The Ethical Conduct of Research Involving Human Subjects

Pharm 543

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Agenda

- Why ethics in clinical research
- Basis in tort law
- Definition of research
- Belmont Report
- Informed Consent
- Common Rule
- Institutional Review Board
- "Exempt" research

Why Ethics in Clinical Research?

- Research ethics have developed in response to events which are today considered 'unethical'
- Human experimentation without consent
  - 1947 Nuremberg Code as a response to Nazi Germany and Japanese research in Manchuria
  - 1950s/60s United States
    - Jewish Chronic Disease Hospital - elderly were injected with live cancer cells to study natural history
    - Willowbrook State School NY - mentally handicapped children injected with live hepatitis viruses
    - Tuskegee Syphilis Study (1932-1972+)
    - and more . . .

Legal Action and Consequences Informed Consent **(patient-provider context)**

Canterbury v. Spence 152 US App DC 263; 464 F2d 772; 1972

The patient's right of self-decision can be effectively exercised only if the patient possesses enough information to enable an intelligent choice.

The patient should make his own determination of treatment. Informed consent is a basic social policy for which exceptions are permitted:

(1) where the patient is unconscious or otherwise incapable of consenting, and harm from failure to treat is imminent; or

(2) when risk-disclosure poses such a serious psychological threat of detriment to the patient as to be medically contraindicated.

Legal Action and Consequences Informed Consent [2]

- Social policy does not accept the paternalistic view that the physician may remain silent because divulgence might prompt the patient to forego needed therapy.
- Rational, informed patients should be expected to act uniformly, even under similar circumstances, in agreeing to our refusing treatment.

Why Informed Consent?

- Cornerstone of health law
  - tort theory of battery
    - tort - a wrongful act, not including a breach of contract or trust, that results in injury to another's person, property, reputation, or the like and for which the injured party is entitled to compensation
    - battery - an unlawful attack upon another person by beating or wounding, or by touching in an offensive manner

What is Research?

- Research
  - Systematic investigation, including research development, testing and evaluation, designed to develop or contribute to *generalizable knowledge* 45CFR46.102 (d)
- 1979 - The Belmont Report
  - Established 3 ethical principles for conducting biomedical and behavioral research

The Belmont Report

- Non-validated practices
  - Application of novel procedures as ... When deviations from common drug administration … are tried in the course of rendering treatment
  - Concern that innovative therapies are being applied in an unsupervised way, as part of practice

Elements of Informed Consent

- 1980s - President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research
  - disclosure
  - comprehension
  - voluntariness
  - competence
  - consent

The Belmont Report

Principle	Application
Respect for persons	Informed Consent ■information ■comprehension ■voluntariness
Beneficence	Risk/Benefit Assessment
Justice	Selection of Research Subjects

PROTECTION OF HUMAN SUBJECTS
45 CFR §46.116 and §46.117

1. Study involves research, an explanation of purposes, expected duration of the subject's participation, procedures, and identification of researchers
2. Reasonably foreseeable risks or discomforts
3. Benefits to the subject or to others which may reasonably be expected from the research
4. Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

PROTECTION OF HUMAN SUBJECTS
45 CFR §46.116 and §46.117

5. Extent, if any, to which confidentiality of records identifying the subjects will be maintained
6. For research involving more than minimal risk, whether any compensation, and an explanation as to whether any medical treatments are available if injury occurs, and, if so, what they consist of or where further information may be obtained

PROTECTION OF HUMAN SUBJECTS
45 CFR §46.116 and §46.117

7. An explanation of whom to contact for questions in event of a research-related injury to the subject
8. Voluntary, no penalty or loss of benefits for refusal, subject may discontinue participation at any time

"The Common Rule"
5 USC 301; 42 USC 300v-1(b); and 42 USC 289
45 CFR 46 Subpart A

- *Human subject* means a living individual, about whom an investigator (whether professional or student) conducting research obtains:

1. Data through intervention or interaction with the individual, or
2. Identifiable private information

"The Common Rule"
45 CFR §46.102 (f)

- The Common Rule requires that a research institution, as a condition for receiving federal research support, establish and delegate to an IRB the authority to review, stipulate changes in, approve or disapprove, and oversee human subjects protections for all research conducted at the institution

from Advisory Committee on Human Radiation Experiments

Institutional Review Board (IRB)
45 CFR §46.111

1. Risks to subjects minimized
2. Risks to subjects must be reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent must be sought as per the regulations
5. Informed consent must be documented
6. Adequate provision for data monitoring to ensure subject safety
7. Adequate provisions for privacy protection
8. If relevant, additional safeguards for "vulnerable" populations

Research Exempt from Federal Regulations 45 CFR §46.101

- Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subject
- Other … like some educational research
- Research that is not funded by Federal Agencies or representatives of such agencies

Investigational New Drugs (INDs)

21 CFR 56
21 CFR §312.23

- An IRB will be responsible for initial & continuing review and approval
- Investigator will report
  - Protocol changes
  - Unanticipated problems involving risk to subjects/others

So how big an issue is this?

(see USN&WR story Oct. 11/99)

- National Cancer Institute audits:
  - Researchers neglected to record or report serious adverse reactions to experimental drugs - including deaths
  - Patients were coerced into waving legal rights in case of malpractice
  - Researchers placed patients in trials that were medically inappropriate

So how big of an issue is this?[2]

- National Cancer Institute audits:
  - Institutions allowed researchers who had financial interests in cancer studies to conduct reviews of those studies, in violation of federal regulations
  - Doctors failed to accurately inform patients of the benefits and risks of a study or to describe alternatives that might be more efficacious

Death on Gene Therapy

- Jesse Gelsinger
- 18yo, ornithine transcarbamylase deficiency syndrome
- Adenovirus vector
- Multiple organ failure → death

- Conflict of interest, data safety monitoring, informed consent

FEDS TO INVESTIGATE CANCER CENTER TRIALS

- SEATTLE (AP) The surgeon general has called for a federal investigation into cancer trials at the Fred Hutchinson Cancer Research Center that are the subject of a proposed class-action lawsuit.

- The lawsuit filed last month in Kitsap County Superior Court claims violations of laws on medical ethics, consumer protection and the use of humans in research in the mid-1980s trials. It seeks unspecified damages on behalf of 82 Hutchinson center patients….

Apr 12, 2001; AP

Further lessons from the TGN1412 tragedy

- First trial of TeGenero's TGN1412 (a T cell agonist) in humans
  - Parexel's clinical pharmacology research unit at Northwick Park Hospital, London.
  - Six subjects
  - Immediately suffered potentially lethal 'cytokine storms'
  - 2 left with long-term disabilities
  - TeGenero went bankrupt last July
- Predicting safe dose in humans

BMJ 2006;333:270-271 (5 August); Nature Biotechnology 25, 485 - 486 (2007)

- National Institutes of Health
  - **Office for Human Research Protections (OHRP)**
  - www.hhs.gov/ohrp/

- University of Washington
  - Human Subjects Division
  - www.washington.edu/research/hsd/index.php

New NIH Requirements

Policy: Beginning on October 1, 2000 the NIH requires education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects.

Summary

- Clinical research ethics have evolved in response to historical events and legal action
- What counts as “clinical research” can be difficult to identify - be careful
- The Belmont Report is the critical document that concisely establishes the basic ideas of ethical biomedical and behavioral research