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)
- 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

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 ‘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 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
[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
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

• 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
• When can a placebo control be used?
  – Cold
  – Hypertension
  – Depression
  – Cancer
Case

- In a clinical trial testing the safety and efficacy of a novel intervention that has promise as an important treatment- is it more ethical to enroll mildly-moderately ill young adults or severely ill children?
• Stress informed consent
  – Adults should be enrolled because they can consent. As long as able to answer the scientific question, not necessary to enroll patients who cannot consent.
• Stress risk-benefit and social value
  – Informed consent is not an absolute requirement. The infants are at least as well off in the trial as in clinical care and will be contributing to scientific knowledge. Finding an effective treatment is more important for those with severe disease. The risk/benefit assessment is also more favorable since the severely ill infants have more to gain from successful treatment and less to lose if they suffer side effects than do the mildly ill young adults
• Cannot enroll ill infants since they are vulnerable

• Stay tuned…
Links to more information

- [http://www.wma.net](http://www.wma.net)
- [http://www.cioms.ch](http://www.cioms.ch)
- [http://ohrp.osophs.dhhs.gov](http://ohrp.osophs.dhhs.gov)
- [http://ohsr.od.nih.gov](http://ohsr.od.nih.gov)
- [http://www/fda.gov](http://www/fda.gov)
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