History of research Ethics

Origin of International Guidelines
History of Medical Research
Edward Jenner (1789)
Smallpox Vaccine

Claude Bernard (1865)
Ethical Maxims

Louis Pasteur (1885)
Rabies Vaccine

Walter Reed (1900)
Yellow Fever
During World War II

- Nazi doctors conducted as many as 30 different types of experiments on concentration-camp inmates
- performed these studies without the consent of the victims
- Who suffered indescribable pain, mutilation, permanent disability, or in many cases death as a result
The International Military Tribunals in Nuremberg 1946
The Nuremberg Military Tribunals in 1946

- 23 German physicians
- “performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts.”
Nazi Doctors Trial

- 11 supplemental trials
- 23 Nazi physicians were charged with conducting inhuman experiments on German civilians and nationals of other countries
- 16 defendants were convicted
- 7 were sentenced to death
The Nuremberg Code

- 1947
  - Developed by International Military Tribunal
  - The judgment included a set of standards known as the Nuremberg Code, an ethical yardstick.
  - First internationally recognized code of research ethics
The Nuremberg Code (1947)

As part of the verdict, the Court enumerated some rules for "Permissible Medical Experiments", now known as the "Nuremberg Code". These rules include:

- voluntary consent
- benefits outweigh risks
- ability of the subject to terminate participation

http://www.hhs.gov/ohrp/references/nurcode.htm
Nuremberg Code (1947)

- Informed consent from volunteers must be obtained without coercion.
- Human experiments should be based upon prior animal experimentation.
- Anticipated results should justify the experiment.
- Only qualified scientists should conduct research.
- Physical and mental suffering should be avoided.
- There should be no expectation of death or disabling injury from the experiment.
Study at Jewish Chronic Disease Hospital New York 1960’s

- 22 Elderly patients
- some with dementia, some spoke only Yiddish
- The participants were not informed that the injected material contained live cancer cells
- No review committee and no approval was sought from attending MDs providing care.
- Need for informed consent in research
- guardians not asked for permission
- consent deceptive, inadequate, & not translated

The Thalidomide Study 1961

- Thalidomide was approved as a sedative in Europe in the late 1950’s.
- The FDA never approved the drug, but samples were sent to US doctors.
- By 1961 thalidomide was shown to be very harmful to the fetus, interfering with the normal development of arms and legs.
The Thalidomide Study

Results

- These events lead to the passage of the Drug Amendments of 1962 to the Food, Drug and Cosmetic Act

- This was the first US statues that required subjects be informed of a drugs experimental nature and to consent before starting the research study
The Milgram Study (1963)

- The study was on obedience and humans’ response to authority.
- The subjects were deceived as to the nature of the study and were told it was a teacher/learner experiment.
- The “teachers” were told to give the “subject” an electrical shock for missed answers.
Criticism of the Milgram Study

- Informed consent had not been obtained because of the Deception
- Federal regulations specifically allow for deception in research, but only in limited conditions and only with IRB approval
- Extreme psychological stress experienced by most subjects
Declaration of Helsinki (1964)

- Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964

- It is the mission of the physician to safeguard the health of the people
- Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects
Declaration of Helsinki

- **Respect for Persons** – people are not a means to an end; researchers have duty to protect life, health, privacy and dignity of research participants

- **Standard of care** must be best available, even for control group

- Proxy consent and assent for vulnerable populations

- Placebo
“The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent…”

In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.”
Willowbrook Hepatitis Study
(1956-1972)

- 800 Children - Willowbrook State School for the Mentally Retarded
- Newly admitted mentally disabled children were inoculated with infectious hepatitis
- Objective: to determine the period of infectivity for the disease
- Researchers injected students with mild form of hepatitis
- Parents were not informed of the risks
- Benefit of study for participants: better hospital facilities and care for the children
- Coercion of parents
22 published medical studies presenting risk to subjects without their knowledge or approval

Published in some of the most prestigious journals and conducted at some of the most prestigious institutions

- perform heart catheterizations on patients getting a bronchoscopy [look at breathing passages through a tube]

- placebo control groups in life-threatening diseases with known effective treatments - several

- randomize soldiers with strep throat to penicillin vs. treatments known-to-be-ineffective [ineffective treatment may lead to rheumatic heart disease]
NIH Director and Surgeon General requested that the National Advisory Health Council review human subject protections.

Council recommended prior institutional review for PHS supported research to:
- Protect the rights and welfare of the subjects
- Assure appropriate methods of informed consent
- Determine acceptable balance of risks and benefits

Adopted as Public Health Service policy in 1966.

U.S. Federal Regulations Policy and Guidelines

- DHHS - 45 CFR Part 46 (The Common Rule)
- FDA - 21 CFR (First developed and promulgated 1962-1966)
  - Part 50 (Informed Consent)
  - Part 56 (IRBs)
  - Part 312 (Drugs)
  - Part 812 (Devices)
- Department of Education
  - 34 CFR Part 97
- NIH assurance (FWA)
The main elements of the Common Rule

- requirements for assuring compliance by research institutions;
- requirements for researchers obtaining and documenting informed consent;
- requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.
- additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children
45CFR.46 Protection of Human Subjects

- Composition and function of a local institutional review board (IRB)
- Criteria for IRB approval of proposals
- Requirements regarding informed consent
The Tuskegee Study of Untreated Syphilis in the Negro Male
Tuskegee Syphilis Experiment
(1932-1972)

- US Public Health Service study on natural history of syphilis
- 399 black men with syphilis were recruited. They were mostly illiterate
- They were not informed about their disease, the nature of the study, the risk to the partner
- Offers for free examination, medicines, insurance, hot meal, transportation.
- No treatment for the disease.
Second phase began in 1933

- To strengthen validity and gain more data
- A control group of 201 black men were added
- Autopsies of deceased subjects
- No informed about the purpose of the study
- Government doctors were examining people for bad blood
Syphilis Study

The rationale published by the investigators for their decision regarding the lack of treatment provided to the infected "Negro" population:
"...Such individuals seemed to offer an unusual opportunity to study the untreated syphilitic patients from the beginning of the disease to the death of the infected person. An opportunity was also offered to compare the syphilitic process uninfluenced by modern treatment with the results attained when treatment had been given."
“Sometimes, with the best of intentions, scientists and public officials and others involved in working for the benefit of us all, forget that people are people. They concentrate so totally on plans and programs, experiments, statistics - on abstractions - that people become objects, symbols on paper, figures in a mathematical formula or impersonal ‘subjects’ in a scientific study.”

*Atlanta Constitution, 1972*
Several bills to regulate research were introduced in congress in 1973

Senator Edward Kennedy held hearings on Experimentation with human subjects, the study was stopped and treatment was given as needed

Government would pay all medical expenses for the survivors, their wives and children who were born with congenital syphilis
President Clinton issued a formal apology to the subjects and their families.
1974 The National Research Act

- Regulations for the protection of human subjects
- Requirement for informed consent
- Review research by the institutional review boards
- Created the commission for the protection of human subjects of Biomedical and Behavioral research
The Commission

- Identifying the basic ethical principles
- Develop guidelines to assure that the research is conducted in accordance with those principles
- Consider the boundaries between medical practice and research
- Role of assessment of risk and benefit
- Selection of subjects
- Nature and definition of informed consent
1979 National commission wrote the “Belmont Report”
The Belmont Report

Basic Ethical Principles:

- Respect for Persons
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- Beneficence
  - Maximize benefits and minimize harms
- Justice
  - Equitable distribution of research costs and benefits
CIOMS/WHO Guidelines

Council for International Organizations of Medical Sciences

• Their scope reflects the changes, the advances and the controversies that have characterized biomedical research ethics.

• CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects,
CIOMS/WHO Guidelines

- provides guidance for the proper application of the principles of the Declaration of Helsinki and focuses particularly on research sponsored by or initiated in developed countries and carried out in developing countries.

- The CIOMS-WHO Guidelines added, among other things, a requirement for review and approval of all proposed research by an "ethical review committee"
Other Guidelines

- ICH GCP Guideline 1996
- UNAIDS guidance document: Ethical consideration in HIV Preventive Vaccine research, 2000
- WHO Operational Guidelines for Ethics Committees that review Biomedical research, 2000
- WHO Surveying and Evaluating Ethical Review practices, 2002
The aim of these guidelines is to provide guidance for ethics committees concerning appropriate operating procedures.
Research Ethics Milestones

Trigger Events

*The Nazi Experiments 1946
Jewish Chronic Disease Hospital 1960
The Thalidomide Study 1961
*Milgram Study 1963
Willowbrook 1972

Ethics Milestones

Nuremberg Code 1947
Amendments to the FDA Act 1962
Declaration of Helsinki 1964

*From “Protecting Study Volunteers in Research” Dunn & Chadwick
Research Ethics Milestones

**Trigger Events**

*The Beecher Article 1966*

*The Syphilis Study Expose*

**Ethics Milestones**

US Federal Regulations

The Belmont Report 1979

Consolidated HHS/FDA Regulations 1981

CIOMS Guidelines 1982

ICH GCP

National Bio-Ethics Advisory Committee
Developed to observe the “rules of the road” for research involving human participants.
The Evolution of Research Ethics

Codes, guidelines and regulations developed to observe the rules of the road for research involving human participants.
The Nuremberg Code

- Informed consent is absolutely essential
- Qualified researchers use appropriate research designs
- Favorable risk/benefit ratio
- Participant must be free to stop at any time
The Declaration of Helsinki

• “The well-being of the subject should take precedence over the interests of science and society”

• Consent should be in writing

• Use caution if participant is in dependent relationship with researcher

• Limited use of placebo

• Greater access to benefit
The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

- Respect for persons
- Beneficence
- Justice
The U.S. Code of Federal Regulations (also called *The Common Rule*)

- Prior approval by ethics committee
- Written informed consent and documentation
- Equitable recruitment of research participants
- Special protection for vulnerable groups
- Continuing review of approved research
Council for International Organizations of Medical Science (CIOMS) Guidelines

- informed consent
- research in developing countries
- protection of vulnerable populations
- distribution of the burdens and benefits
- role of ethics committees
International Conference on Harmonisation (ICH)

- Standardize drug development and approval process
- Protocol development standards
- Review by ethics committee
- Researcher responsibilities
- Sponsor responsibilities
National Bioethics Advisory Committee (NBAC)

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

- Responsive to local needs
- Community involvement
- Placebo use only when justified
- Access to benefits
- Focus on informed consent
From Fundamental Ethical Principles to Local Guidelines

- Respect for Persons, Beneficence, Justice
  - National regulations
  - Institution operational guidelines
  - International recommendations
Local Regulations and Guidelines

- Many countries now have national guidelines
- Rapid growth of research on a global scale
- Greatest need is in developing countries
Summary—Principles and Foundations of Research Ethics

- All codes and regulations advocate 3 fundamental principles:
  - respect for persons
  - beneficence
  - justice

- Research is a privilege, not a right

- The well-being of the participant is paramount