

Fundamental Principles of Human Subjects Research

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Overview

- The evolving understanding of the ethical foundations of research
- Ethical principles of research
- Three pillars of subject protection

Early Protections

- Self-experimentation
- Great attention to minimization of risk
- Distinctions between normal volunteers and patient-subjects with respect to consent

Nuremberg Code

- Voluntary Consent
- Anticipate scientific benefits
- Benefits outweigh risks
- Animal experiments first
- Avoid suffering
- No intentional death or disability
- Protection from harm
- Subject free to stop
- Qualified investigators
- Investigators stop if harm occurs

Declaration of Helsinki

- Issued by the World Medical Association in 1964
- Major revisions in 1975, 1983, 1989, 1996, and 2000 (with 2 later clarifications regarding placebos and access to effective therapies following research)
- Three part document
 - Introduction
 - Basic principles
 - Research combined with clinical care

Ethics and Clinical Research

- Henry Beecher
- Chronicles 22 'unethical' studies, from publications in respected medical journals
- Published in the *NEJM* June 1966

Willowbrook Hepatitis Experiments

- Inoculation and injection of hepatitis
- Institutionalized children
- Admission through the research unit

Jewish Chronic Disease Hospital Cancer Experiments

- Injection of live cancer cells
- Hospitalized elderly patients
- Patients not told of live cancer cell injection

US Public Health Services Study of Untreated Syphilis in the Negro Male

- Often referred to as the “Tuskegee Syphilis Study”
- Poor, rural community
- Initiated as a natural history study when there were no effective treatments
- Promise of “funeral benefits”
- Effective treatments (penicillin) arose in course of study, but not made available to subjects

National Commission Belmont Principles

- Respect for Persons
- Beneficence
- Justice

Respect for Persons

- Philosophical principle of autonomy
- Political principle of liberty
- The right to be left alone

Beneficence

- *Beneficentia* = Favor, benefit
- In health care, an obligation to improve health
- In research, an obligation to maximize benefits and minimize risks

Justice

- Fairness
- Treat equals as equals
- Originally conceived as protection, now as access

Three Pillars of Protection

- Investigators and sponsors
- Informed consent
- Oversight

Investigators and Sponsors

Good Clinical Practice

- Protection of participants
- Credibility of results

Credible Results

- Scientific design
- Responsible conduct of research
- Responsibilities of sponsors
- Responsibilities of investigators

Informed Consent

- Two senses of consent
- The process of consent
 - Threshold
 - Decision-making capacity
 - Voluntariness
 - Information
 - Disclosure
 - Understanding
 - Consent

The Need for Oversight

- Many research scandals emanated from practices that did not meet current standards and prospective review might have avoided the occurrence
- Independence may serve as a check on the enthusiasm of investigators and sponsors
- Randomization with masking (or blinding or concealment) poses special issues for providing protection for those enrolled in these trials and in properly interpreting adverse events

Oversight

- Institutions
- Federal agencies
- Accrediting bodies (PHRP, AAHRPP)
- DMCs
- IRBs

Institutional Review Boards

- Prospective review
 - Selection of subjects
 - Minimize risks and maximize benefits
- Continuing review of research, at least annually
- Informed consent
- Adverse events

The I in IRBs: Why Local Review?

- Assumption that ethics is local and that local oversight would be the best means of ensuring the protection of research participants
- Concern about bureaucratic hassles and insensitivity to local interests/values that would be associated with a centralized or government panel review

Enlarging the Scope

- Attention to the design of research
- The importance of community input and partnerships
- Responsibilities regarding access to experimental treatments

Concluding Comments

- The regulation of research ethics is a public activity
- Attention to the ethics of research is essential to respect those who choose to participate
- Although investigators and sponsors retain significant moral responsibility for protecting the rights and interests of participants in research, 'external' bodies can provide additional protection
- The key to successful oversight often involves an independent group review

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