

# Framework for Ethical Conduct of Clinical Research

Christine Grady, RN PhD  
*Chief, Department of Bioethics*  
*NIH Clinical Center*

# 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

- Should we do research with human beings?
- If yes, how should we do it?

# 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

# IMPACT OF NIH RESEARCH

## Impact of NIH Research

[Our Health](#)

[Our Society](#)

[Our Knowledge](#)

[Our Stories](#)

## 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:

### Leveraging NIH Research to Respond to COVID-19

NIH investments in research over the years have provided a strong platform to jumpstart development of viable COVID-19 diagnostics, vaccines and treatments in record time, ensuring a rapid public health response to the COVID-19 pandemic.<sup>1</sup> Vaccines targeting SARS-CoV-2, the virus that causes COVID-19, were generated at unprecedented speed because knowledge from previous NIH-funded research on the 1918 Spanish flu and other coronaviruses like Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) was rapidly applied to the current pandemic. Rapid progress is also being made in the search for treatments for COVID-19, with drugs approved for other conditions being investigated for the treatment of COVID-19 which may speed up the development pipeline. For example a broad-spectrum antiviral, remdesivir, previously investigated for treating MERS and SARS, is now approved by the FDA for or the treatment of COVID-19 in hospitalized adult and pediatric patients.<sup>2</sup> Leveraging advances resulting from previous NIH-investments will not only help to stem the pandemic, but will also allow normal activities to resume and the economy to recover.

### 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.<sup>3</sup> 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.<sup>4</sup> MTF findings indicate that youth are particularly attracted to cartridge-based e-cigarette flavors such as fruit and mint—much more so than



# Other benefits of clinical research

## NIH Funding Contributes Directly to Economies across the Country

- 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.<sup>1</sup>
- In FY 2017, NIH extramural funding generated an estimated **\$68.8 billion in economic output nationwide**.<sup>2</sup>
- 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.<sup>3</sup>
- Discoveries arising from NIH-funded research provide a foundation for the U.S. biomedical industry, which contributed **\$69 billion to our GDP**.<sup>4,5</sup>

## NIH Research Drives Economic Growth

- A \$1.00 increase in public *basic* research stimulates an additional **\$8.38 of industry R&D investment** after 8 years. A \$1.00 increase in public *clinical* research stimulates an additional **\$2.35 of industry R&D investment** after 3 years.<sup>7</sup>
- The NIH's Human Genome Project (HGP) has resulted in nearly **\$1 trillion of economic growth...**
- NIH-funded basic research fuels the **entry of new drugs into the market** and provides a **positive return to public investment** of 43%, by some estimates.<sup>9,10</sup>

## Healthier Citizens Lead to a Healthier Economy

- Research-related gains in average life expectancy for the period from 1970 to 2000 have an economic value estimated at **\$95 trillion**, about **\$3.2 trillion per year**.<sup>12</sup>
- <https://www.nih.gov/about-nih/what-we-do/impact-nih-research/our-society>


# 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 and burden to learn how to benefit others.
- Participants are the *means* to developing useful knowledge; and are thus at risk of exploitation






# Ethics of Clinical Research



Promote responsible and useful research to benefit society and future patients



Minimize harm and exploitation by protecting and respecting participants' rights and welfare

# 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

- 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

# Ethical clinical research

- Historical Lessons
- Ethical Reasons

# Lessons from History



# 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 from other jurisdictions

# 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



# 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?
  - Sponsors?



## 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.<sup>1</sup> 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<sup>2</sup>, and the most recent version from 2013 continues to include

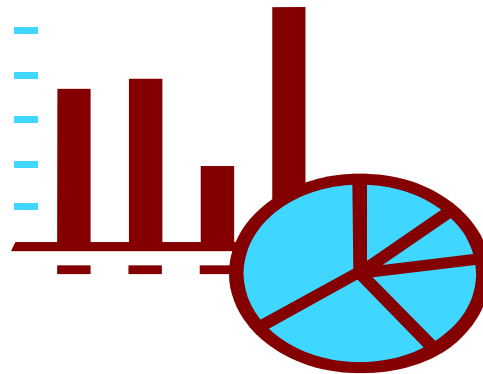
value, even calling it the ethical justification of health-related research.<sup>5</sup>

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 about the social value of research the same as



# 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

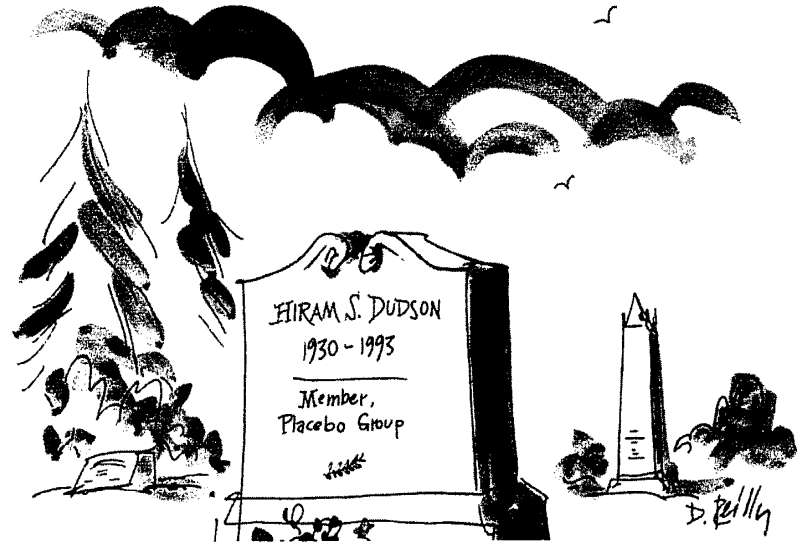
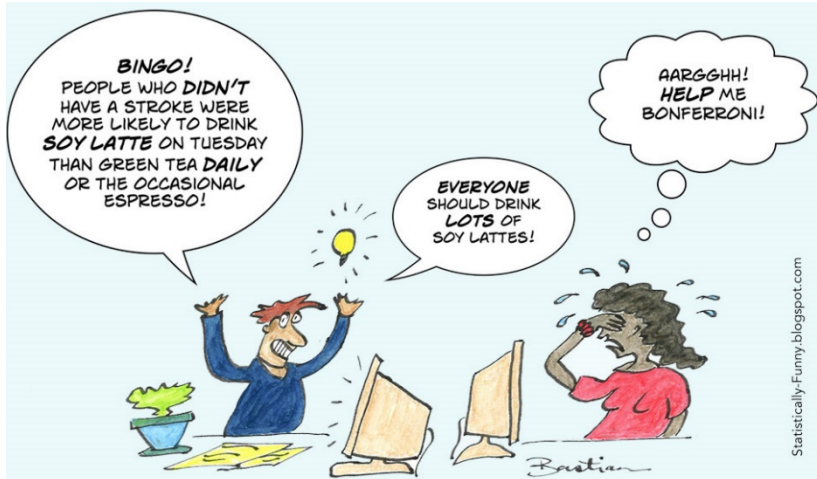
- Choice of endpoints
  - e.g. ischemic or hemolytic stroke
- Choice of design
  - E.g. Randomized double blinded control; Noninferiority or superiority
- Choice of procedures
  - E.g. Measures of outcome, length of follow- up
- Statistical methods and data management
  - E.g. Power, sample size, methods,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



CONTROL GROUP



OUT OF CONTROL GROUP.



# 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'

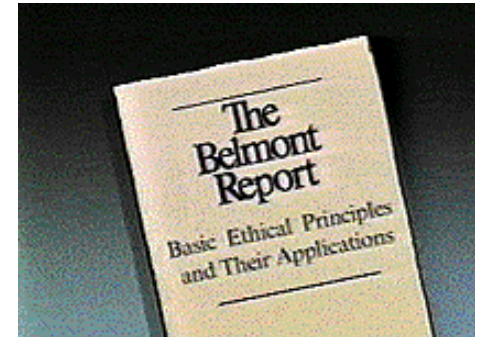
Subjects need  
access

# 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 participants 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, 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



# History of Ethics of Clinical Research: Five Eras

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

## The New York Times

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

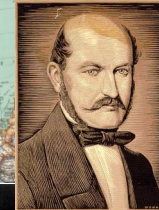
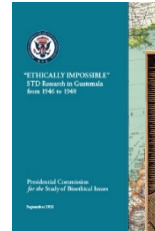
By JEAN HELLER  
The Associated Press

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



JOSEF MENGELE

