

Ethics of Human Subjects Research: The Evolution of Public Policy

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NATIONAL RESEARCH ACT: 1974

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
 - **Identify** the ethical principles which should underlie the conduct of research involving human subjects.
 - Make **recommendations for guidelines** for “the protection of the rights and welfare of human research subjects”.

ETHICAL PRINCIPLES

- Respect for persons
- Beneficence
 - Nonmaleficence
- Justice [distributive]
 - Historical order

ETHICAL NORMS [RULES]

- Beneficence
 - Good research design
 - Competent investigators
 - Risk/benefit balance [favorable]
- Respect for persons
 - Informed consent
 - Privacy and confidentiality
- Justice
 - Equitable selection of subjects

NUREMBERG CODE: 1947

- Research done on ‘**asocial**’ persons
 1. The voluntary consent of the human subject is **absolutely essential**.
 2. The experiment should...yield...results for the **good of society** .
 4. Avoid all **unnecessary** physical and mental **suffering and injury**.
 6. Risk should never exceed...the **humanitarian importance** of the problem to be solved.

RESPECT FOR PERSONS

- Act so as to treat humanity, in every case, as an end and never as a means only. [Kant]
- RFP incorporates at least 2 ethical convictions [National Commission]:
 1. That individuals should be treated as autonomous agents.
 2. That persons with diminished autonomy and thus in need of protection are entitled to such protection.

Beneficence

- Primum non nocere: First (or above all) do no harm
- About diseases two things: to help or at least to do no harm [Hippocrates: Epidemics]
- Two general rules: 1) do no harm; 2) maximize possible benefits and minimize possible harms. [Nat'1 Commission]

NUREMBERG CODE

- No important impact
 - Unrelated to the real world of biomedical research
 - Classified secret
- World Medical Association: Medical Ethics Committee - 1953
 - Nuremberg gives standards for criminal prosecution

DECLARATION of HELSINKI

1964

- Interprets Nuremberg principles for biomedical research
- In case of legal incompetence, informed consent should be obtained from the legal guardian...permission from the responsible relative.... Article I.11
- Some risks justified by “potential therapeutic or diagnostic value for the patient”. Article II.6

HELSINKI'S IMMEDIATE EFFECTS

- National organizations and journals require statements of compliance.
- Exposés
 - Henry Beecher
 - Questionably ethical research
 - New England Journal of Medicine

US SURGEON GENERAL 1966

- Prior review of the judgment of the investigator by a **committee** of “institutional associates”.
 1. Rights and welfare
 2. Methods of informed consent
 3. Risks and potential medical benefits

JUSTICE (distributive)

- Fair sharing (equitable distribution) of both burdens and benefits.
- Special consideration (protection) of the vulnerable or disadvantaged.

EXPOSÉS

- Tuskegee
- Willowbrook
- Jewish Chronic Disease Hospital
- San Antonio Contraceptive Study
- Tea Room Trade
- Obedience to Authority

PROTECTIONISM

- From injury; from exploitation
- United States:
 - Policy for the Protection of Human Research Subjects
 - Office for Protection from Research Risks

Vision of the 1960s

- “Conscription” of subjects to “sacrifice” themselves in the “service of the collective”
Hans Jonas 1968
- “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical...experimentation.”
 - Covenant on Civil and Political Rights; Article 7, U.N. 1966

PROTECTIONISM

- Nazi experiments
- Thalidomide
- Tuskegee (etc)

AZT vs PLACEBO: 1986

- Enrollment as a benefit; access to:
 - Investigational new drug
 - Medical care
- Perception of benefit so strong:
 - Falsification of inclusion criteria
 - Physicians cooperated

VISION OF 1980s

- Investigational new drugs and devices as “promising new therapies”
 - Expanded access; parallel track
- Participation in clinical trial as beneficial; access to:
 - Investigational drugs; medical care
 - Benefits for the group

CRITERIA FOR INCLUSION AND EXCLUSION

- Children (and other vulnerable groups)
- Women
- Ethnic minorities

INTERIM SUMMARY

- Current vision that research is benign and beneficial is just as wrong as earlier vision that it was all harmful and exploitative. We must continue to encourage the conduct of good, beneficial research while remaining vigilant to avoid abuses.

PHASE I ONCOLOGY

- Dose escalation:
 - 1st dose: Risk low; benefits negligible.
 - Highest dose: Risk very high; benefits nearly negligible.
- Benefits in Phase I (1,248 subjects)
 - Partial response: 2%
 - Complete response: 0.16%
- Cohort specific consent?

ALTERNATIVES

- “Alternatives which could be considered in your case include different drugs or drug combinations or radiation therapy. Another alternative is **no further therapy**, which would probably result in **continued growth** of the tumor. At this time it is felt that **no other therapy is more beneficial** than the treatments now proposed.”