Research Ethics

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Objectives

- Historical events
- Development of ethical principles
- Role of Institutional review boards
- Essential elements of informed consent

Research Ethics

Definition

Ethics have been defined as the science of the ideal human character; the discipline dealing with what is good and bad with moral duty and obligation; a group of moral principles or set of values; a code of conduct or behavior governing an individual or a group.(Members of a profession, e.g. Medical Ethics); Ethical implication resonates such as moralistic, noble, principled, righteous, right-minded, virtuous.

The Nuremberg Doctors Trial of 1946

- The Nazi regime exploited human beings by forcing them to participate in research without consent.
- The mortality rate of these war time research studies was typically 25 - 30%.
- The Nuremberg Trials were heard from 12/46 to 8/47
- defendants (20 were physicians) were charged with murder, torture and other atrocities committed in the name of medical science.
- Many defendants argued that the experiments were morally justified since the participants were going to die anyway and their sacrifice would provide scientific knowledge benefiting many.
- 15 of the 25 defendants were found guilty and 7 were sentenced to death.
- The judgement included a set of standards known as the Nuremberg Code, an ethical yardstick.

The Nuremberg Code

- Developed as a direct result of the Nazi medical experiment atrocities committed during World War II that were revealed at 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 meaning **sacred**

Basic Principles
The Nuremberg Code

- Informed consent of volunteers must be obtained without coercion in any form
- Human experiments should be based upon prior animal experiments
- Anticipated scientific results should justify the experiment
- Only qualified scientists should conduct medical research
- Physical and mental suffering and injury should be avoided
- There should be no exception of death or disabling injury from the experiment

The Jewish Chronic Disease Hospital Study

- Studies begun in 1963 at New York City's Jewish Chronic Disease Hospital to develop information on the nature of the human transplant rejection process.
- Studies involved the injection of live cancer cells into patients who were hospitalized with various chronic debilitating diseases.
- Previous studies had indicated that healthy persons reject cancer cell implants promptly. Patients with widespread cancer also reject homographs, however, rejection is delayed substantially when compared with healthy subjects.

The Jewish Chronic Disease Hospital Study

- Researchers said that consent had been given orally, but was not documented. Documentation was felt unnecessary because it was customary to undertake much more dangerous medical procedures without the use of consent forms.
- 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.

The Willowbrook Study

- From 1963 through 1966, studies were carried out at the Willowbrook State School, a New York State institution for "mentally challenged persons."
- These studies were designed to gain an understanding of the natural history of infectious hepatitis and subsequently to test the effects of gamma globulin in preventing or ameliorating the disease.
- The subjects, all children, were deliberately infected with the hepatitis virus; early subjects were fed extracts of stools from infected individuals and later subjects received injections of more purified virus preparations.

The Milgram Study

- The study was on obedience and human's 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.

The Milgram Study

- 60% of the “teachers” were persuaded to give shocks up to the highest level, even after the “subject” (acting the part) appeared to lose consciousness.
- At the study debriefing many of the “teachers” justified their actions by saying they were only following instructions.
- The role of deception in human subject research continues to be debated even today.

The Thalidomide Study

- 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.
- Lead to the 1962 passage of the Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act.

Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act

- Passed in 1962 in response to the thalidomide disaster.
- Amended the Food, Drug and Cosmetic Act of 1938
- Required the sponsor to prove efficacy in order for a drug to be marketed.
- Authorized the FDA to establish official names for drugs.
- The first US statue that required subjects be informed of a drugs experimental nature and to consent before starting the research study.

The Beecher Article

- Beecher HK. Ethics and clinical research. The New England Journal of Medicine, 1966, 274: 1354–1360.
- Cited serious ethical problems including inappropriate risk exposure, questionable scientific design and no documentation of consent in 22 research studies.
- This lead to the 1982 Council for the International Organization of Medical Sciences (CIOMS) guidelines: the International Ethics Guidelines for Biomedical Research Involving Human Subjects.

Declaration of Helsinki

- 31 principles
- Is the international standard for the conduct of clinical research
- Is the standard for the conduct of clinical research adopted by International Conference on Harmonization (ICH) Good Clinical Practice (GCP Adapted from the Nuremberg Code by The World Medical Association to address the needs of the biomedical community
- First published in 1964, revised five time most recently in 2001
- Lists) standards

Declaration of Helsinki Basic Principles

1. Conform to accepted scientific principles
2. Design formulated in experimental protocol
3. Conducted by qualified persons
4. Importance in proportion to inherent risk
5. Assessment of risks vs. benefits
6. Safeguard subject's integrity (privacy)
7. Abstain unless hazards are predictable
8. Preserve accuracy when publishing
9. Adequately inform/right to withdraw
10. Obtain true informed consent
11. Reliance on legal guardian
12. State compliance with Declaration

Declaration of Helsinki, Basic Principles

- "Concern for the interests of the subjects must always prevail over the interests of science and society"
- The experimental protocol must be reviewed by a "specially-appointed committee independent of the investigator and the sponsor."
- Distinguishes between research "in which the aim is essentially diagnostic or therapeutic for a patient" and research "which is purely scientific."
- In research which does not offer the prospect of direct benefit to the participant is restricted to healthy volunteers or volunteers "for whom the experimental design is not related to the patient illness."

Declaration of Helsinki, Basic Principles

"In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists."

- One of the most controversial stipulations in the declaration. Interpreted by some as prohibiting the use of placebo whenever effective therapy is available.

The Study of Untreated Syphilis (Tuskegee Study)

- Started in Macon County, Alabama in 1932 on Male Blacks
- Penicillin was accepted as the treatment for syphilis in 1943.
- It was widely available for syphilis treatment by 1952 but was withheld from the study subjects.
- The study was exposed in 1972, the subjects were given treatment by 1973 and the treatment was extended to the families of the subjects in 1975.

Outcomes of the Syphilis Study

- This lead to the National Research Act of 1974, requiring regulatory protection for human subjects.
- The National Research Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- This commission wrote the "Belmont Report" in 1979, which is the cornerstone statement of ethical principles for treatment of research subjects.
- In 1981 the DHHS and the FDA published convergent regulations that were based on the Belmont Principles.
- In 1991, after 10 years of negotiation, 17 federal departments and agencies agreed to adopt the basic human subjects protections. This is referred to as the "Common Rule".

National Research Act

- Passed in 1974 as a result of the publicity from the Tuskegee Syphilis Study
- 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 which should be followed to assure that such research is conducted in accordance with those principles.

The Belmont Report

- Issued in April of 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Made necessary due to a long history of various questions, concerns,difficulties and problems that arose in medical experimentation and other forms of research efforts involving the enrollment of human subjects
- Distinguished between medical practice (treatment) and research
- Established the responsibility of the investigator to submit research activity for review by an institutional review board
- Established three ethical principles that should guide the resolution of ethical problems arising from research involving human subjects
  - » Respect for Persons
  - » Beneficence
  - » Justice

Belmont Report

Part A

Boundaries between Practice & Research

<u>Practice</u> "refers to interventions that are designed to enhance the well being of an individual or patient that have an expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, treatment or therapy for an individual.

Belmont Report part A

- Research ‘ designates an activity to test hypothesis, permit conclusions to be drawn, and thereby to develop or to contribute to generalizable knowledge.

Research is described in a formal protocol that sets objectives and set of procedures designed to reach that objective (s).

Basic Principles
The Belmont Report

RESPECT FOR PERSONS

The freedom and capacity of subjects must be protected.

Each subject is an autonomous agent.

Special measures must be taken to protect the rights and welfare of persons with diminished autonomy.

Informed consent is central to protecting the autonomy of human subjects.

Belmont Report Part B

Beneficence

1. Do not harm
2. Maximize possible benefits and minimize possible harms

Basic Principles
The Belmont Report

JUSTICE

...Researchers must ask: *"Who should receive the benefits of research and bear its burdens?"*

...There must be fairness in the distribution of the risks and benefits of the research.

...Each person must equally share in the risks/benefits distribution: according to individual need, individual effort, societal contribution, and merit.

U.S. Federal Regulations

- Directly derived from the ethical principles of the Belmont Report
- Adopted in 1991 by 17 federal departments and agencies, hence the name "the Common Rule"
- Governs research that is conducted or supported by these federal agencies
- Main elements of The Common Rule include:
  - » 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

U.S. Federal Regulations

Codified as Title 45 Code of Federal Regulation 46 (45 CFR 46) Federal Policy for the Protection of Human Subjects and consists of 4 parts:

- Subpart A - Basic DHHS Policy for the Protection of Human Research Subjects
- Subpart B - Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization
- Subpart C - Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional DHHS Protections for Children Involved as Subjects in Research.

U.S. Federal Regulations

The Food and Drug Administration (FDA) has a separate set of regulations governing human subjects research

- 21 CFR 56 – governing IRBs
- 21 CFR 50 – governing Informed Consent

The basic requirements for IRBs and for Informed Consent are congruent between the two sets of regulations.

- The Common Rule is based on federal funding of research.
- FDA regulations are based primarily on use of FDA regulated products: drugs, devices, or biologics.

Human Radiation Experiments

- Expose in the November 1993 Albuquerque Tribune
- Subjects were unknowingly injected with plutonium
- The research was government sponsored
- The Advisory Committee on Human Radiation Experiments (ACHRE) was formed in January 1994
- This lead to the National Bioethics Advisory Commission (NBAC)

National Bioethics Advisory Commission (NBAC)

- Established October 3, 1995 by Executive Order to provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding:
  - The appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior
  - Applications, including the clinical applications, of that research.
  - Identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.
- Is not responsible for the review and approval of specific projects

Informed Consent Requirements (ICR)

What is Informed Consent?

- Inform: to impart information, to teach…
- Consent: to allow what is planned, voluntary acceptance…

Valid Informed Consent

To be valid, informed consent can only be granted when the subject fully understands the information that has been presented

Responsibility of Informed Consent

The clinical investigator

- It may be delegated but ultimate responsibility remains with the clinical investigator, ensuring that informed consent is obtained from each research subject participating in the research study.

Informed Consent Regulations

- FDA Regulation 21 CFR Part 50
  Protection of Human Subject
- DHHS Regulation 45 CFR Part 46
  Protection of Human Subject

Required Basic Elements of Informed Consent

1. Statement:
   - Study involves research
   - Duration of the study
   - Description of all procedures
2. Description of:
   - Foreseeable risks to the subject
3. Benefit to the subject or to others expected from research

Required Basic Elements

4. Disclosure of alternative procedures or courses of treatment
5. Maintaining Confidentiality of records
6. Research involving more than Minimal Risk, whether treatment or compensation are available, if an injury occurs.
7. Contact information

Required Basic Elements

8. Statement:

   Participation is Voluntary

   Refusal to participate without penalty or loss of benefits.

   Discontinuing participation without penalty or loss of benefits.

Additional Elements

1. Treatment or procedure may involve risk to the subject or(to embryo or fetus) if the subject is or may become pregnant which is currently unforeseeable.
2. The Investigator may terminate the subjects participation regardless opf the consent.

Additional Elements

3. Additional costs of participation
4. Approximate number of subjects involved in the study.
5. Orderly termination of participation if the subject withdraws from the study.
6. Significant new findings developed during the course of the research will be provided to the subject.

Institutional Review Board (IRB)

Definition of IRB

Any board, committee or group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects

IRB Membership

- Minimum of 5 members are required to formulate the IRB.
- Members should have varying background to adequately review research proposals.
- Diversity including consideration of race, gender, cultural backgrounds and sensitivity community attitudes.
- Members should be knowledgeable when reviewing research for vulnerable populations such as (children, prisoners, pregnant women, handicapped or mentally disabled persons)

Duties of IRB

1. Review of research
2. Informed consent
3. Assurance of compliance by the institution.

IRB Regulations

21 CFR 56
- general standards for IRB's

21 CFR 50
- informed consent requirements

21 CFR 312
- contains IND requirements

21 CFR 812
- contains IDE requirements

Working within the boundaries

- Research Question
- Proposal
- References
- Conducting Research
- Data collection
- Interpretation of collected data
- Results
- Publications

Ethical Responsibility

- Investigators bear the ultimate ethical responsibility for their work with human subjects.
- Society entrusts them with the privilege of using other humans to advance scientific knowledge.
- Society expects investigators to show respect for research subjects.
- The research community as a whole suffers when even a few investigators ignore basic principles of ethics.
- Compliance should be seen as the “right thing to do” because it helps protect the rights and welfare of the subjects of human research.

Conclusion

"It is essential that the research community come to value the ethics of research as central to the scientific process."

National Bioethics Advisory Commission

Thank You