are the means in which useful knowledge is generated – maybe at risk of exploitation.
- Can such a goal be accomplished with full protection of the rights and dignity of the individual?

History of Medical Research

- Cowpox vaccination by Edward Jenner to protect children from smallpox (1798).
  - Noticed that milkmaids were less likely to contract smallpox.
  - Tested cowpox vaccine on his own child and other youngsters in the neighborhood.

Yellow Fever

- Italian bacteriologist, Guiseppe Sanarelli, claimed that he discovered a bacillus that caused yellow fever, since he found the isolates in 50% of the patients and caused yellow fever like symptoms in dogs injected with the agent (1897).
- Infected 5 persons with organisms that he claimed caused yellow fever, but never told the subjects.
- US surgeon general commissioned Walter Reed to identify the cause of yellow fever (1900).
  - Self-experimentation with members of the Yellow Fever Board serving as subjects.
  - Only adults enrolled.
  - Wrote contract stating the risks of the study and offered $100 to those willing to be exposed and another $100 to those who became ill with yellow fever.

Nazi War Crimes on Medical Research

- 23 Nazi doctors and bureaucrats were tried by the Allies at Nuremberg after WWII for using thousands of concentration camp prisoners as subjects in inhumane experiments (1946).
- 1750 victims officially identified in the indictment – many others not named.
- Telford Taylor, US brigadier general and chief counsel for the trial outlined the studies that were conducted.

Nazi Germany Experiments

- High-altitude (low-pressure) experiments
  - Prisoners were put into low-pressure tanks to see how long they could survive with little oxygen. Many who did not die immediately were put under water until they died. Autopsy followed.
- Freezing experiments
  - Prisoners were forced to remain outdoors without clothing in freezing weather for 9-14 hrs or forced to remain in bath of freezing water for 3 hrs at a time. Re-warming was attempted without success.
- Malaria experiments
  - Prisoners were infected with malaria and then given anti-malaria drugs, which killed the prisoners.
- Mustard gas experiments
  - Prisoners were deliberately wounded and the wounds then infected with mustard gas or forced to inhale mustard gas. Experiments for various treatment followed.

Nazi Germany Experiments (cont.)

- Typhus experiments
  - Prisoners were injected with an anti-typhus vaccine and then infected with typhus. Control group were infected with typhus but no vaccine.
- Poison experiments
  - Various poisons were fed to prisoners through their food. Those that did not die were killed for autopsy.
- Incendiary bomb experiments
  - Prisoners were burned with phosphorus material taken from incendiary bombs to study wounds.
- Sterilization experiments
  - Prisoners were subjected to chemical and x-ray sterilization experiments since surgical means were too costly and time-consuming.

Nuremberg Code

- During the Nuremberg Doctor's Trial, the judges specified ten conditions known as the Nuremberg Code summarized as follows:
  - "The voluntary consent of the human subject is absolutely essential."
  - Importance of scientific problem being investigated.
  - The careful design of the study.
  - The avoidance of death, suffering, or injury.
  - Need to assess risk.
  - The preparedness of the investigator to do the work.
  - The right of the participant to withdraw at any time.

Research in US

- Nuremberg Code and the Nazi Doctors' Trial did not provoke much response in US because they were considered an anomaly.
  - Assumed that researchers in democratic countries were immune from such acts.
- Secret experiments were being conducted during the war under the Manhattan Project in which hospitalized patients were injected with plutonium, without their knowledge.
  - Purpose was to assess and improve the safety of radiation workers and secondarily to evaluate the potential use of plutonium in bone cancer treatment.
- In December 1946, new civilian Atomic Energy Commission in the US suspended human studies involving the use of radioisotopes until standards were established and research was approved.
- One of the standards was to use the "informed consent".

Tuskegee Syphilis Study – "*Study in Nature*"

- 400 African American men with syphilis, 200 uninfected controls.
- No informed consent; told they were treated for "bad blood" – syphilis, anemia, fatigue
- They received free medical exams, free meals, and burial insurance.
- In early 1940's penicillin became widely available and was known to be an effective treatment for syphilis.
- The participants were neither informed nor received treatment.

Tuskegee Syphilis Study Revealed (1972)

- In July 1972, the Associated Press released the story to the nation
- Public outcry results in Ad Hoc Advisory Panel to review the study.
  - The men had agreed freely to be examined and treated, but were never told of the study or its real purpose.
  - Penicillin, drug of choice for syphilis in 1947 was not offered and subjects were not given the opportunity to quit the study and get proper treatment.
  - Recommend stopping the study at once in October, 1972
- Assistant Secretary for Health and Scientific Affairs stops the study in November 1972.
- 74 of the subjects were still alive and at least 28 but perhaps more than 100 had died directly from advanced syphilitic lesions.

Tuskegee Settlement

- In 1974, a $10 million out-of-court settlement was reached for study participants and their families.
- The Tuskegee Health Benefit Program (THBP) was established to provide lifetime medical benefits and burial services to all living participants.
- As of 2007, 19 widows, children and grandchildren are receiving medical and health benefits from THBP.
- Formal apology from the federal government was issued by President Clinton, accompanied by a $200,000 grant for the creation of the Tuskegee University National Center for Bioethics in Research and Health.

Tuskegee Aftermath

- National Research Act became law in 1974.
- Creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, as well as the enactment of federal regulations governing research with humans.
- Undermined the utilitarian justification of research and a push for informed consent as a moral obligation.

Summary

- Medical research has many examples where the rights and welfare of the participants have been violated.
- Need to understand how and why such events occurred and how the society dealt with the events.
- Past history reflect the larger social and ethical questions that still remain with us today.

Research Ethics

- Discipline that informs and responds to clinical and regulatory practice.
- Subsequent protective guidelines and regulations have been instituted in response to investigations that violated fundamental human rights and dignity.

Declaration of Helsinki (1964)

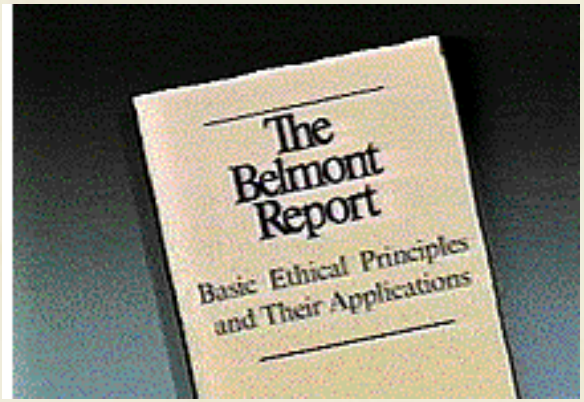
- Ethical principles for medical research involving human subjects.
- Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, June 1964.
- Allows for a legal guardian's consent when a participant is unable to provide consent.

US Policies

- Predecessor of Department of Health and Human Services (DHHS) issued policies for the protection of human subjects in 1996.
- It was not after the Tuskegee Syphilis Study was revealed that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 to make recommendation for the conduct of research involving humans.
- In 1979, the National Commission published a statement of the ethical principles that should guide a system of research with humans, the Belmont Report.

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 Principle

- Respect for persons
- Beneficence
- Justice

Respect for Persons

- This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorized representatives).
  - maximize individual autonomy
  - protection of individuals with reduced autonomy
    - Information to research subjects
    - Subject's comprehension of this information
    - Voluntariness of their consent

Beneficence

- This principle requires that researchers benefits and minimize harms associated with research. Research-related risks must be reasonable in light of expected benefits.
  - Maximize benefits and minimize harms

Justice

- This principle requires equitable selection and recruitment and fair treatment of research subjects.
  - Equitable distribution of research costs and benefits

Other Proposals by the National Commission

- Development of general guidelines for federally funded research with humans.
  - Informed participant consent
  - Prior ethical review by an institutional review board (IRB)
  - Proposed specific protections for certain historically vulnerable populations: children, pregnant women, fetuses, prisoners, and persons institutionalized with mental disabilities.

US Food and Drug Administration (FDA)

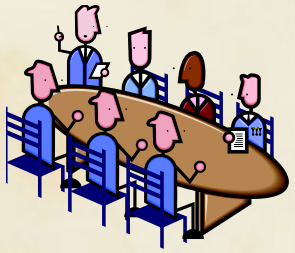
- FDA is responsible for the approval and licensure of drugs and devices for sale in the US.
- FDA requirements are largely in agreement with the Common Rule, particularly concerning the requirements of prior IRB review and of informed consent.

Ethical Framework
(Wendler et al., 2000, 2004)

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects
- Collaborative partnership

Institutional Review Board and Responsibilities

- A committee whose purpose is to ensure that the rights and welfare of human subjects are protected in all medical, behavioral and social sciences research.
- In accordance with federal and state regulations governing research, an IRB must review and approve research involving human subjects prior to its initiation.



Types of IRB

- Local – IRB at universities, hospitals, institutions, etc.)
- Commercial – IRB for multi-center, industry-sponsored, usually FDA drugs/device studies
- Consortium among universities (reciprocal, central, etc.)

Institutional Review Board Responsibilities

- The IRB has responsibility to determine:
  - whether proposed research exposes subjects to unreasonable or unnecessary risk
  - that the proposed research has scientific merit
  - to review informed consent forms and consent process
  - to monitor the progress of research

The Relationship between the IRB and the Principal Investigator

- The IRB's tasks are to help the principal investigator understand:
  - What is and is not appropriate research on human subjects.
  - The necessary prerequisites before research may be conducted on humans.
  - How best to protect each participant during the entire course of the research study.

Key Questions an IRB must ask

- How can the IRB protect human participants in this research?
- Is this study important enough to be carried out on human participants?
- What type of study is this?

Types of Clinical Research

- Medical Research
  - New medical products – look at safety and effectiveness of medical devices and prescription medicines.
  - New invasive medical interventions
- Social-Behavioral Research
  - Focus group
  - Survey
  - Epidemiological

Basic Concerns of IRB Work

- Conflict of Interest
- Participant Safety
- Informed Consent
- Materials Reviewed

Written Policies for Exempt Status

- IRB must have clear policy that allows for research that is exempt to be referred for further review or even be disqualified from exempt status altogether.

So, you need to submit an IRB application?

Types of Submission

Initial Submission

- Full Study
- Expedited
- Exempt

- Addendum
- Final Report

Elements of Consent Form

- Research statement (beneficence)
- Procedure - description of overall experience
- Foreseeable risks or discomforts
- Expected benefits to participants or others
- Alternatives

Elements of Consent Form (cont.)

- Confidentiality (respect for persons)
- Compensation or treatment for injury
- Contact information
  - research, rights as a research subject, and research-related injuries
- Voluntary participation statement (respect for persons)

IRB Decision Matrix

BENEFICENCE	JUSTICE
Risk/Benefit Analysis Experimental Design Qualifications of PI	Subject selection Inclusion/exclusion Recruitment

RESPECT FOR PERSONS

Informed consent Surrogate consent Assent	Privacy & Confidentiality Protection of subjects (especially vulnerable populations)