Ethical Issues and Professionalism in Human Subjects Research

Research Ethics - M261

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Nuremberg Code, 1947

"The great weight of evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:"

Nuremberg Code, 1947

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other means…
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of disease or other problem under study that the anticipated results will justify the performance of the experiment.

cont.

Nuremberg Code, 1947

4. The experiment should be conducted so as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur...
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

cont.

Nuremberg Code, 1947

7. Proper preparations should be made…to protect the experimental subject….
8. The experiment should be conducted only by scientifically qualified persons.
9. During the experiment the human subject should be at liberty to bring the experiment to an end…
10. During the experiment the scientist must be prepared to terminate at any stage if….the experiment is likely to result in injury, disability or death.

The compelling argument for human research

- In 1939, a surgical procedure was developed for angina pectoris. The internal mammary artery was ligated to increase myocardial blood flow.
- Clinical results were favorable: ¾ of patients reporting improvement or elimination of symptoms.
- 1959 controlled trial of internal mammary artery ligation included 17 patients: 8 received the actual operation, 9 had sham surgery. No difference in outcomes between groups.

Gastric freezing for duodenal ulcer

- Patient swallowed a balloon attached to tubes through which a cold liquid was pumped for one hour to cool the stomach and reduce acid production, thus relieving ulcer pain.
- Case series impressive
- “Since 1961, no patients with duodenal ulcer referred for elective operation have been operated on in the senior author’s service. This circumstance itself bespeaks the confidence in the method by patients as well as surgeons.”
  - President of Am Coll Surg

Gastric freezing for DU

- 2500 gastric freezing machines placed in clinical service
- Estimated 15,000 patients chilled

- Double blind RCT in late 1960's with outcome of surgery, bleed or intractable pain: Sham group 44%, Freeze group 51%.

Observational findings later disproved

- Cardioprotective effects of estrogen
- β-carotene and α-tocopherol and cancer
- Fiber and colon cancer

Federal Definitions

- Research: "A systematic investigation , including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge"
- Human subjects: "Living individuals about whom the investigator conducting research obtains: (1) data through intervention or interaction with the individual, or (2) identifiable private information."

Historical Perspective

- 1946-9: Nuremberg trial of 23 Doctors
- 1963: NYC Jewish Chronic Disease Hospital
- 1963-6: Willowbrook State School
- 1931-71: PHS Natural History of Syphilis
- 1966: Henry Beecher, Experimentation in Man. *NEJM*
  - » Call for Journal editors to require ethical review
  - » Call for national policy on IRB review

Historical Perspective

- 1966: NIH Office for Protection of Research Subjects created
- 1969-71: San Antonio SW Fnd Contraceptive Study
- 1974: National Research Act: formal IRBs
- 1979: The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research: Belmont Report
- Suspensions: Duke, U Colorado, U Alabama, U Illinois, WLAVA, Johns Hopkins
- 2011: Advanced notice of proposed rulemaking: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

The Belmont Report:
Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- Sets forth theoretical basis of protecting human subjects and practical basis of informed consent for research

The Belmont Report:
Practice versus Research

- Practice: Interventions that are designed solely to enhance the well being of an individual patient…and that have a reasonable expectation of success.
- Research: An activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.

Practice versus Research

- A significant departure from standard practice -- innovation -- does not necessarily constitute research.
- Radically new procedures should be subjected to research to determine safety and effectiveness.

Is it Practice or Research?

- An oncologist modifies dosing in a chemotherapy regimen in a way never tried before in order to decrease side effects.
- A surgeon develops a radically new method of performing a surgery.
- A reproductive endocrinologist develops a way to merge ovum and sperm in a test tube.
- A clinician performs a procedure shown to be effective, but only in patients different than the target patient.

Is it Practice or Research *(cont)*?

- A clinician develops an implantable device to fulfill a clinical function previously only carried out by the human body.
- A clinician scientist uses an approved medication for an unapproved indication.
- A clinician uses an unapproved medication in clinical care.

Is there a Standard of Care?

- Published literature
- Community practice and professional judgment
- Professional Society Guidelines

The Clinical Trial

- "Equipoise" (Fried, 1974): The state of uncertainty that must exist in order for a controlled trial to be justified.
- "Clinical Equipoise" (Freedman, 1987): A remaining disagreement in the expert community, despite the available evidence, about the merits of the intervention to be tested.

The Clinical Trial

- Meier (1979): Consider the prospective subject as an individual with a legitimate sense of self-interest but also with a certain sense of community altruism, leading to a desire to help settle important clinical questions.
- In considering the legitimacy of initiating a clinical trial, the investigator should imagine himself as such a person and ask whether or not he would be willing to volunteer to be in the trial.
  - » Brody BA. *The Ethics of Biomedical Research*. Oxford Univ Press, 1998.

The Belmont Report: Basic Principles of Research on Human Subjects

- Respect for persons
- Beneficence
- Justice (resources)

The Common Rule

"An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."

45 *CFR* 46.116

Basic Principles of Research on Human Subjects

- Respect for persons
  - Choices of autonomous individuals should be respected
  - People incapable of making their own choices should be protected
  - Voluntary subjects with adequate information

Autonomous Person

- *"Appeals to the principle of respect for persons are often viewed with suspicion not only because they appear to remove people from time but also because they appear to remove people from their communities."*

J Childress. *Practical Reasoning in Bioethics*, 1997

Informed Consent

- Information
  - » Research procedure and Purposes
  - » Risks and benefits
  - » Alternative procedures
  - » Ask questions, withdraw, identified researcher
- Comprehension
- Voluntariness

How Much Information in Informed Consent?

- Reasonable Volunteer: "Extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge."

Threats to Respect for Persons

- Inadequate information
- Inadequate voluntariness

Comprehension in Informed Consent

- Information must be tailored to the research subject.
- Investigators must ascertain that the subject understood the information
  - Might quiz subjects about purpose, risks, etc.
- Surrogate consent if judgment is limited

Voluntariness may be compromised when:

- Coercion or threat to obtain participation
- Excessive inducements
- Pressure from authority figures
- Requiring participation to receive health services

Case 1:
Prisoners as research subjects

HIV is common in prisons and provision of antiretroviral medications is an important part of medical care in this venue. This provides a practical venue test new interventions to enhance adherence to antiretroviral medication, which are sometimes difficult to take as prescribed. Prisoners are particularly drawn to the research because it removes them from general prison area and into the clinic area, which is much nicer.

Coercion

When an overt threat of harm is intentionally presented by one person to another in order to obtain compliance

Coercion *(cont.)*

- Exactly what is Coercion?
  - To be coercive, subject who refuses must be made worse off than if never approached
  - Requires presence of a threat
- Perceived coercion in research can occur with
  - Prisoners
  - Students and staff
- Payment for research is not coercive:
  - Payment is an offer not a threat

-After: Caligiuri M. Research Ethics, UCSD

Inducement

- Inducements are offers that get people to do things they would not otherwise do
- Inducements in Research:
  - Anything that encourages participation
  - Usually monetary
  - Medical/diagnostic services

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Undue Inducement or Undue Influence

- An offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance
  - Leads people to do something to which they normally would object based on risk or other fundamental value

Undue Inducement: Examples

- Monetary inducement that alters individual's decision-making process such that they underestimate risks;
- Payments that undermine a person's capacity to exercise a free choice invalidates the consent process

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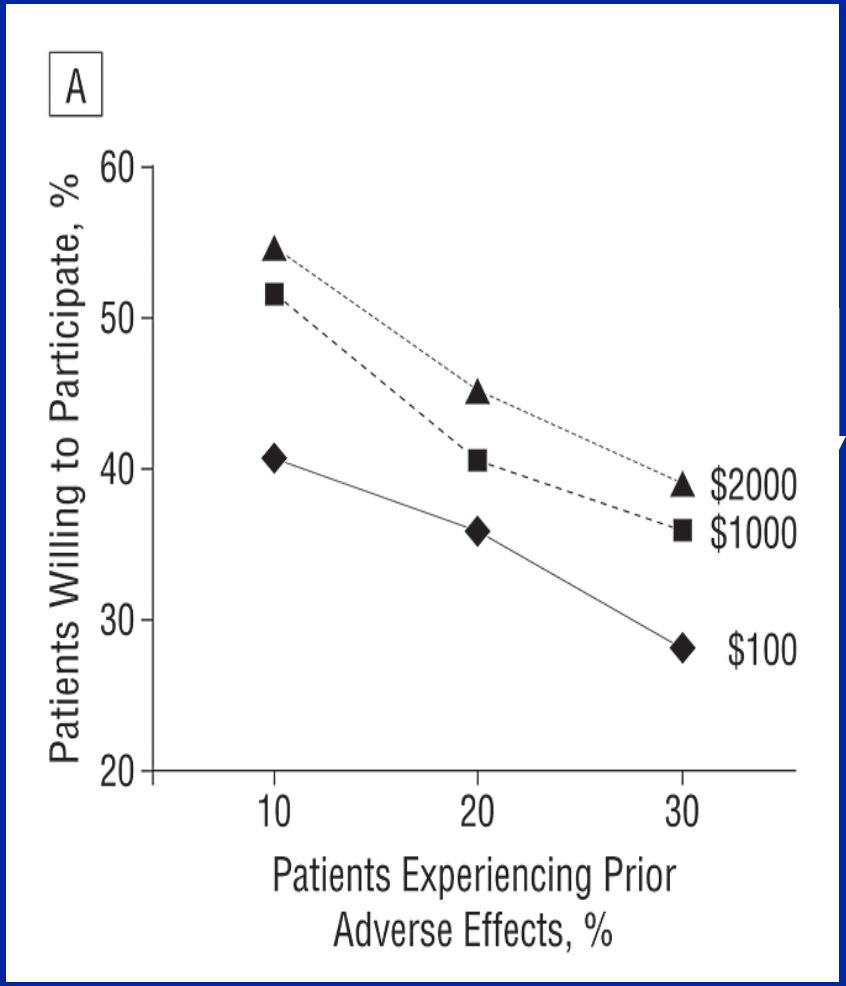
Undue Inducement

Risk is likely more important than money when considering enrollment



Halpern, S. D. et al. *Arch Intern Med*. 2004

-After: Caligiuri M. Research Ethics, UCSD

When Withholding Information is Essential to the Research

- Only permitted under rare circumstances in which all 3 of the following are true:
  - Incomplete disclosure is necessary to accomplish the goals of the research
  - No undisclosed risks that are more than minimal
  - Adequate plan for debriefing subjects
- May not withhold disclose to make research more convenient.

“Therapeutic Misconception”

- Patients often misconstrue that research is designed to optimize their individual care.

Case 2: Informed Consent

- A researcher believes that subjects want to participate in the research project and that participation will benefit the subjects who will receive variable dosing of a new, otherwise unavailable, medication. But potential subjects are frightened by the long informed consent form. She obtains full verbal consent and disguises the written document in a series of forms to be signed.

Basic Principles of Research on Human Subjects

- Beneficence
  - Participation in research is associated with a favorable balance of potential benefits and harms
  - “Maximize possible benefits, minimize potential harms”

Favorable Risk-Benefit Ratio

- Potential risks to subjects must be minimized
- Potential benefits to subjects are maximized
- Potential benefits to individual subjects and to society are proportionate to the risks

Assessment of Risks and Benefits

- Nature and scope of risks and benefits
  - physical harm
  - psychological harm
  - legal harm
  - social harm
  - economic harm
  - breach of confidentiality
- Systematic assessment of risks and benefits
  - “risks and benefits must be balanced and shown to be in a favorable ratio”

Standards of a "Favorable" Risk-Benefit Ratio in Research

- Some approved medications:
  - IL-2 for renal cell ca
    - » 14% response rate (5% complete)
    - » median response duration 20 months
    - » substantial toxicity
  - Camptosar for colon ca
    - » 2 month survival prolongation
  - Gemcitabine for pancreatic ca
    - » 5% response, some improvement in QOL
- From Agrawal & Emanuel. JAMA 2003; 290:1075-82.

What Standard Determines a Favorable Risk-Benefit Ratio?

- Sick patients willing to accept more burden than healthy people
  - Willing to undergo chemo with substantial adverse effects for what chance of cure?

    1% - metastatic tumor patients

    10% - physicians

    50% - nurses

    50% - general public

- From Agrawal & Emanuel. JAMA 2003; 290:1075-82.

Basic Principles of Research on Human Subjects

- Justice
  - Equitable distribution of the burdens and benefits of research
  - May not exploit vulnerable individuals or exclude without good reason eligible candidates who may benefit

Fair Subject Selection

- Based on the principle of justice
- Scientific goals of the study – not vulnerability, privilege or other factors unrelated to the purpose of the study – is the primary basis to select individuals to be recruited.
  - Vulnerable patients may not be targeted for risky research
  - Privileged groups may not be targeted for potentially beneficial research.

Case 3: “Best v practical sample”

- Studies of AIDS medications are more difficult and expensive if subjects do not adhere to the many medications many times per day and who “drop out” of studies. Thus, researchers launching a promising drug study who want to quickly complete a trial (to publish it first) enroll highly educated gay men and exclude IVDU subjects.

Exploitation

- An exploitative transaction is one in which one person takes unfair advantage of another person.
- Concern when vulnerable individuals are paid to enroll in medical research
- Potential solutions to avoid exploitation:

  -Pay vulnerable patients more?

  -Engage patient advocates?

  -Exclude vulnerable populations?

  -IRB member expertise

-After: Caligiuri M. Research Ethics, UCSD

Informed Consent & Recruitment

- How will you identify the subjects?
- How will you contact the subjects?
- How will you recruit the subjects?
  - Flyers
  - Letters
  - Announcements (script)
- Outline by subject population

Application of Ethical Principles in Human Research

Principle	Aspect of Research
Respect, Resources	Social or scientific value
Respect, Resources	Scientific validity
Justice	Fair subject selection
Respect	Respect for subjects
Beneficence, Respect	Favorable risk/benefit ratio
C of I; Professionalism	Disclosure/External review
Respect	Informed consent

–Emanuel, Wendler, Grady. JAMA. 2000;283:2701-11.

Research must have Value

- An evaluation that could lead to improvements in health or well being to the population relevant to the potential subject.

Asking the Right Question

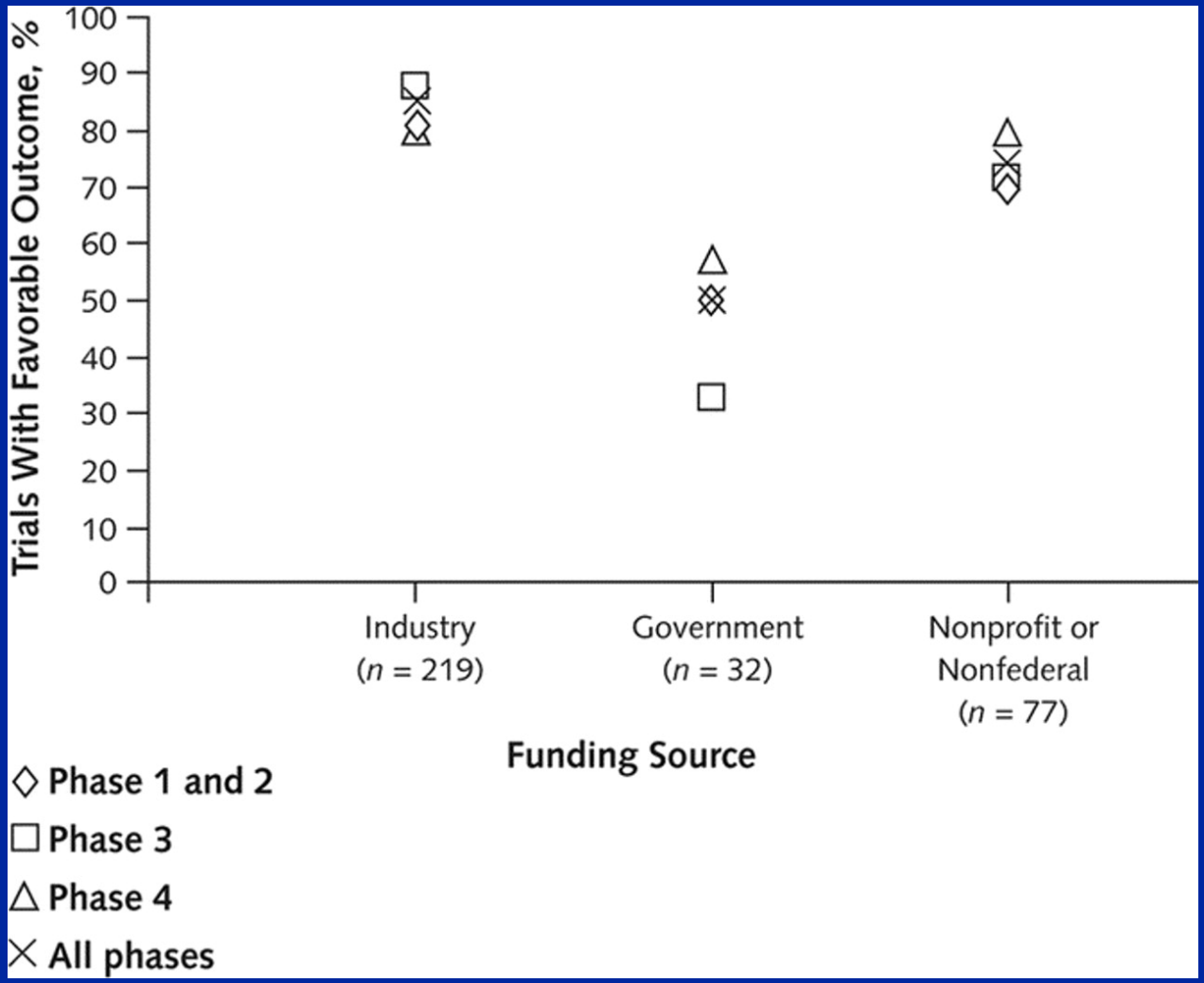
Research without Value

- Question already fully answered
- Results have no chance to be valuable to relevant population
- Results will not be disseminated and thus cannot have an effect

Scientific Validity

- Methodologically sound
- Feasible
- Adequately powered
- Analytic plan pre-specified

Percentage of trials with reported favorable outcomes, by trial phase within funding source



-Bourgeois F T et al. Ann Intern Med. 2010;153:158-66.

Privacy Protection: HIPAA

- Obtaining human subjects information for research
  - De-identified health information is not Personal Health Information (PHI)
  - PHI may be used and disclosed for research with an individual's written permission (Authorization).
  - PHI may be used and disclosed for research without an Authorization in limited circumstances:
    - » Under a waiver of the Authorization requirement
    - » As a limited data set with a data use agreement
    - » For research on decedents' information
- ANPRM: Mandatory standards for data security and information protection whenever data are collected, generated, stored or used. Level of protection required by these standards would be calibrated to the level of identifiability of the information based on HIPAA.

HIPAA: Waiver of authorization

- IRB or Privacy Board approval and satisfies the following criteria:
  - The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals
  - The research could not practicably be conducted without the waiver or alteration
  - The research could not practicably be conducted without access to and use of the PHI

The IRB’s Responsibilities

- Risk/benefit analysis
- Informed consent
- Selection of subjects
- Privacy and confidentiality
- Monitoring and observation
- Add'l safeguards for vulnerable subjects
- Incentives for participation
- Continuing review

Research and QI

Research ⇔ Quality Improvement

Best available treatment?

Approved therapeutics?

Able to opt out of treatment?

Treatment selection method?