Framework for the ethics of research with human subjects

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Disclaimer

- The views expressed in this talk 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

Ethics of clinical research

- Should we do research involving human beings?

- If yes, how should it be done?

Ethics of Clinical Research: should we do it?

- Clinical research results in compelling societal health benefits – development of therapies, diagnostic and preventive strategies, improvement in quality of life, and understanding of health and disease

- Clinical research provides evidence which clinicians use to know how to safely and effectively treat, prevent, or diagnose diseases or promote health

- Clinical research has other important benefits, e.g. economic,

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

Ethics of clinical research- how should it be done?

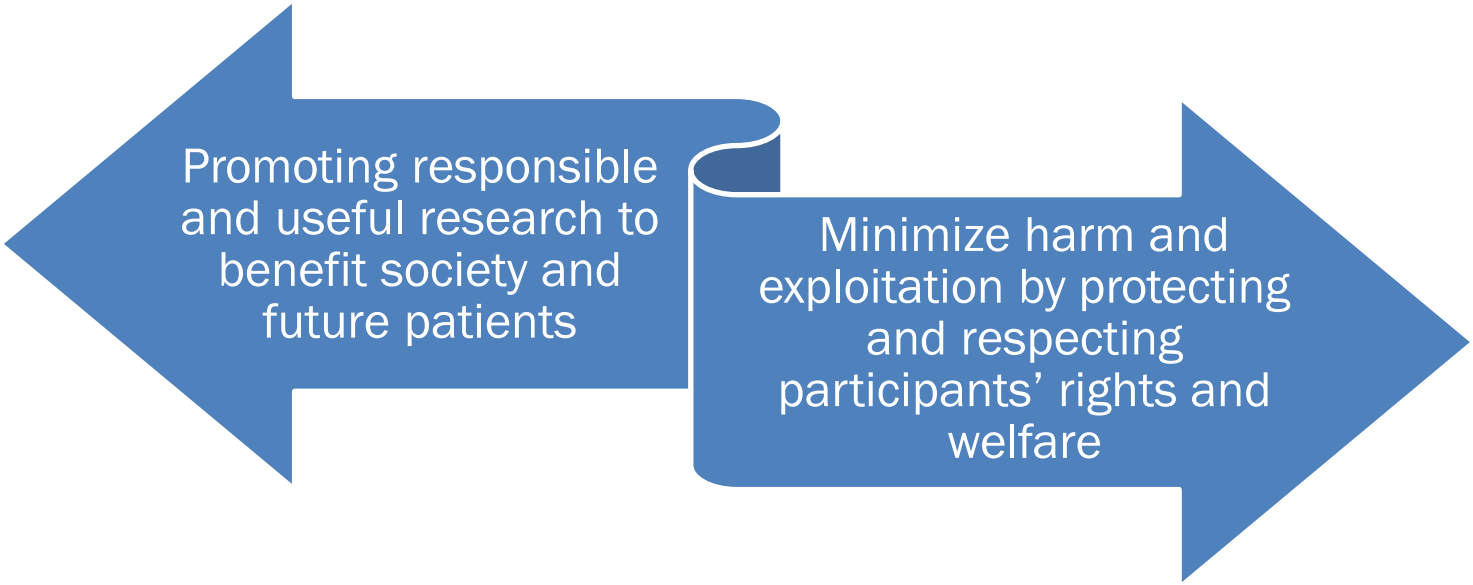
- The goal of clinical research is to generate useful knowledge about human health and illness

- A small number of participants are asked to accept risk to benefit the many. Benefit to participants is *not* the purpose (although it does occur)

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


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

Ethics of Clinical Research



How should research be done ethically?

The New York Times

New Drugs Stir Debate on Rules of Clinical Trials

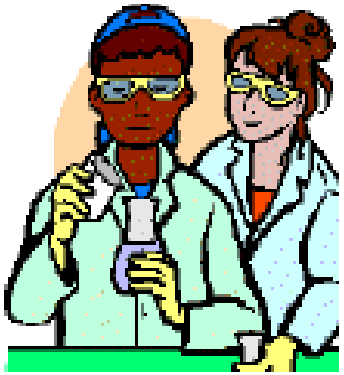
By AMY HARMON, September 18, 2010

"Defenders of controlled trials say they are crucial in determining whether a drug really does extend life more than competing treatments. Without the hard proof the trials can provide, doctors are left to prescribe unsubstantiated hope — and an overstretched health care system is left to pay for it. ...

"... critics ...argue that the new science behind the drugs has eclipsed the old rules and ethics - of testing them...in some cases, drugs under development... may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering."

Clinical research and clinical practice

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



Ethics of Clinical Research: how should we do it?

- Ethical requirements in clinical research:
  - Promote the responsible conduct of useful clinical research and progress in understanding and intervening in human health and illness
  - Minimize the possibility of exploitation and harm
  - Ensure that the rights and welfare of subjects are respected while they contribute to the generation of knowledge
  - Help to maintain public trust

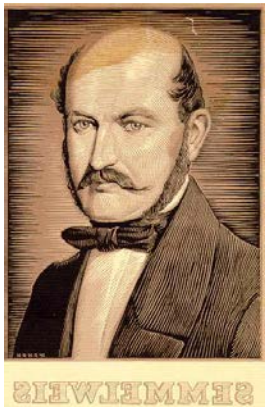
Ethics of Clinical Research: History

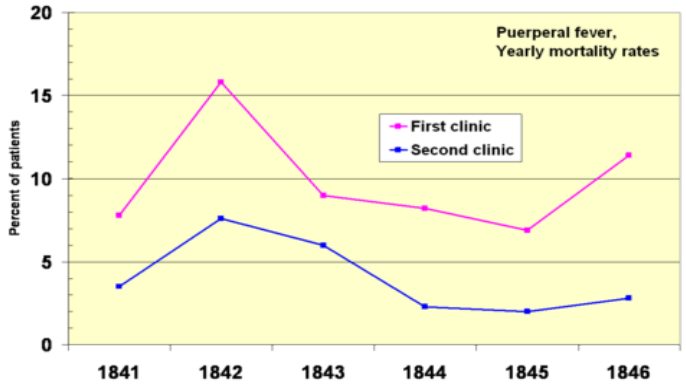
- *Few rules. Physicians experimenting to benefit individuals*
- "Utilitarian era" emphasis on benefit to society, inclusion of vulnerable groups
- Examination of the scope and limitations
- Rules and Regulations. Protection of human subjects
- Participation in research as a benefit

History

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

History





- Ignaz Semmelweis
- First noticed a difference in the rates of puerperal fever and death between 2 clinics.
- By careful examination of variables and data collection, concluded that the difference was the type of practitioner (obstetricians versus midwifes) (1841-1846)
- Later, he showed that using chlorinated lime to sterilize obstetricians' hands significantly reduced the rate of puerperal fever. (1847)

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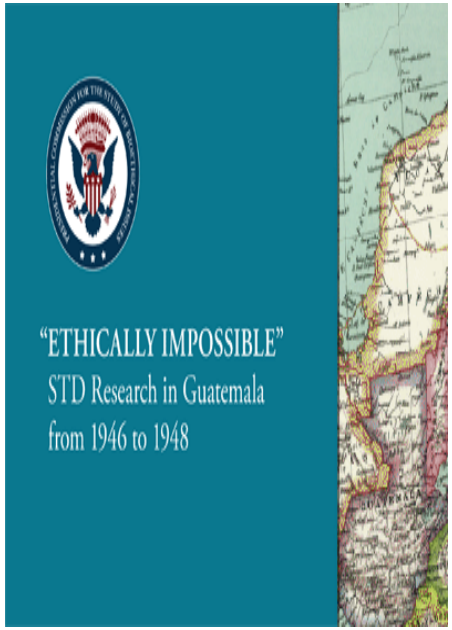
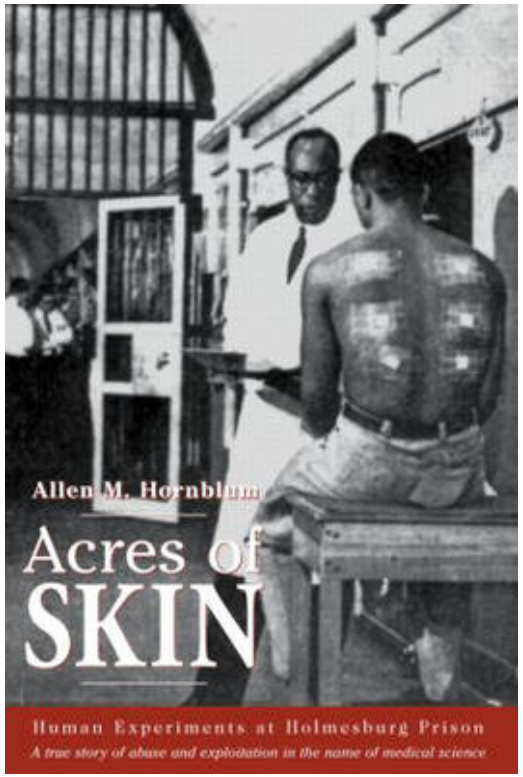
Utilitarian: Research with vulnerable groups





History- Salk polio vaccine trials

1954

- Almost 2 million children in the US
- Salk inactivated polio vaccine vs. placebo vs. no vaccine
- 80-90% effective against paralytic polio

Ethics of Clinical Research: History

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Examination of scope and limitations

- Henry Beecher (NEJM 1966)

- 22 examples, including:
  - Withholding antibiotics from men with rheumatic fever,
  - Injecting live cancer cells into nursing home patients (Jewish Chronic Disease Hospital),
  - Transplanting melanoma from daughter to mother, who died about a year later.

PHS Syphilis studies

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,

Ethics of Clinical Research: History

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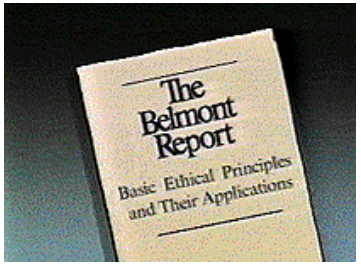
Protection of human subjects

- National Research Act (1974) establishes 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

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

Ethics of Clinical Research: History

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Influence of AIDS activism

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

Ethics of Clinical Research

- 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, 2015)
- ICH/GCP-International Conference on Harmonization-Good Clinical Practice (1996, 2016)

U.S. Regulations

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

U.S. Regulations

- Office of Human Research Protections (OHRP) http://www.hhs.gov/ohrp
- Federal Wide Assurance (FWA)
- Intramural Office of Human Subjects Research http://ohsr.od.nih.gov/

Confusion reigns…

Guidance and regulations

- Most guidance developed in response to historical events
- Some divergent recommendations
- Differences in 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 facilitated by planning and working 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
  - 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 research question?
- How is value to be judged?
- To whom is answering the question valuable? (who are the beneficiaries?)
  - Participants
  - Community in which participants live?
  - People with similar condition?
  - Society, future people etc?

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EDITORIAL

SUBSTANTIATING THE SOCIAL VALUE REQUIREMENT FOR RESEARCH: AN INTRODUCTION

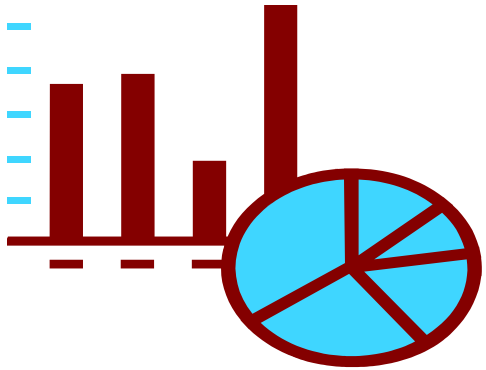
For decades, ethical codes, guidelines and regulations for research involving humans have held that research must have social value in order to be ethical. The idea was present in the foun ding documents of modern research governance and h as been widely promulgated ever since. For example, in 1947 the Nuremberg Code requ ired 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 t he importance of the objective [2],and the most recent version from 2013 continues to include va lue, even calling it the ethical justification of health-related research [5].

Despite its widespread reco gnition a t the lev el of policy and guidance , social value remains rela tivel y unexplored in the resear ch ethics litera ture as a concept and an ethical requir ement. Man y fundamental questions have not been sa tisfactoril y addressed Consider, f or example: f or example: Exactl y wha t mak es research sociall y valuable? How does the social value of research rela te to its scientific value? Is social value a necessary ethical requirement f or resear ch – and, if so , w h y? W hen conducting research in low- and middle-income countries or with vulnera b le popula tions , is social value f or the stud y popula tion necessary? Or is social v alue f or the stud y popula tion a uni versal requir ement f or resear ch? To what extent does the social value of research studies (or pr ogrammes) depend on ho w their benefits ar e distrib uted within popula tions? Who should mak e judgments a bo ut t he social value of r esearch? And are these

SOCIAL VALUE: CASE EXAMPLES

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

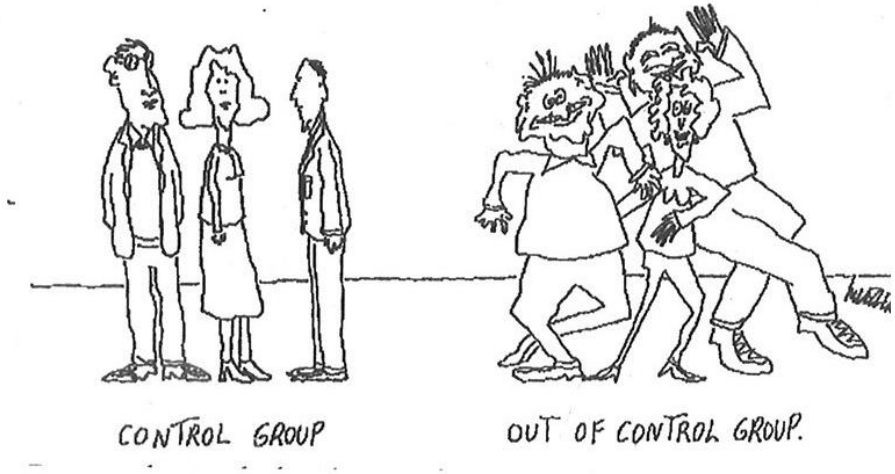


Research

- 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
  - Power, sample size, methods, level of significance
- Feasiblity


CONTROL GROUP
OUT OF CONTROL GROUP.


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group

Scientific Validity

- Examples of design controversies
- Feasibility

Fair subject selection

- Scientific objectives should guide inclusion criteria, recruitment strategies, and selection (not privilege or easy availability or vulnerability)
- Minimize harms and fairly distribute harms and benefits
- No exclusion without justification
- JUSTICE AND BENEFICENCE

Research as burden or benefit?

Research as ‘burden’

Subjects need protection

Research as ‘benefit’

Subjects need access

Fair subject selection: Case examples

- 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

Case: Risks and Benefits

- Dr. Jones is planning a study of adults and children with type 2 diabetes compared to age, sex, race, and BMI matched controls.

- Study involves 1 to 2 outpatient visits during which the following will be done:
  - A physical exam
  - Blood (approx. 1/3 cup) and urine tests
  - Pregnancy test
  - Psychological testing (Questionnaires and interviews about individual and family eating habits and exercise habits, emotional health, and quality of life. (1-2 hours)
  - Oral glucose tolerance test (12 hours of fasting, glucose drink, regular blood draws over 2 hours through an IV)
  - Full body MRI
  - DEXA scan to determine % body fat (approximately 1 hour on a flat scanner table, small amount of radiation exposure)
  - Fitness test (20-30 minutes on a treadmill or exercise bike- measuring O_2 and CO_2)
  - Genetic testing/ DNA tests- stored indefinitely and used for future studies of diabetes and obesity

- Not a treatment study -no therapeutic benefits to the participants.
- Financial compensation is offered for time and procedures up to ~$300 per visit.

Challenges

- Identifying risks- which ones count?
- Minimizing, limiting risks
- Direct vs. indirect benefits

Independent review

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

Criteria for IRB Review
(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

Contemporary Challenges

- Stored data and biospecimens
- Pragmatic trials, learning health care systems
- Digital data

- What kind of consent is appropriate?
  - What and how should information be disclosed?
  - What level of understanding?
  - Voluntary choice?

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

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

Ethical framework: 8 principles

Systematic and sequential

Necessary

– Procedural requirements may be waived

Universal

– Adapted and implemented according to context

Requires balancing, specification

Ethical framework: 8 principles

Conflicts occur between the principles. e.g.,

- Enhancing scientific validity could increase risks.
- What seems necessary to respect enrolled subjects or obtain informed consent may compromise scientific validity.

Ethical framework: 8 principles

In order to apply the principles, reconcile conflicts and make informed judgments about ethical research, need:

- Educated and informed investigators, research teams, partners who work together

- Educated and informed IRBs with diverse members including investigators, statisticians, ethicists, and community members.

- Good judgement