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

Ethics of Clinical Research

- Why should we do research with human beings?

- If yes, how should we do it?

Why 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

Our Health

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Discoveries emerging from NIH-funded research have led to new ways to treat, diagnose, and prevent illness, ultimately effecting the health of the nation and the world.

The following represent some key areas in which NIH-funded discoveries have helped to make people healthier:

NIH Impact in the News

In January 2020, the FDA issued a policy prioritizing enforcement against, among other things, certain unauthorized flavored cartridge-based products that appeal to kids, including fruit and mint flavors.[1] The policy was informed by findings from studies in which NIH played a major role, including the Population Assessment of Tobacco and Health (PATH) study, and the Monitoring the Future (MTF) study. PATH findings indicated that flavored e-cigarette products particularly appeal to youth and promote initiation of vaping.[2] MTF findings indicate that youth are particularly attracted to cartridge-based e-cigarette flavors such as fruit and mint—much more so than tobacco or menthol flavored e-cigarettes, which are not flavors that are prioritized for enforcement.[3]

Americans are Living Longer, Healthier Lives

- Between 1970 and 2016, the **life expectancy of the average American increased** by eight years, from 70.8 to 78.6.[4]
- Between 1969 and 2015, **the death rate in the U.S. for all causes has decreased by 43%**, from 1279 per 100,000 people to 733.[4]

Other important benefits of clinical research

- E.g. economic:
- With a 2018 budget of $37 billion, NIH is the **largest single public funder of biomedical research** in the world. **Every state** and almost every Congressional district has earned a share of this investment.[1]
- In FY 2017, NIH extramural funding generated an estimated **$68.8 billion in economic output nationwide.**[2]
- In FY 2009 alone**, NIH funded 50,885 grants that directly supported 313,049 full- and part-time positions**, according to a recent, in-depth analysis conducted by NIH staff.[3]
- Discoveries arising from NIH-funded research provide a foundation for the U.S. biomedical industry, which contributed **$69 billion to our GDP.**[4,5]

https://www.nih.gov/about-nih/what-we-do/impact-nih-research/our-society#:~:text=With%20a%202018%20budget%20of,a%20share%20of%20this%20investment.&text=In%20FY%202017%2C%20NIH%20extramural,billion%20in%20economic%20output%20nationwide

Why clinical research is 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 (participants do sometimes benefit)

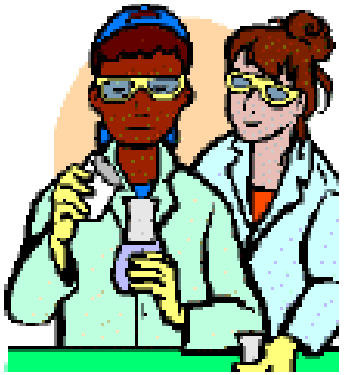
- We ask a small number of participants to accept risk to learn how to benefit others.

- 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

Clinical research and clinical practice

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



Different Obligations

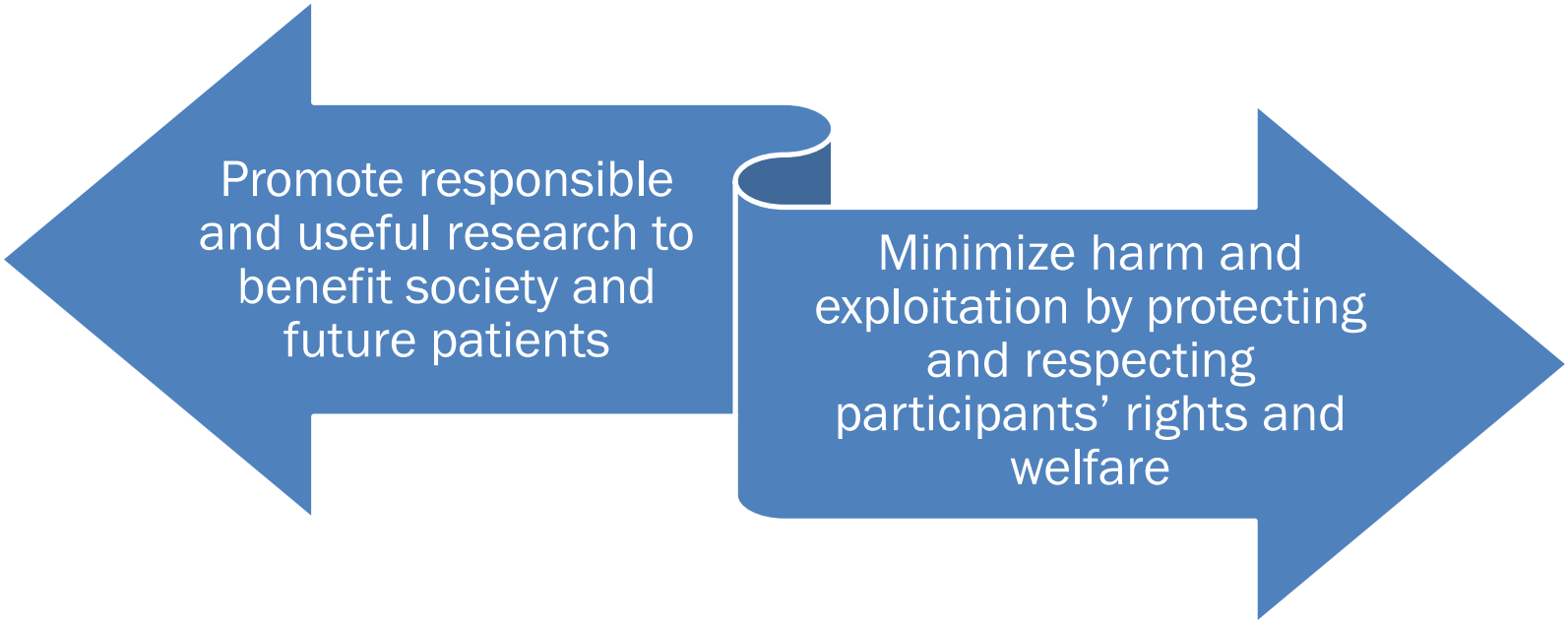
Clinical Care

- 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

Ethics of Clinical Research



Ethics of Clinical Research

- Ethical requirements and guidance:
  - 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
  - Ensure that participants' rights and welfare are respected while they contribute to generating knowledge
  - Help to maintain public trust

Conducting clinical research ethically

- Historical Lessons
- Ethical Reasons

Lessons from History

History of Ethics of Clinical Research: Five Eras

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

Codes/guidelines/regulations

Selected codes and guidelines

- Nuremberg Code (1949)
- Declaration Of Helsinki (1964-2008)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002)
- 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 from other jurisdictions

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

Confusion reigns…

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

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

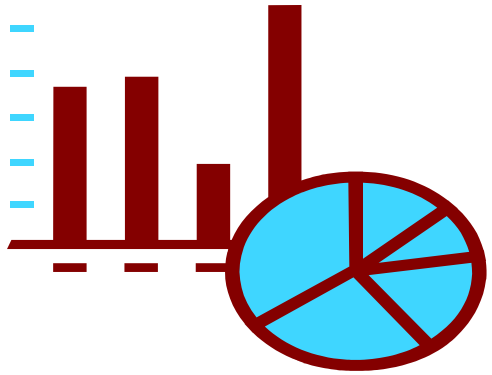
SUBSTANTIATING THE SOCIAL VALUE REQUIREMENT FOR RESEARCH: AN INTRODUCTION

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

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

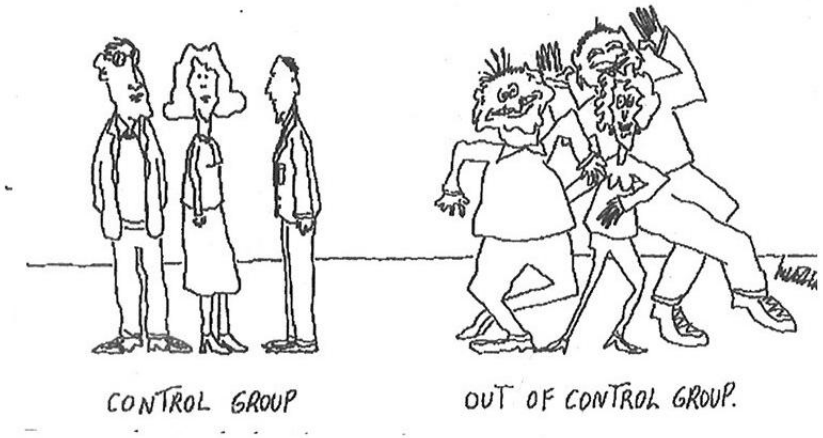


Research

- 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
- 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

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’

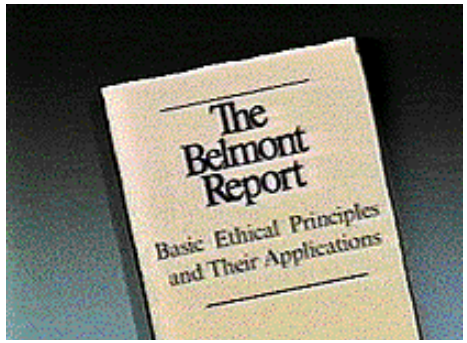
Subjects need access

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?

Protection of human subjects

- 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

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

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

U.S. Oversight

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

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 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

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