The Belmont Report

The basis of the ethical guidance and legal regulation of human subjects research in the United States.

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National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Commission was directed to consider:
- (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine,
- (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects,
- (iii) appropriate guidelines for the selection of human subjects for participation in such research and
- (iv) the nature and definition of informed consent in various research settings.

Major principles

- Respect for persons (Autonomy)
  - Self-determination
  - Kant's maxim: Always treat persons as ends in themselves, never as mere means to an end.
  - Human subjects research "'uses" persons as means to the end of producing new knowledge. The only way that this can be justified is if the participants understand it and voluntarily agree to participate.
- Beneficence
  - In clinical care, this means to promote the patient's best interest
  - Maximize benefits and minimize harms
  - Problem: In research (as distinguished from clinical care) we don't know what is in the patient's best interest and there may be unknown harms.
- Justice: Fair distribution of benefits and burdens of research participation.
  - Burdens of research risks should not be disproportionately borne by persons or classes that are disadvantaged or vulnerable to exploitation
  - Benefits of research should not accrue disproportionately to those who are favored or privileged.

Prerequisites for informed consent

- Disclosure
  - Not only disclosure at the beginning of the subjects decision to join, but also disclosure of new information that would bear on the decision to continue or not as the study progresses.
  - Must include disclosure of reasonable alternatives, whether clinical or other research protocols.
- Comprehension
  - Comprehension cannot be assessed by simply asking "Do you understand?"
  - Must be assessed by asking open ended questions and asking the prospective subject to put into their own words.
  - People will answer "yes" when they don't understand:
    - Because they don't want to admit they don't understand
    - Because they don't want to make their healthcare provider upset
    - Because they cannot read well.
- Voluntariness (absence of coercion)
  - Not only at the beginning, but freedom to withdraw without penalty or losing access to care, etc.

Tuskegee

Fundamental problems with Tuskegee Study of Syphilis

- Even before the development of penicillin, there were treatments for syphilis, effective in up to 30 % of patients, although bad side effects. It was unethical from the beginning not to offer them treatment in a study that was designed to observe the curse of the disease over a lifetime until death.
- Such as study had already been done in Oslo Norway, but the investigators shared the unsubstantiated myth that Africans were in effect a different "species" of human than Caucasians, so the Oslo results did not apply to American blacks
- The advertisements stated the research would provide free treatment for these men.
- When penicillin was developed the researchers went around to local physicians and convinced them not to give it to the Tuskegee participants, and even tried to convince the US Military not to treat them when they went off to World War II.

Knowledge of the Tuskegee Study and Its Impact on the Willingness to Participate in Medical Research Studies

- % with knowledge of the Tuskegee Study
  - 81% of African Americans
  - 28% of whites
- % with knowledge that resulted in less trust of researchers
  - 51% of African Americans
  - 17% of whites
- % with knowledge that would affect future research decisions
  - 46% African Americans
    - 49% unwilling to participate in medical research
  - 34% whites
    - 17% unwilling to participate in medical research
- Savers VL, Lynch CF and Burmeister LF, Journal of the National Medical Association, 2000

The Jewish Chronic Disease Hospital Case (1964)

- Physician researchers injected live cancer cells into patients in the Jewish Chronic Disease Hospital without informing them that the injections were of cancer cells.
- Patients testified that they were not even asked for consent at all, much less informed of the nature of the injections.
- New York Board of Regents imposed a one year suspension on the chief investigator.

The Willowbrook School Case

- NY State School for Retarded Children
- Many residents and staff contracted hepatitis
- Physician researchers from NYU injected group of new residents with experimental antibodies and then injected them with hepatitis and injected the experimental antibodies into a control group.

“Consent Form”

- November 15, 1958; Willowbrook Study Staten Island, New York
- Dear Mrs. _____:
- We are studying the possibility of preventing epidemics of hepatitis on a new principle. Virus is introduced and gamma globulin given later to some, so that either no attack or only a mild attack of hepatitis is expected to follow. This may give the children immunity against this disease for life. We should like to give your child this new form of prevention with the hope that it will afford protection.
- Permission form is enclosed for your consideration. If you wish to have your children given the benefit of this new preventive, will you so signify by signing the form.

Critique

- Should not have studied this in children before studying it in adults.
- No adult employee of the institution was asked to participate. (Because they were employees, that could be coercive, too.)
- Studies should not be done on institutionalized populations if they can be done on non-institutionalized subjects who are not in coercive environment.
- The rationalization of the study was the high rate of hepatitis in the institution, but the reason for the high levels of hepatitis was due to overcrowding and lack of sanitation.
- The physicians and authorities should have improved the conditions to prevent or reduce hepatitis instead of using it to do research on the most vulnerable subjects.

Research on prisoners

Coleman, et. al., The Ethics and Regulation with Human Subjects, pp.635-637

- From 1919-1922 hundreds of California prisoners participated in testicular transplant experiment to determine whether lost male potency could be "reinvigorated."
- 1960s and early 1970s major drug companies used prisoners for drug research. In 1969 85% of all new drugs were tested on prisoners.
- Prisoners in Oregon and Washington State were exposed to radiation to test how much radiation could be tolerated by astronauts. Testicles exposed to radiation which caused painful, enduring effects. Half later died from this exposure.

Distinction between practice and research

Different Goals

Practice

- Goal is to provide best care for the individual patient

Research

- Goal is to produce generalizable knowledge to benefit future patients.

Different means of achieving goals

Treatment

- Increase or reduce dosage of a drug
- Add, subtract, or substitute drugs

Research protocol

- Restrict variation to specified parameters in order to
- Reduce variables that might confound results

Research uses means unacceptable in practice

Practice

- Choice of intervention based on best interests of patient and patient choice
- No randomization
- No placebo
- Physician and patient know what intervention selected

Research

- Random assignment to intervention or control arms
- Subject may receive placebo
- Blinding of investigator and subject

Crucial to keep the distinction in focus

- **Clinical research is typically done in the context of clinical practice:**
  - therefore,
    - easy for patient to be confused about whether she is a patient or a research subject at any given time

    &
    - hard for physician to restrict instinctive desire for patient best interest in order to produce valid results

Crucial to keep the distinction in focus

- Especially when elements of research and practice are combined
- Examples:
  - Standard of care coronary artery bypass graft, but research protocol investigating the effectiveness of an experimental anesthesia drug.
  - Standard of care chemotherapy followed by a trial comparing x ray photon radiation to proton radiation

Correct terminology helps to keep the distinction in focus

Practice	Research
Physician	Investigator
Patient	Subject or participant
Treatment	Research intervention
Standard care	Research protocol