

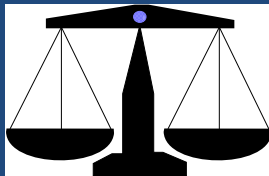
Ethics of clinical research

- The goal of clinical research is to generate useful knowledge about human health and illness, and ways to prevent, diagnose and treat diseases.
- The goal is not benefit to the individuals who participate (although there is sometimes benefit)
- People are the *means* to developing useful knowledge; and are thus at risk of exploitation



Ethics of clinical research

- Promote benefits to society and future patients
- Protect and respect rights and welfare of participants



Ethics of Clinical Research: Lessons From 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

Selected Codes and Guidelines

- Nuremberg Code (1949)
- Declaration Of Helsinki (1964- 2000, 2008?)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002)
- ICH/GCP-International Conference on Harmonization- Good Clinical Practice

The Belmont Report

- Ethical principles underlying the conduct of research:
 - Respect for persons
 - Beneficence
 - Justice



<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

Distinction between clinical research and clinical practice

- Goals
- Methods
- Risks

– The Belmont Report



U.S. Regulations and Guidelines

- The Common Rule (US 45CFR.46)
- FDA regulations (US 21CFR50 and 56, and others)
- NIH policy and guidelines

45CFR.46 Protection of Human Subjects

- Composition and function of a local institutional review board (IRB)
- Criteria for IRB approval of proposals
- Requirements regarding informed consent

45CFR 46

- Subpart B- Fetuses, pregnant women, and human *in vitro* fertilization
- Subpart C- Prisoners as subjects
- Subpart D- Children

FDA REGULATIONS

- 21CFR.50 Protection of Human Subjects (informed consent)
 - Subpart D on research with children
- 21CFR.56 IRB composition and function
- IND and IDE 21CFR.312 and 21CFR.812

Existing guidance

- Most developed in response to specific problems
- Some issues incompletely addressed, include divergent recommendations
- Need for a systematic, coherent, universally applicable framework

Ethical framework: 7 principles

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel L, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000, 283(20):2701-11; [Oxford Textbook of Clinical Research Ethics 2008](#)

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

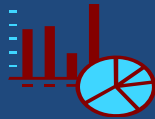


Social Value

- Promote benefit to society
- Minimize exploitation
- Justify asking individuals to accept risk or burden
- Responsible use of resources

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



Scientific validity, e.g.

- Choice of endpoints
 - e.g. infection, survival, viral load, tumor response, cardiac function
- Choice of design
 - RCT or not, blinded or not?
 - Choice of control?
 - Primary outcome
- Choice of procedures
 - Measures of outcome, length of follow-up
- Statistical methods
 - Power, methods, level of significance
- Feasibility



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)
- Fairly distribute harms and benefits
- No exclusion without justification



Research as burden or benefit?

Research as
'burden'
Subjects need
protection



Research as
'benefit'
Subjects need
access

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

Risks in research

- Defining risks
 - Probability and magnitude
 - Types of risk
 - Uncertainty
- Minimizing risks
- Limiting risk

Benefits in research

- Defining benefits
 - Direct versus secondary benefits
- Maximizing benefits
- Balancing risks and benefits

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

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)
- NPRM proposals

Informed Consent

- The goal of informed consent is to ensure 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

Informed Consent

- The voluntary consent of the human subject is absolutely essential. Nuremberg Code
- For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject...or authorized representative. CIOMS guidelines

Informed Consent

- “To the degree subjects are capable, they should be given the opportunity to choose what shall or shall not happen to them”. The Belmont Report
- Extra protections for those with limited capacity to consent

Informed consent

- Disclosure of information
- Understanding
- Voluntary decision making
- Authorization



IRB review of consent

Does the plan for informing participants about the objectives, risks, benefits, and alternatives of the study, assessing understanding, and seeking their voluntary agreement seem adequate?

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
 - Post trial planning

Respect for enrolled subjects

- During the course of the experiment the human subject should be at liberty to bring the experiment to an end... Nuremberg Code
- ...Every precaution should be taken to respect the privacy of the subject ,the confidentiality of the subject's information, and to minimize the impact of the study on ... physical and mental integrity and on the personality of the subject. Helsinki 2000

7 principles

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
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Framework

- Systematic and sequential
- Necessary
 - Procedural requirements may be waived
- Universal
 - Adapted and implemented according to context
- Require balancing, specifying

Balancing principles

- Example: Randomized Controlled Trials
- Balancing the need for a rigorous design with the obligation to maximize benefits and minimize harms

Ethical framework

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

- Educated and informed investigators and research teams
- Educated IRBs with diverse members including investigators, statisticians, ethicists, and lay people.

Changing Landscape

- Multi-site and multinational studies
- Learning Health Care systems, Quality improvement
- Comparative effectiveness research and usual care research
- Research using databases or samples
- Genomic data and sharing



Links to more information

- <http://www.hhs.gov/ohrp/>
- <http://ohsr.od.nih.gov>
- <http://www.fda.gov>
- <http://grants.nih.gov/grants/policy/hs/index.htm>
- <http://www.wma.net>
- <http://www.cioms.ch>
