Framework for the ethics of research with human subjects

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Disclaimer

- The views expressed here are my own and do not represent the position or policies of the NIH, DHHS, or US government

- I have no conflicts of interest to declare

Why should we do research with humans?

- Results in compelling societal health benefits– new therapies, diagnostic and preventive strategies, improvement in quality of life, and understanding of health and disease

- Provides evidence so clinicians can safely and effectively treat, prevent, or diagnose diseases or promote health

- Other important benefits, e.g. economic,

AAMC 2011. https://www.aamc.org/download/265994/data/tripp-umbach-research.pdf

Why is clinical research ethically challenging?

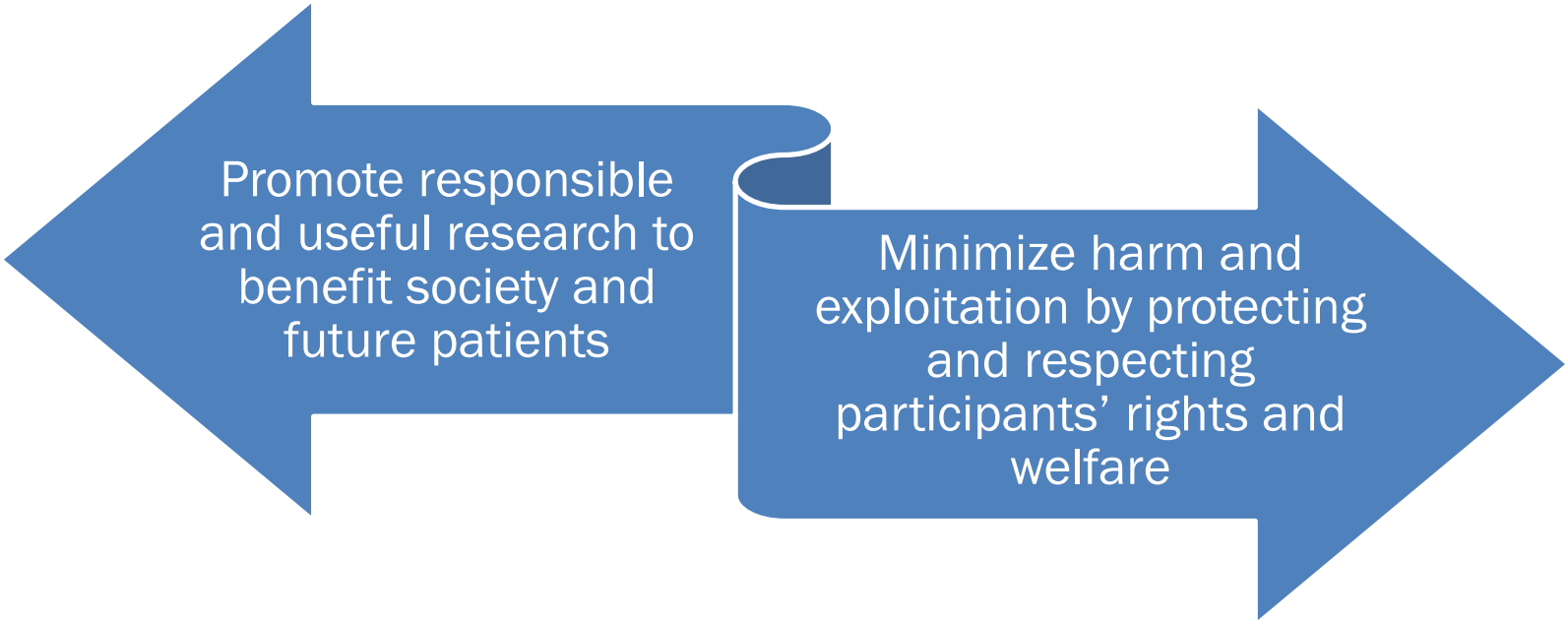
- The goal of clinical research is to generate useful knowledge about human health and illness, the primary goal is not benefit to participants

- We ask a small number of participants to accept risk to learn how to benefit others. (participants do sometimes benefit)

- Participants are the *means* to developing useful knowledge; and are thus at risk of exploitation

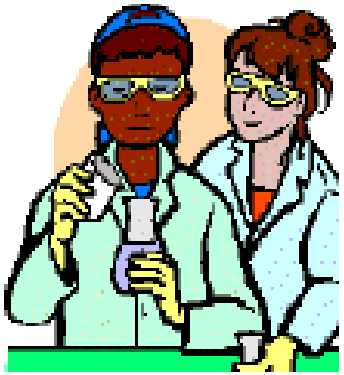

APRIL 22, 2002
Powell's Mission Impossible
TIME
HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO...
HUMAN GUINEA PIGS

Ethics of Clinical Research



Clinical research differs from clinical practice

- Different Goals
- Different Methods
- Different justification for risk to individuals



Ethics of Clinical Research

- Ethical requirements in clinical research provide guidance that:
  - Promotes the responsible conduct of research while seeking progress in understanding and intervening in human health and illness
  - Minimizes the possibility of exploitation and harm
  - Ensures that participants' rights and welfare are respected while they contribute to generating knowledge
  - Helps to maintain public trust

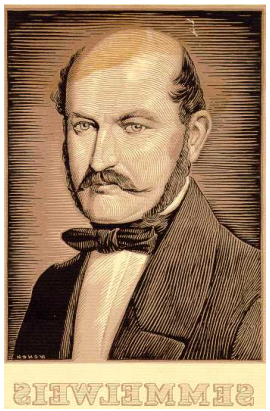
History of the Ethics of Clinical Research

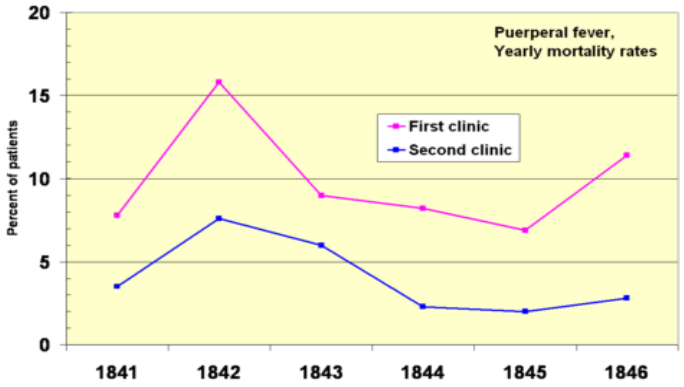
- *Few rules. Physicians experimenting to benefit individuals*
- "Utilitarian era" emphasis on benefit to society, inclusion of vulnerable groups
- Examination of the scope and limitations
- Rules and Regulations. Protection of human subjects
- Research as a benefit

History: few rules

- Louis Pasteur and Joseph Meister
- Joseph severely bitten by rabid dog. Brought to Pasteur in hopes of preventing the disease and death
- Pasteur was developing a rabies vaccine
- He was not a medical doctor and had never successfully used the vaccine on a human.
- Joseph did not get rabies and Pasteur was hailed as a hero

History: few rules





- Ignaz Semmelweis
- Noticed a difference between 2 clinics in the rates of puerperal fever and death.
- Carefully collected data, examined variables, and concluded that the difference was the type of practitioner (obstetricians versus midwifes) (1841-1846)
- Later showed that when obstetricians used chlorinated lime to sterilize their hands, the rate of puerperal fever was significantly reduced. (1847)

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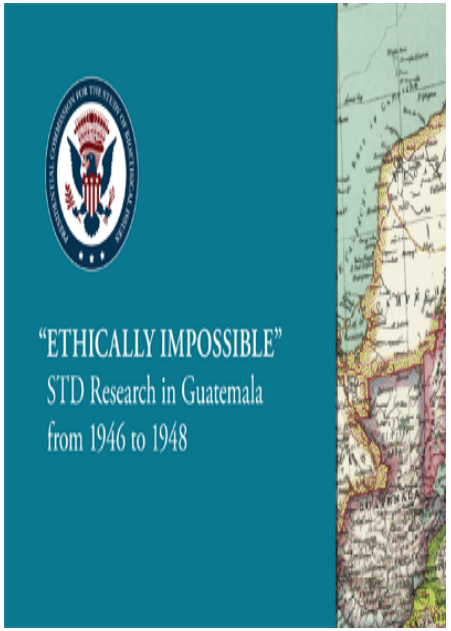
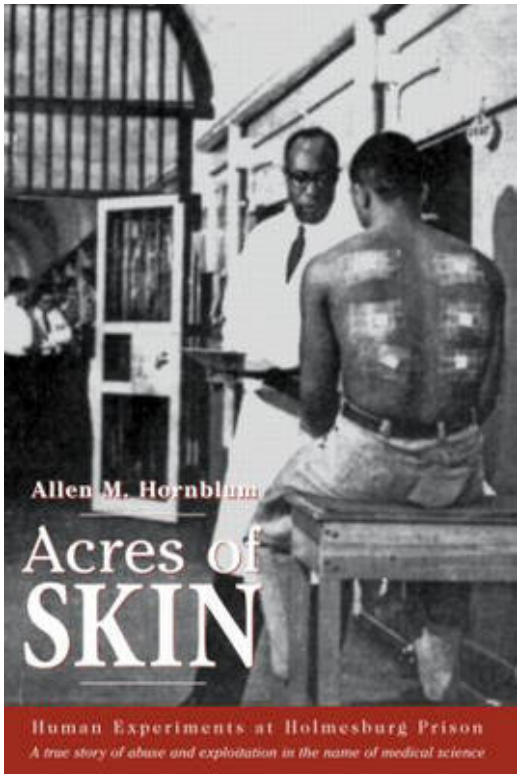
Utilitarian: Research with “vulnerable” groups





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Examination of scope and limitations


Henry K. Beecher

Henry Beecher (NEJM 1966)

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

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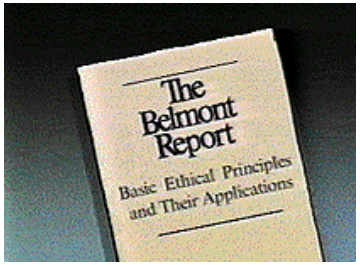
Protection of human subjects

- US Congress passed National Research Act (1974) which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Ethical principles underlying the conduct of research:
  - Respect for persons
  - Beneficence
  - Justice



- Boundaries between Practice and Research

U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report 1979

Protection of Human Subjects

- U.S. Regulations
- International codes and guidelines
- Laws and regulations from other jurisdictions
- Institutional policies and guidelines

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Influence of AIDS activism

Explicit recognition of benefit from research for “therapeutic orphans,” like children

Protection of human subjects

- Codes and Guidelines
- Laws and Regulations
- Principles

Codes and Guidelines

- Nuremberg Code (1949)
- Declaration of Helsinki (1964- multiple revisions-2013)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002, 2016)
- ICH/GCP-International Conference on Harmonization- Good Clinical Practice (1996, 2016)

U.S. Regulations

- The Common Rule (US DHHS -Title 45CFR.46)
- 45CFR.46 Subparts B, C, D, E
- US FDA regulations (Title 21CFR50 and 56, as well as IND (312-314) and IDE (812) regs, and others)

Common Rule Revisions

(effective January 2019)

Goal- enhance protections and reduce burden

- Certain activities removed from research definition
- Expand exempt research
- Update expedited review
- Eliminate certain continuing reviews
- Require use of single IRB review for multisite studies
- Change informed consent requirements
- Add broad consent option for secondary research

U.S. Regulations

- Office of Human Research Protections (OHRP) http://www.hhs.gov/ohrp
- Federal Wide Assurance (FWA)
- Intramural:
  - Intramural Office of Human Subjects Research http://ohsr.od.nih.gov/
  - Intramural Institutional Review Board Office https://irbo.nih.gov/confluence/display/IRBO/Home

Confusion reigns…

Guidance and regulations

- Most guidance in response to historical events
- Different regulations/guidance apply
- Some divergent recommendations and interpretation
- Need for a systematic, coherent, universally applicable framework

Ethical framework: 8 principles

- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *J Am Med Assoc.* 2000; 283(20):2701-11; Chpt 11 Oxford Textbook 2008
Emanuel E, Wendler D, Killen J, Grady C. *J Infect. Diseases* 2004; 189:930-7

Collaborative Partnership

- Ethical clinical research should be a collaborative partnership with the relevant partners, e.g.
  - Collaboration in planning, conducting and overseeing research, and integrating research results into the health system
  - Respect for contributions of partners
  - Collaboration with existing systems of health care

Collaborative Partnership

- Collaborative partnership with:
  - Policy makers and health systems
  - Community advisory boards and communities
  - Patient advocates on scientific advisory boards
  - Advocates for research funding
  - Collaborating investigators
  - Practicing clinicians
  - Participants
  - Etc.

Collaborative partnership, selected examples

Valuable Scientific Question

Ethical clinical research should answer a valuable question, i.e., one that will generate new knowledge or understanding about human health or illness, i.e. a socially, clinically, or scientifically useful question

Social Value

- What is the value of answering the research question?
- How will value be judged?
- To whom will the knowledge be valuable? (who are the beneficiaries?)
  - Participants
  - Community in which participants live?
  - People with similar condition?
  - Society, future people etc?

bioethics

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EDITORIAL

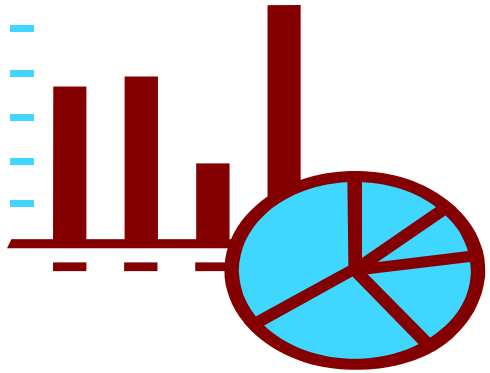
SUBSTANTIATING THE SOCIAL VALUE REQUIREMENT FOR RESEARCH: AN INTRODUCTION

For decades, ethical codes, guidelines and regulations for research involving humans have held that research must have social value in order to be ethical. The idea was present in the founding documents of modern research governance and has been widely promulgated ever since. For example, in 1947 the Nuremberg Code required that medical experiments on human beings must have the potential to yield fruitful results for the good of society [1]. The 1964 Declaration of Helsinki stated that clinical research cannot be legitimately carried out unless the risks to participants are justified by the importance of the objective [2], and the most recent version, from 2013, continues to include value, even calling it the ethical justification of health-related research [5].

Despite its widespread recognition at the level of policy and guidance, social value remains relatively unexplored in the research ethics literature as a concept and an ethical requirement. Many fundamental questions have not been satisfactorily addressed. Consider, for example: for example: Exactly what makes research socially valuable? How does the social value of research relate to its scientific value? Is social value a necessary ethical requirement for research – and, if so, why? When conducting research in low- and middle-income countries or with vulnerable populations, is social value for the study population necessary? Or is social value for the study population a universal requirement for research? To what extent does the social value of research studies (or programmes) depend on how their benefits are distributed within populations? Who should make judgments about the social value of research? And are these judgments only relevant before starting the research, or are

Valid Scientific Methodology

- Ethical clinical research should be designed in a methodologically rigorous manner (design, methods, statistical power and methods, etc.) that will yield valid, reliable, generalizable, and interpretable data, and that is feasible

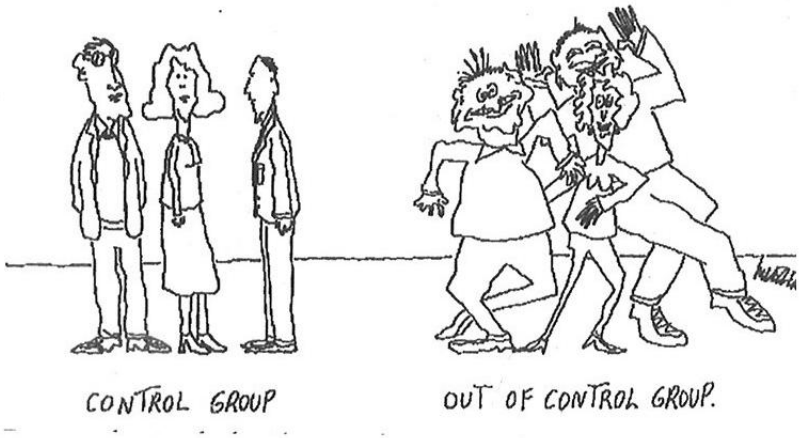


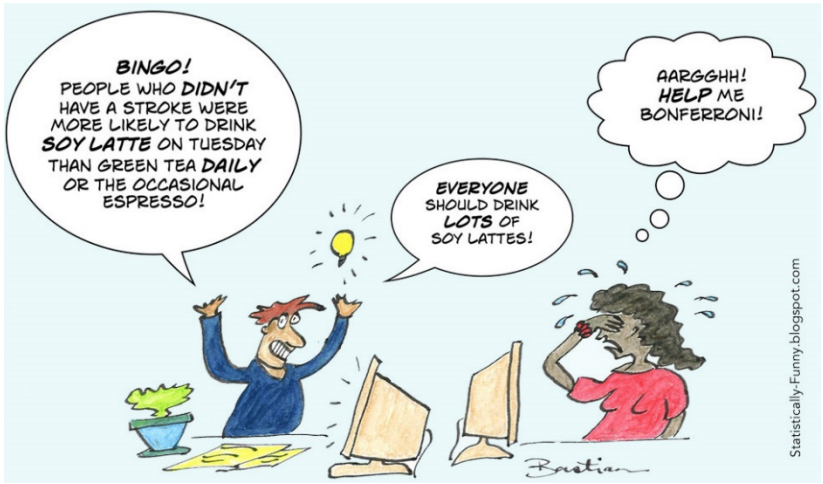
Research

- Science
- Ethics

Scientific validity: considerations

- Choice of endpoints
  - e.g. ischemic or hemolytic stroke
- Choice of design
  - Randomized double blinded control
  - Noninferiority or superiority
- Choice of procedures
  - Measures of outcome, length of follow- up
- Statistical methods and data management
  - Power, sample size, methods, level of significance
- Feasiblity


CONTROL GROUP
OUT OF CONTROL GROUP.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EVERYONE SHOULD DRINK LOTS OF SOY LATTES!
AARGGHH! HELP ME BONFERRONI!
Statistically-Funny.blogspot.com


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group

Fair subject selection

- Scientific objectives should guide inclusion criteria, recruitment strategies, and selection (not privilege or easy availability or vulnerability)
- No exclusion without justification
- Fairly distribute harms and benefits
- Justice and Beneficence

Fairly distribute harms and benefits

Research as ‘burden’

Subjects need protection

Research as ‘benefit’

Subjects need access

Fair subject selection

- Protecting vulnerable groups
- Selecting the appropriate participants?
  - Is it preferable to test an early potentially risky therapy in healthy affected adults who can consent but have mild disease or in severely ill infants who are otherwise likely to die as infants?

Favorable risk-benefit

- Are risks to subjects necessary and minimized?
- Are risks justified by benefit to individual subjects and/or the importance of the knowledge to society?
- Are benefits enhanced?

Non-maleficence and Beneficence

Benefits and Risks in Research

[I]nterests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. The Belmont Report

Minimize risks and enhance benefits

- Study of adults and children with T2DM
- No treatment, no therapeutic benefit
- Requirements: PE, blood and urine, pregnancy test, 1-2 hours of surveys about eating, exercise, emotional health, quality of life, oral glucose tolerance test, full body MRI, DEXA, treadmill exercise test, DNA.
- Financial compensation up to $300/visit

Challenges

- Identifying risks and benefits- which ones count?
- Minimizing, limiting risks
- Direct vs. indirect benefits
- Determining level of risk and prospect of benefit

Independent review

- To ensure regulatory and ethical requirements have been fulfilled
- To check investigator biases and conflicts
- To assure the public that research is not exploiting individuals or groups

Regulatory Criteria for IRB Review

(US 45CFR.46.111 and 21CFR56.111)

- Risks … are minimized.
- Risks are justified by anticipated benefits, if any, to the subjects or the importance of the knowledge to be gained
- Subjects will be selected and treated fairly
- Informed consent is adequate

Challenges in Independent review

- Volume
- Conflicts
- Varied interpretations (inconsistency)
- Single IRB review and reliance

Informed Consent

Informed consent ensures that individuals have the opportunity to decide whether they want to participate in research or continue participation and whether it is compatible with their goals, values and interests

Respect for Persons

Informed consent

- Disclosure of information
- Understanding
- Voluntary decision making
- Authorization

Informed consent challenges

- The quality of informed consent
- Capacity to consent
- Approaches to informed consent
- Changing research methods (e.g. big data)

Respect for enrolled subjects

- Ethical research requires continued respect for the rights and welfare of participants throughout research, including:
  - Protecting confidentiality
  - Monitoring welfare
  - Recognizing right to withdraw
  - Providing new information
  - Informing participants of findings
  - Planning for after the trial

Ethical framework: 8 principles

Systematic and sequential

Necessary (procedural requirements may be waived)

Universal (adapted and implemented in context)

Require balancing, specification, judgement

Need informed investigators, IRB members

What makes clinical research ethical?

Principle	Explanation
Collaborative Partnership	Respectful partnerships with relevant communities and stakeholders
Social value	Clinically, scientifically, or socially valuable question
Scientific validity	Appropriate, rigorous, and feasible design, end points, methods
Fair subject selection	Scientifically appropriate, with attention to risk and vulnerability,
Risk- benefit	Risks minimized and justified by potential benefits to participants and/or to society
Independent review	*Evaluate adherence to ethical guidelines and check conflicts*
Informed consent	*Informed and voluntary participation*
Respect for enrolled subjects	Respect for participants' rights and welfare

Emanuel , Wendler, Grady 2000, 2004, 2008