

THE ETHICAL FOUNDATIONS OF CLINICAL RESEARCH

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- I. Why Should We Value the Ethics of Research?
- II. The Content and Relevance of Ethics in *The Belmont Report*
- III. Identification of Contemporary Concerns and Problem Areas

Words About Ethics

Normative ethics examines what is right, good, and virtuous and relies upon rational arguments to determine what is morally justifiable.

Research ethics = focused attention on how to conduct medical research in accord with defensible and socially-acceptable moral standards and relationships.

- Vanderpool, ed., *The Ethics of Research Involving Human Subjects*, pp. 1-4.

Ethical reasoning and decision-making rely on

- Common/shared values and moral sensibilities
- The facts insofar as they can be known
- Coherent and convincing reasons

I. Why Should We Value the Ethics of Research

A. Because attention to ethics exposes inhumanity of research based on ideological or self-serving ends

Chapters in a Sordid Past

- The Nuremberg Trial of Nazi war criminals in 1945-47
- Research abuses identified by Henry K. Beecher in 1966
- The “Tuskegee” Syphilis Study in 1972
- Government-sponsored radiation experiments on unsuspecting soldiers
- The wrongful death of Jesse Gelsinger

Rationales for Abusive Research

- Ideologies of national superiority
- Assumptions that benefits of research outweigh rights of research subjects
- Rationales re racial and social inferiority
- Self-serving fame and fortune

B. Because Explicit Attention to the Ethical Foundations of Research Protects Subjects and the Integrity of Medical Research



Thomas Percival in 1803

- Experimentation is warranted only when
 - (1) Standard practices are ineffective
 - (2) Experiments contribute to the public good
 - (3) And offer “Especial advantages” to the poor.

- Moral guidelines that should govern these experiments:
 - (1) Probability of benefit based on “sound reason” and “well authenticated facts.”
 - (2) To protect subjects from harm, “no trials . . . should be initiated without prior consultation.”

- Percival, *Medical Ethics*, 1803, ch. I, Sec. XII.

Claude Bernard in 1865



The principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, that is, to the health of others.

- Bernard, *Introduction to the Study of Experimental Medicine*, 1865.

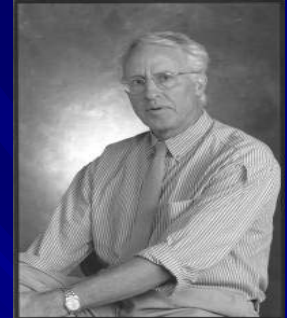
Henry K. Beecher in 1966

Evidence is at hand that many of the patients in the examples to follow never had the risks satisfactorily explained to them . . . although grave consequences have been suffered as a direct result of experiments described here. I am aware that these are troubling charges. They have grown out of troubling practices. They can be documented . . . by examples from leading medical schools, university hospital . . . governmental institutes . . . and industry.



- Beecher, "Ethics and Clinical Research," *NEJM*, 16 (June 1966) 1345-60.

Vanderpool in 1996



Social practices – including research – are always based on assumptions and rationales that function as moral justifications. The ethics of research must negotiate between the moral imperatives of protecting and respecting human subjects and enabling researchers to continue historic battles against disease, disability, and death.

- *The Ethics of Research Involving Human Subjects*, pp. 5-14.

C. Because knowledge and applications of *research ethics enhances expertise re IRB reviews of clinical protocols.*

In the Opening Paragraphs of *The Belmont Report:*

“Ethical principles and reasoning serve as a basis upon which specific rules of research – rules set forth in The Nuremberg Code, the Declaration of Helsinki, and the Code of Federal Regulations (CFR Title 46 Part 46) – can be “formulated, criticized and interpreted.”

- The meaning of the CFR must often be interpreted
- Innovative protocols sometimes call for innovative applications of codified rules
- Federal “Guidance” documents point to incompleteness of codified regulations

- Vanderpool, “An Ethics Primer for IRBs,” in *Institutional Review Board: Management and Function*, Amdor and Bankert, eds., pp. 3-8

These Points Re the Value of Research Ethics Raise Two Questions:

- (1) What aspects of human subject research raise ethical issues/problems that call for moral governance and guidance?***
- (2) What ethical standards provide that governance and guidance?***

II. The Content and Relevance of Research Ethics and *The Belmont Report*

- *The Belmont Report* continues to serve as a foundation for research ethics.
- This *Report* was composed by the National Commission for the Protection of Human Subjects in 1979

II. The Content and Relevance of Research Ethics and *The Belmont Report* (Cont'd)

Congress charged the Commission to do the following:

- “. . . Identify the basic ethical principles that should underlie the conduct . . . of research involving human subjects and . . . develop guidelines which should be followed to assume that such research is conducted in accordance with those principles.”

- *Belmont's answer to the question:
What aspects of research raise ethical
issues/ problems that call for moral
governance
and guidance?*

-All aspects/stages of clinical research -

- (1) Study design, purpose, procedures used, and number of subjects required.
- (2) Analysis of foreseeable risks and harms.
- (3) Selection of prospective subject population.

- (4) How subjects are recruited and enrolled – what they are told, whether persuasion is permissible, and so forth.
- (5) How subjects are treated re their value, autonomy, and privacy.

*Belmont's answer to the second question:
What ethical standards provide governance
and guidance to these aspects of research?:*

Standards are provided by “basic ethical principles” generally accepted in our culture that serve as basic justifications. . . . And [moral] evaluations of human actions.”

Belmont's Theoretical Point of View

1. Ethical values and principles are perennial features of human life.
2. Humans rely on basic, universally accepted moral standards when they assess which human actions are right or wrong, praiseworthy or blameworthy.

3. These principles include

- Beneficence (the duty to benefit others)
- Non-maleficence (duty not to harm others)
- Truth-telling
- Promise-keeping
- Gratitude
- Reciprocity
- Justice/Fairness

Belmont's Theoretical Point of View

(Continued)

4. All general and basic moral duties function as a *prima facie* (on its face) principles
 - that humans assume should be honored unless,
 - By reason and experience one is “overruled” by another
 - E.g. When truth-telling is outweighed by duty of not harming

Re Research Ethics

5. **Three** basic and general moral principles are “*particularly relevant to the ethics of research*”:

- Beneficence [which the Commissioners combined with Non-maleficence]
- Justice
- Respect for persons, i.e., for each person’s autonomy or self-determination

The outline of *The Belmont Report* thus reflects the following analytical framework on schema:

The Principle of:

Applies to:

These Aspects/Features
of Clinical Research:

Respect for Persons

Informed Consent

- Information
- Comprehension
- Voluntariness

Beneficence

All Risk/Benefit
Assessment

Justice

Selection of Subjects

1. Respect for Persons =

- Respect for the free, autonomous choices of competent persons, as well as
- Special protection for those who lack or have a diminished level of autonomy.

- Respect for persons directly applies/pertains to Informed Consent (IC).
- Which Belmont holds is comprised of 3 Components:
(1) Information, (2) Comprehension, and
(3) Voluntariness
- *Why must IC incorporate these components?*
- *What all does each require?*

2. Beneficence = the moral duty/obligation to

- Maximize benefits for subjects and
- Protect subjects from harm
- These duties apply to assessments and control of probable harms and benefits

Question: *To conform with these moral duties, what all does this assessment require?*

To conform with duties of beneficence and non-maleficence, harm/benefit analysis must include:

- Systematic, explicit, and thorough analysis
- Of the probable benefits and harms
- Of all procedures and medical interventions
- Such that foreseen benefits to subjects are favorably balanced with foreseen harms.

Questions Re the Relevancy and Reach of Harm/Benefit Analysis:

- *What types of harms and benefits should investigators and IRB members consider?*
- *Is it moral to allow probable benefits to society to outweigh risks to subjects?*

3. Justice =

- Equal sharing of the burdens of research by all who stand to benefit from the research
- Opposition to undue burdens on emotionally, socially, economically disadvantaged
- Equalization of benefits of research to populations of sick persons in need

Principle of justice: Particularly relevant to the selection and recruitment of subjects

- Can we identify instances of unjust research on vulnerable subjects?
- Of greater justice for persons with under-researched medical problems?
- What groups of prospective subjects are most vulnerable to injustice?

III. Contemporary Concerns and Problem Areas

- A. *Belmont's* principles and applications can and should be used to revise the CFR
- B. The principle of respect for persons should be expanded beyond autonomy to duties of due regard and appreciation for research volunteers.

C. Serious problems over Conflicts of Interest (COI) threaten to undermine the accuracy and integrity of clinical research

- Therefore, in addition to the ethical principles explicated in *Belmont*,
- The principle of truth-telling should be defined and applied to clinical research
- Special attention should be given to COIs and the roles of industry in medical research.

DISCUSSION

- D. Another problem area: the justice/injustice of recruiting subjects via monetary payments.
- E. Past attention to special ethical problems in medical specialties – e.g., Oncology and Pediatrics – should be extended to other areas: