Framework for the Ethical Conduct of Clinical Research

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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

Ethics of Clinical Research

- What is the value of research?
- Should we do research with humans?
- If yes, how should we do it?

Impact of NIH Research

- Improving Health
- Revolutionizing Science
- Serving Society
- Our Stories

Search Impact of NIH Research

Spotlight:

Cancer death rates dropped 33% from 1991 to 2020 because of NIH-supported cancer research.

More »

NIH works to turn scientific discoveries into better health for all. As the largest public funder of biomedical and behavioral research in the world, NIH is the driving force behind decades of advances that **improve health**, **revolutionize science**, and **serve society** more broadly.

Evidence of the varied, long-term impacts of NIH activities comes from a variety of sources, ranging from studies on specific health topics, to broader analyses of NIH as a whole. Explore the sections below to discover more about how NIH provides value for the public's investment.

https://www.nih.gov/about-nih/what-we-do/impact-nih-research

Improving Health

Discoveries emerging from NIH-

Revolutionizing Science

NIH fuels the biomedical research enterprise...cultivating world-class

Serving Society

NIH-supported research leads to improvements in health that can bolster

Should we do research with humans?

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

- Clinical research provides an evidence base for clinicians to safely and effectively treat, prevent, or diagnose diseases or promote health in their patients

- Human participation is necessary to gain accurate and relevant data to improve well-being by directly studying human biology, behavior, and disease processes

Why is clinical research ethically challenging?

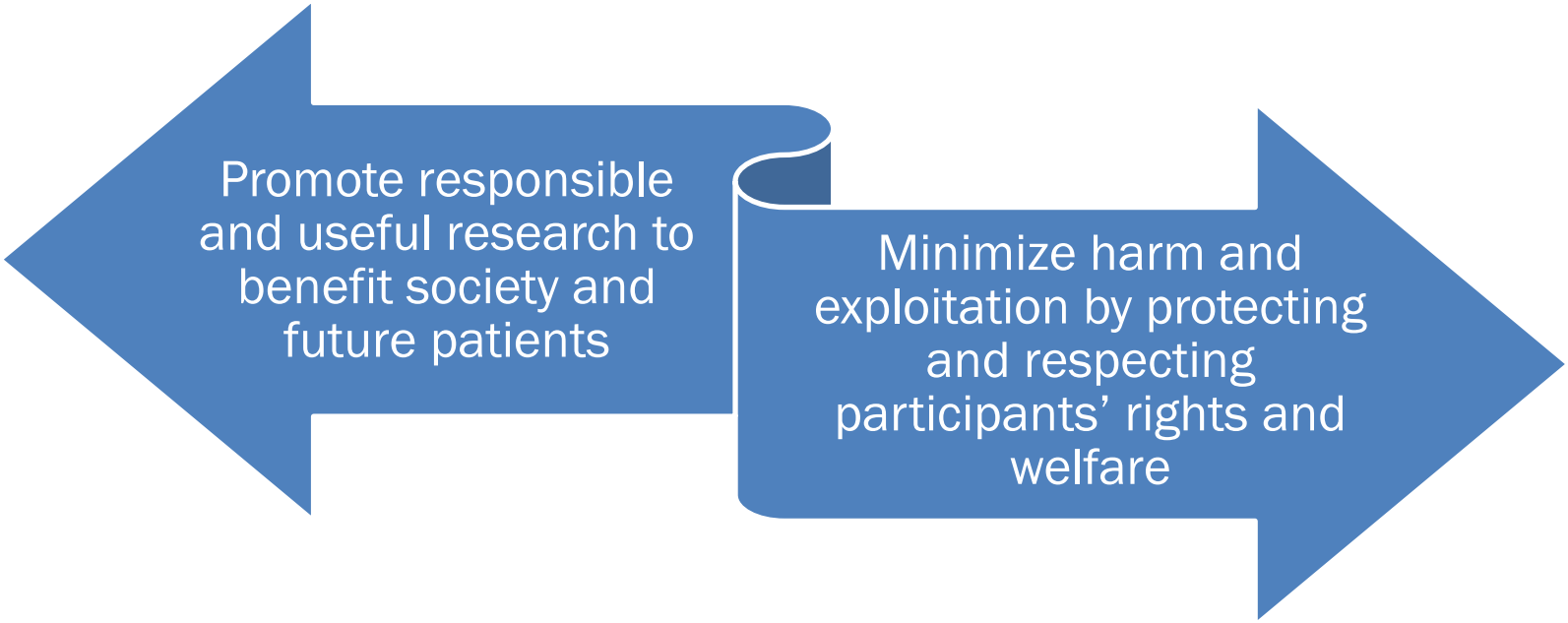
- Primary goal is to generate useful knowledge about human health and illness, NOT to benefit participants (although participants do sometimes benefit)

- A small number of participants asked to accept risk and burden to learn how to benefit others.

- Participants are the *means* to developing useful knowledge; 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



Ethics of Clinical Research

- Ethical requirements provide guidance about how to ethically conduct research in order to:
  - Promote the responsible conduct of research while seeking progress in understanding and intervening in human health and illness
  - Minimize the possibility of exploitation and harm for participants (and communities)
  - Ensure that participants' rights and welfare are respected and protected while they contribute to generating knowledge
  - Help to maintain public trust

Ethics of Conducting Clinical Research

- Historical Lessons

- Ethical Reasons

Ethics of Clinical Research: Five Historical Eras

- Pre-Rules
- Utilitarian
- Scrutiny
- Rules and Regulation
- Research as a Benefit

Emanuel & Grady. Four paradigms of Clinical Research and Oversight. Chpt 22, Oxford Textbook of Clinical Research Ethics 2008

Codes/guidelines/regulations

Selected codes and guidelines

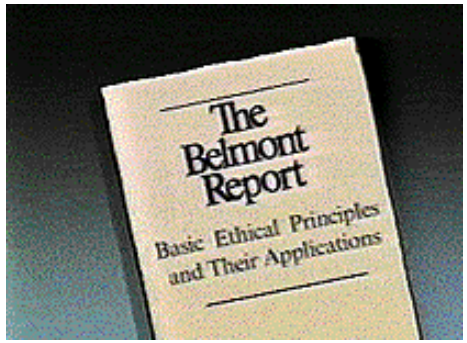
- Nuremberg Code (1949)
- Declaration Of Helsinki (1964-2013)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002, 2016)
- ICH/GCP-International Conference on Harmonization-Good Clinical Practice

Selected regulations

- The Common Rule (US 45CFR.46)
- FDA regulations (US 21CFR50 and 56, and others)
- Institutional (e.g.) NIH policy and guidelines
- Laws and regulations in other jurisdictions

The Belmont Report

- 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

Clinical research and clinical practice

- Different Goals
- Different Methods
- Different justification for risk to individuals
- Different levels of uncertainty
- Different obligations

Different Obligations

Clinical Care

- Clinicians have an obligation to competently offer care and treatment in their patients' best interests.

Clinical Research

- Researchers have an obligation to competently conduct research while respecting and protecting subjects' rights and welfare

Confusion reigns…

Guidance and regulations

- Most guidance in response to historical events
- Different regulations/guidance apply
- Some divergent recommendations or 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

Challenges

- Identifying partners
- Methods of engagement

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? (what will we learn and how useful will it be?)
- 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?
  - Science
  - Sponsors?

Highs and Lows of Research: Exploring Value in Research Cases

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ALAN WERTHEIME

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THE HASTINGS CENTER
REPORT

Article Full Access

The Social Value Requirement in Research: From the Transactional to the Basic Structure Model of Stakeholder Obligations

Danielle M. Wenner

First published: 26 December 2018 | https://doi.org/10.1002/hast.934 | Citations: 14

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Abstract

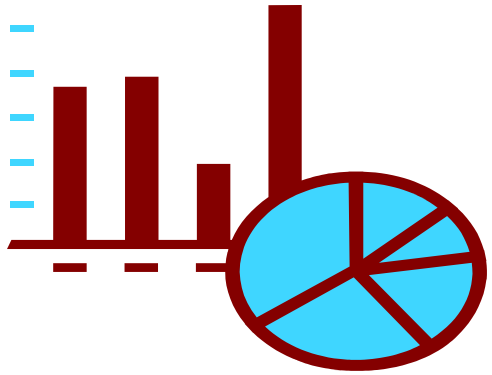
The history of research ethics includes ethical norms that do not neatly fit into a rubric of "human subjects protections" but that are nevertheless seen as fundamental ethical dictates. Among these norms is the so-called social value requirement for clinical research. Recently, however, the ethical foundation for the social value requirement has come under criticism. I seek to clarify the terms of this foundational debate. I contend that much of this discussion—both critiques of the social value requirement as well as recent defenses—is predicated on a framework of research ethics that I refer to as the "transactional model of stakeholder obligations." I argue that this model does not fully capture the ethical considerations that ought to inform the design and conduct of clinical research, and I introduce and defend an

1. Introduction

Research with humans has contributed immense value to society. For example, research has led to dramatic reductions in the incidence of devastating diseases like polio, mortali-

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

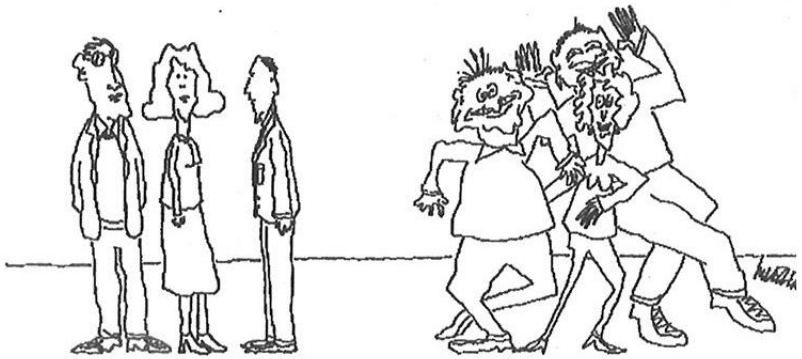


Research

- Science
- Ethics

Scientific validity: considerations

- Choice of endpoints
  - e.g. antibodies or infection or disease
- Choice of design
  - E.g. Randomized double blinded control; Noninferiority or superiority
  - Qualitative or quantitative or experimental
- Choice of procedures
  - E.g. Measures of outcome, length of follow- up
- Statistical methods and data management
  - E.g. Power, sample size, methods, level of significance
- Feasibility


CONTROL GROUP
OUT OF CONTROL GROUP.


BINGO! PEOPLE WHO DIDN'T HAVE A STROKE WERE MORE LIKELY TO DRINK SOY LATTE ON TUESDAY THAN GREEN TEA DAILY OR THE OCCASIONAL ESPRESSO!
EVERYONE SHOULD DRINK LOTS OF SOY LATTES!
AARGGHH! HELP ME BONFERRONI!
Statistically-Funny.blogspot.com


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group

Newer study designs

- Decentralized trials
- Pragmatic trials
- Platform trials
- Secondary analysis of data or biospecimens

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?
  - E.g. 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?

  - E.g. when should a study enroll pregnant persons?

Favorable risk-benefit

- Are risks to subjects necessary and minimized?
- Are risks justified by benefit to individual participants and/or the importance of the knowledge to society (social value)?
- 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

Challenges

- Identifying risks and benefits- which 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

U.S. Oversight

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

- Intramural Office of Human Subjects Research Protection (OHSRP) and Intramural Institutional Review Board https://irbo.nih.gov/confluence/display/IRBO/Home

Challenges in Independent review

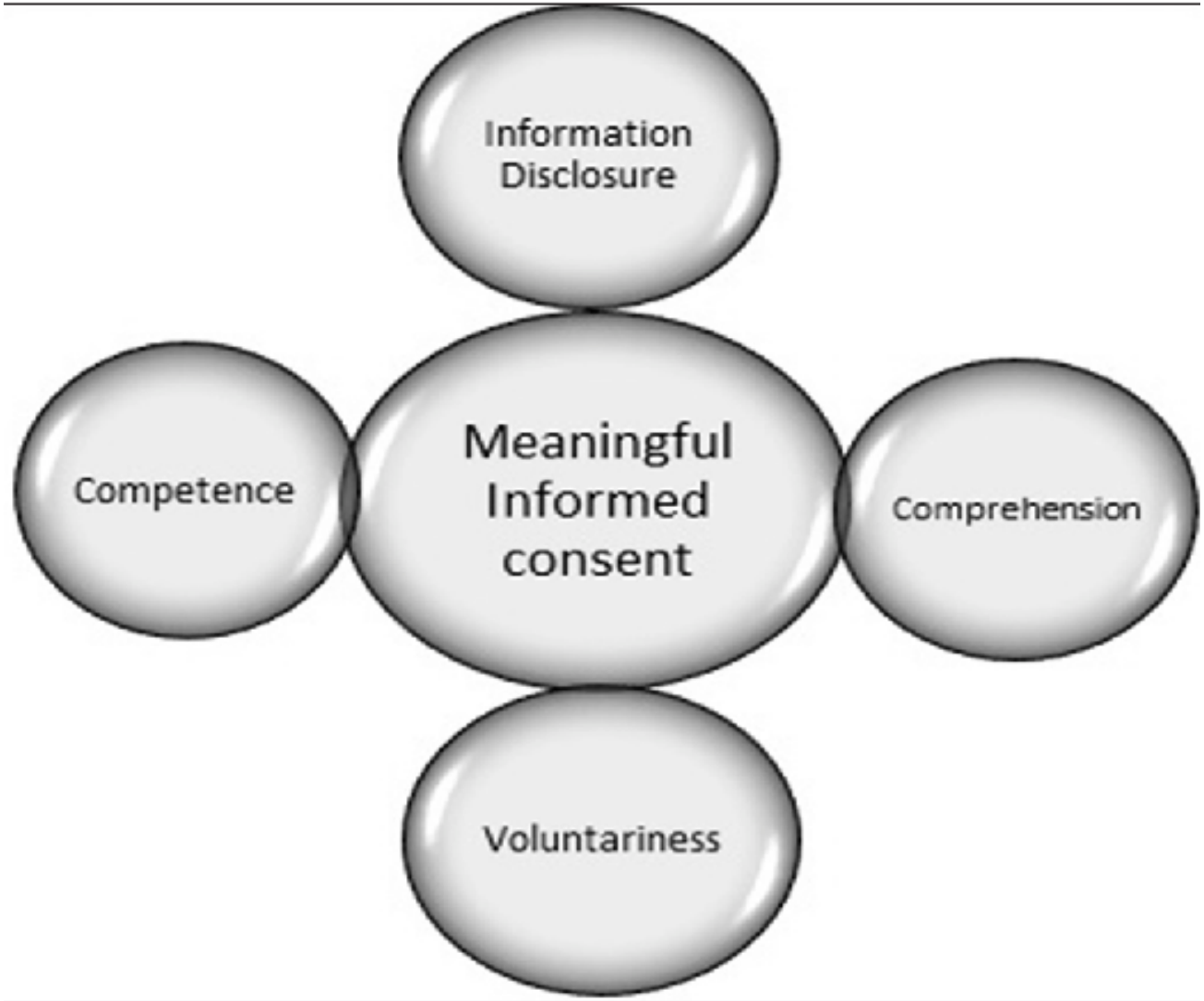
- Quality/effectiveness
- Volume
- Conflicts
- Varied interpretations (inconsistency)
- Single IRB review and reliance

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



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 participants

- 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

Respect for participants challenges

- Providing information and results

- Post trial access to interventions

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, others

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