Ethical Principles in Clinical Research

Christine Grady

Department of Bioethics

NIH Clinical Center

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Ethical principles

Are these studies ethical?

How do we know?

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 E, 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?

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

Respect for enrolled subjects

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