Framework for the 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 in their patients

IMPACT OF NIH RESEARCH

Impact of NIH Research

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

Search Impact of NIH Research

Spotlight:

NIH supports research that includes all people to improve treatments for all

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.

Improving Health

Discoveries emerging from NIH-supported research have led to new ways to prevent, diagnose, and treat

Revolutionizing Science

NIH fuels the biomedical research enterprise—cultivating world-class scientists and catalyzing new scientific

Serving Society

NIH-supported research leads to improvements in health that can bolster the economy, improve productivity, and

IMPACT OF NIH RESEARCH

Impact of NIH Research

Improving Health

Revolutionizing Science

Serving Society

Our Stories

Search Impact of NIH Research

Serving Society

NIH-supported research leads to improvements in health that can bolster the economy, improve productivity, and reduce the costly burden of illness in the U.S. and worldwide. NIH funding also spurs economic growth, both by supporting jobs in research and by generating biomedical innovations that lead to growth in the biotechnology sector.

Explore the sections below to discover more about how NIH serves society.

Printer-friendly version of this page pdf

Direct Economic Contributions

Spurring Economic Growth

Societal Benefits of Improved Health

Societal Benefits from Research

Why is clinical research ethically challenging?

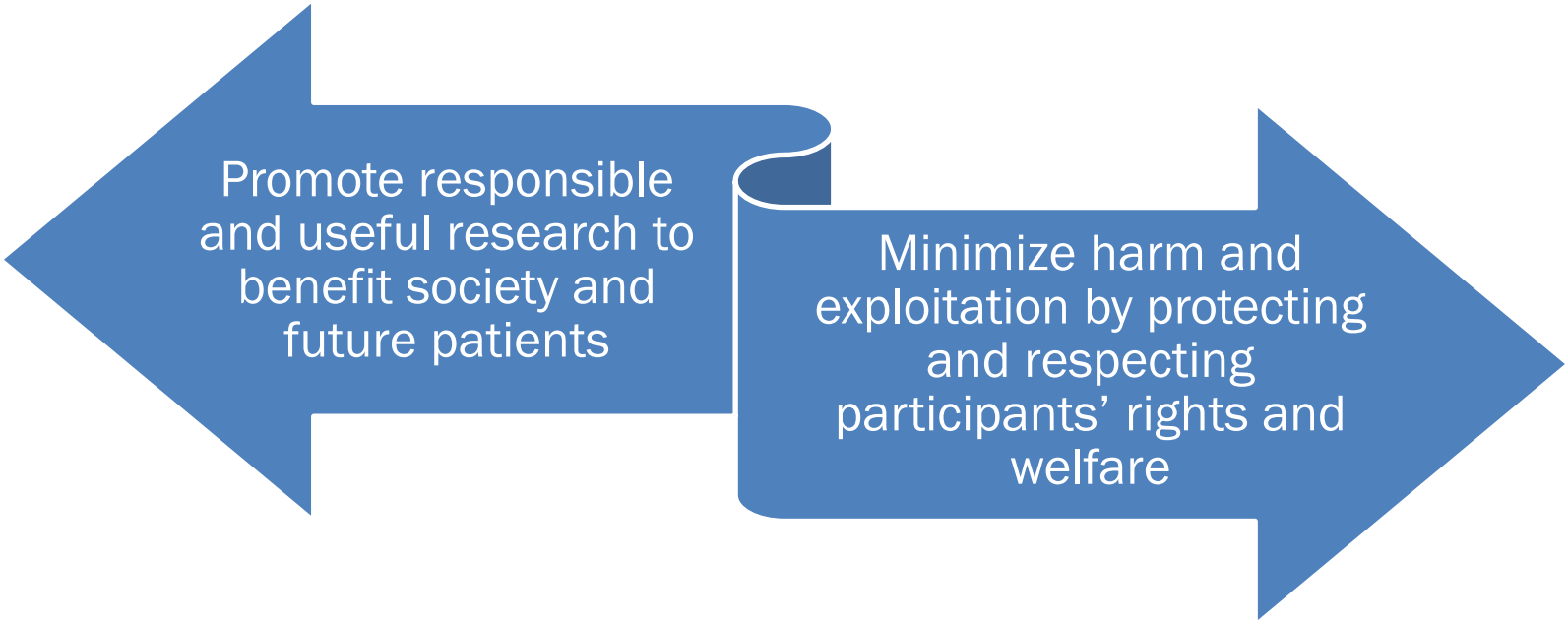
- Primary goal is to generate useful knowledge about human health and illness, NOT to benefit participants (although participants do sometimes benefit)

- 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


APRIL 22, 2002
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 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 and protected while they contribute to generating knowledge
  - Help to maintain public trust

Ethics of Clinical Research

- Historical Lessons

- Ethical Reasons

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

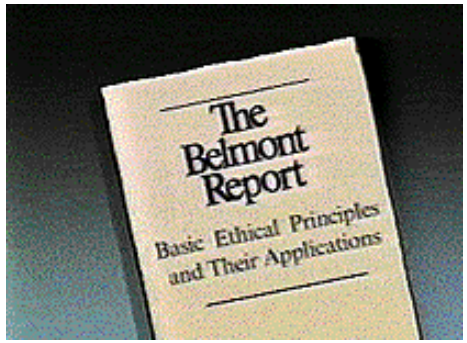
- Nuremberg Code (1949)
- Declaration Of Helsinki (1964-2013)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002, 2016)
- ICH/GCP-International Conference on Harmonization-Good Clinical Practice

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

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

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

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.

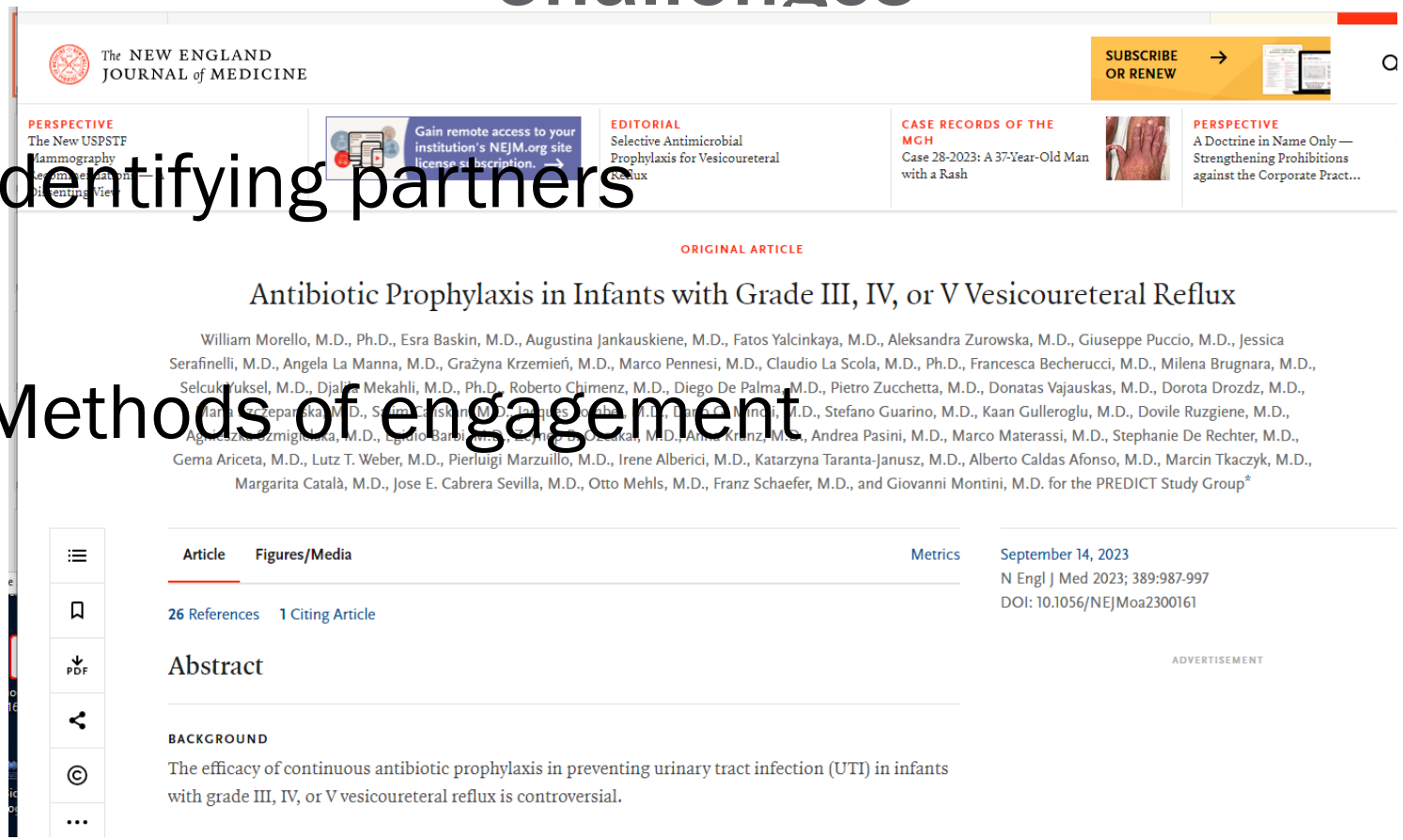
Collaborative partnership

Challenges

- Identifying partners
- Methods of engagement

Challenges

- Identifying partners
- Methods of engagement



292 infants randomized (867 screened), 39 European centers, multiple countries

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?

bioethics

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 31 Number 2 2017 pp 72–76

doi:10.1111/bioe.12321

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

Highs and Lows of Research: Exploring Value in Research Cases

Will Schupmann and Christine Grady

The Oxford Handbook of Research Ethics
Edited by Ana S. Iltis and Douglas MacKay

Subject: Philosophy, Moral Philosophy Online Publication Date: Mar 2022
DOI: 10.1093/oxfordhb/9780190947750.013.3

Abstract and Keywords

One way of conceptualizing the principal achievements and failures of human research is to consider to what extent research has contributed value to society. Research is generally considered to have value if it has the prospect of producing knowledge that can be used toward improvements in health or well-being. The authors selected nine case studies of research during the twentieth and twenty-first centuries that illustrate multiple ways research has achieved or failed to achieve value. Included in the "highs" of research are the development of antiretroviral therapy for HIV, Michael Marmot's Whitehall studies, and the evaluation of hormone replacement therapy, among others. The authors' cases of "lows" include genetic research on the etiology of homosexuality, the US Public Health Service's Guatemala sexually transmitted disease experiments, and the gene transfer experiment that Jesse Gelsinger participated in, among others. A retrospective analysis of how research has and hasn't contributed value may inform more thoughtful assessments of value in future research.

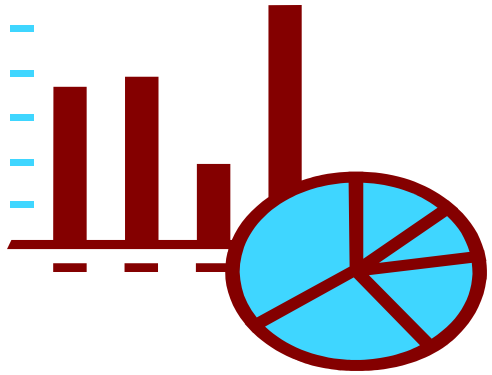
Keywords: research ethics, social value, history, clinical research, social science, epidemiology

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

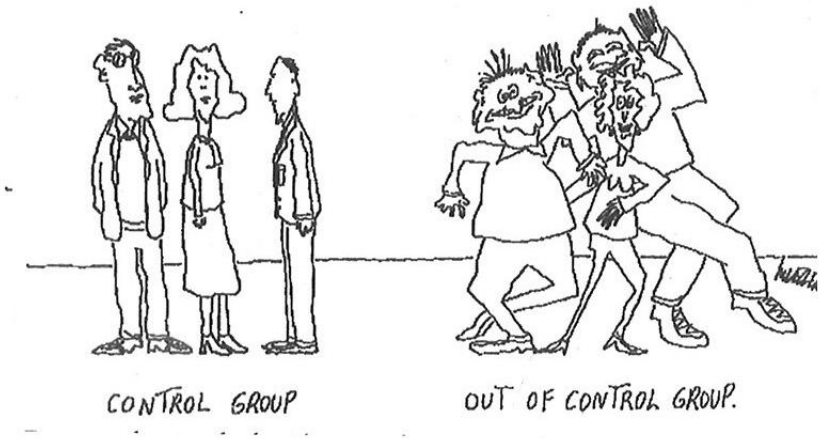


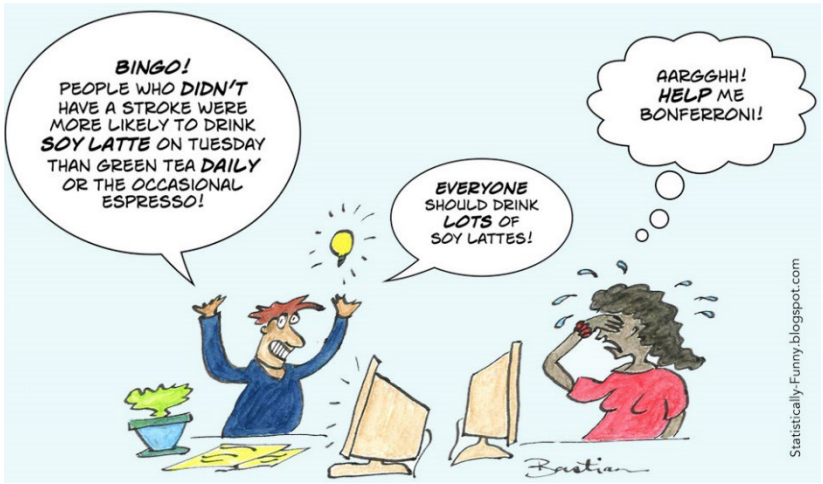
Research

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

Challenges in Independent review

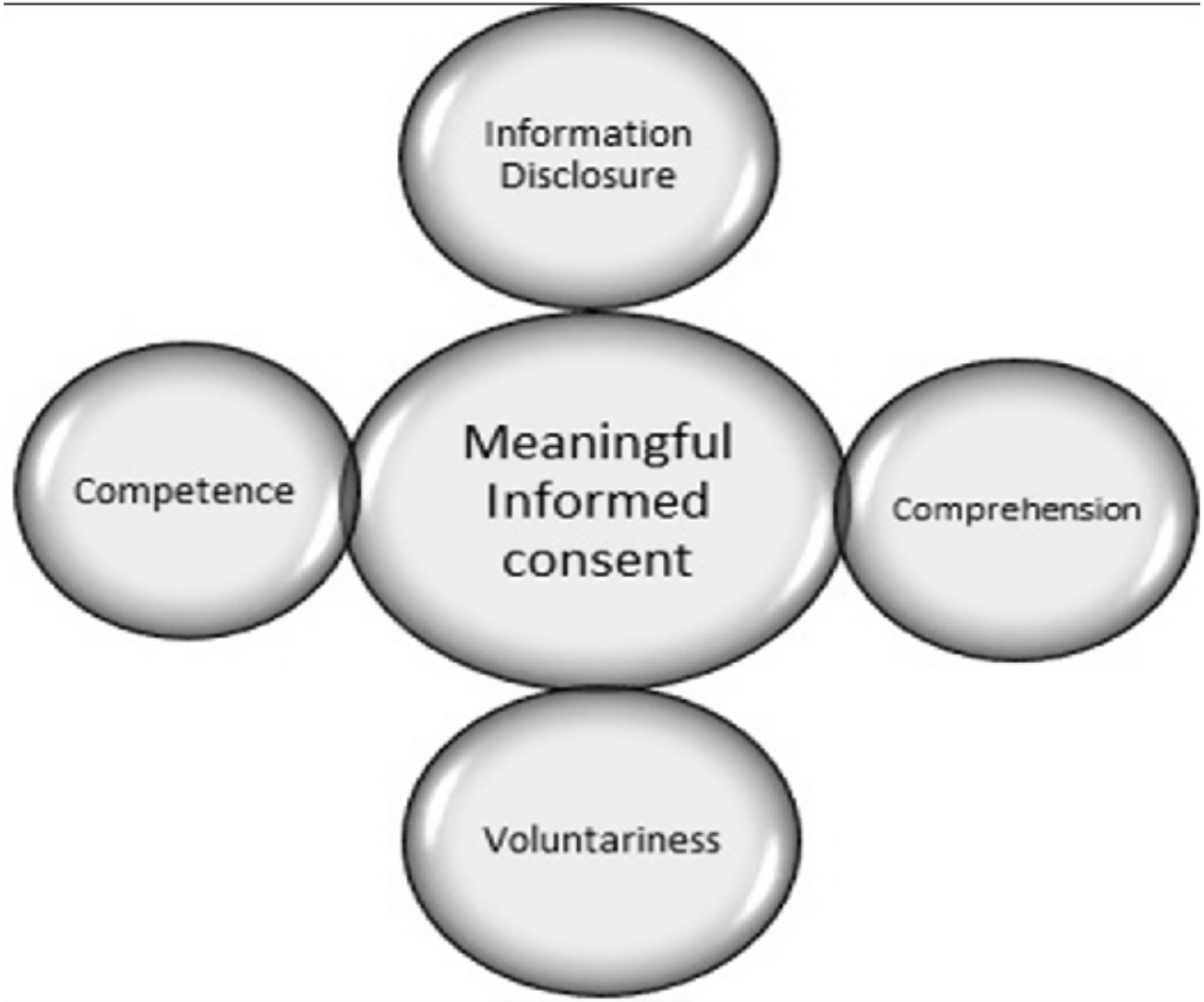
- Quality/effectiveness
- Volume
- Conflicts
- Varied interpretations (inconsistency)
- Single IRB review and reliance

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