Ethical Principles in Clinical Research

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Dr. Progress proposes a placebo controlled study of a new promising drug in children and adults with a serious disease.

How do we know whether or not the proposed study is ethical?

Moral problem in 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

Ethical requirements in clinical research aim to:

minimize the possibility of exploitation;

ensure that the rights and welfare of subjects are respected while they contribute to the generation of knowledge.

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

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

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? *Journal of the American Medical Association* 2000; 283(20):2701-11

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

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

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 a burden
Subjects need protection
Research as benefit
Subjects need access

Vulnerability

There is an order of preference in selecting subjects, for instance, adults before children (Belmont Report)

Exclude vulnerable subjects unless their participation is needed for scientific reasons (CIOMS)

“Vulnerability”

“Relatively or absolutely incapable of protecting their own interests” – CIOMS, 2002

Regulations protecting vulnerable populations

Children (subpart D)

Prisoners (Subpart C)

Pregnant women, human fetuses, and neonates (Subpart B)

Cognitively impaired (? New regulations?)

Vulnerable populations

Additional safeguards:

- Proxy decision makers
- Limitations on risk
- Limitations on the type of research
- Consent monitoring
- Other

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 maximized?

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

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

Cartoon of interrogation process for the consent process.

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

Informed Consent

Federal regulations require the following information in the consent form

1) That it is research, the purpose, duration, and nature of the procedures
2) Risks
3) Benefits
4) Alternatives
5) Confidentiality of records
6) Compensation for injuries
7) Person to contact for answers to questions
8) Voluntariness and right to withdraw

IRB review

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

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Valid scientific methodology
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Favorable risk-benefit evaluation
Independent review
Informed consent
Respect for enrolled subjects

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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

RCT of a new anti-depressant. Investigator proposes a placebo-controlled trial because of the natural history of depression and available data on existing anti-depressants.

Case

Caregivers from the “home” with power of attorney for health care decisions, bring AB (46 year old post-menopausal mentally disabled woman with LCIS) for possible enrollment in STAR trial, randomized trial of tamoxifen v. raloxifene for the prevention of breast cancer in high risk women.

She fulfills all entry criteria but cannot consent.

Case

The physician wants the IRB to reconsider the subject selection criteria for the STAR trial.

The IRB debates the question:
Is it ethical to enroll a mentally incompetent patient in a Phase III randomized chemo-prevention trial to determine which of two hormonal therapies is better at preventing cancer with the fewest side effects?

Case

Stress informed consent.

She cannot consent. There are many eligible participants in the STAR trial. She is not necessary to the trial. Enroll patients who can consent.

Case

Stress risk-benefit ratio and social value

Informed consent is not an absolute requirement. She is at least as well off in the trial as in clinical care and will be contributing to scientific knowledge. (positive risk-benefit) As long as mentally disabled patients are not being unfairly targeted, she should be able to enroll.

Case

Stress fair subject selection

Denying her access to the STAR trial would be unjust. She meets eligibility criteria and has a similar risk-benefit ratio to other potential participants. The only reason for excluding her is unrelated to science but related to mental condition. This is discrimination.

Links to more information

http://www.wma.net
http://www.cioms.ch
http://ohrp.osophs.dhhs.gov
http://ohsr.od.nih.gov
http://www/fda.gov
http://grants.nih.gov/grants/policy/hs/index.htm
http://cme.nci.nih.gov