Ethical Considerations in Clinical Trials: 8 Principles Framework

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When is Clinical Research Ethical?

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

- How do we determine whether this study is ethical?
Goals of Research

- The goal of clinical research is to identify improved ways to prevent, diagnose and treat illness with the goal of improving health.

- Subjects are the means to gathering this information.
Benefits and Risks

• Participation in clinical trials sometimes offers subjects the potential for medical benefit.

• Research interventions and trials also expose subjects to risks and burdens for the potential benefit of future patients.
Primary Ethical Concern

• Exposing subjects to risks and burdens for the benefit of others raises the potential for exploitation.

• The many guidelines and policies for clinical research are designed to address this potential for exploitation.
In 1901, Walter Reed argues that ethical clinical trials require:

- Self-experimentation
- Written agreements with other subjects
- Payment in gold
- Restriction to adult subjects
- Using the phrase “with his full consent” in journal articles
Nuremberg Code

• The Nuremberg trial of Nazi doctors after World War II led to the Nuremberg Code, which contains 10 basic principles for clinical research.

• The first principle states that voluntary consent is “essential” to ethical research.
Declaration of Helsinki

- Adopted by the WMA in 1964, the Declaration of Helsinki has been modified 7 times, most recently in 2013.

- The DoH is intended to address shortcomings in the Nuremberg Code: it requires independent review and allows surrogate permission.
• Intended as an expansion on the DoH, especially for clinical trials in lower-income countries.

• Includes guidelines, along with fairly extensive commentary.

• Currently undergoing review.
Tuskegee

- Natural history study of syphilis started in 1932 in Macon County, Alabama with 400 infected African-American men and 200 controls.

- U.S. Public Health Service actively tried to prevent subjects from receiving penicillin.

- CDC formally decided to continue the study as late as 1969.
Termination

• A 1972 press reports leads the U.S. government to stop the study.

• By then, 74 participants were still alive and about 100 had died from syphilis.
National Commission

- In 1974, in response to Tuskegee, US Congress establishes the National Commission to propose protections for research subjects.

- The Commission issues the Belmont Report and recommendations for human subjects research which form the basis for current US regulations.
Influence of US Regulations

• As one of the earliest systematic national regulations, the U.S. regulations have had significant impact.

• In addition, studies which use US funds, US investigators, or are part of an application for US FDA approval must be consistent with the US regulations.
US regulations

- 45 CFR 46 subparts A-D are enacted in 1981 for the Department of Health and Human Services, including the NIH.

- Subpart A: general rules; B: pregnant women and fetuses; C: prisoners, D: children (Commission’s proposal on adults unable to consent was not adopted).
Common Rule

- In 1991, subpart A is adopted by 16 federal agencies, becoming the Common Rule.

- Because it has been adopted by so many different agencies, the Common Rule is difficult to change (current NPRM).
• FDA has similar regulations (21 CFR 50 and 56) to the Common Rule.

• The FDA regulations apply to trials that are used to support applications for FDA approval of products.
Requirements for IRB Approval

- Risks are minimized
- Reasonable risk/benefit ratio
- Fair subject selection
- Informed consent
- Data monitored
- Privacy and confidentiality protected
- Vulnerable subjects protected
Essential Elements of Consent

1. Purpose, procedures and fact that research
2. Risks
3. Potential Benefits
4. Alternatives
5. Level of confidentiality
6. Compensation, if any, for research harms
7. Whom to contact about the study
8. Statement that participation is voluntary
ICH/GCP

• Guidelines developed to harmonize drug development in the Japan, Europe and the US.

• Contain extensive requirements on informed consent and guidelines on conducting clinical trials.
Comparison

• Existing guidelines were developed for specific reasons, including past scandals and the desire for consistent drug approval process.

• As a result, while there is a good deal of overlap, there are also differences and outright conflicts between the guidelines.
Need for a Framework

• For example, the DoH, but not the Nuremberg Code, allows research with individuals who cannot consent.

• The gaps and conflicts in existing codes raise the need for a consistent framework.
8 Ethical Requirements

1) Collaborative partnership
2) Social Value
3) Scientific Validity
4) Fair subject selection
5) Favorable risk-benefit ratio
6) Independent review
7) Informed consent
8) Respect for human subjects

*Journal Infectious Dis 2004; 189:930-937; JAMA 2000; 283:2701-2711*
#1: Collaborative Partnership

• Community should be involved in the design, and conduct of research studies.

• Involvement of the community helps to ensure other principles are satisfied.

How identify the relevant community? How obtain input? Disagreements?
#2: Social Value

- Data obtained from study (typically in combination with other studies) should contribute to overall health. Results should be shared.

Should evaluation be comparative? Most difficult and ignored requirement?
Evaluation

- What treatments are available for the disease Dr. J wants to study?
- How safe and effective are they?
- Value of testing a new treatment?
- What about the particular drug suggests it might offer added value?
- Will this study as proposed answer a valuable and unsettled question?
#3: Scientific Validity

Design should answer the scientific question

- Include sufficient numbers, the requisite comparison groups, necessary tests?
- Appropriate laboratory and animal studies?
- Dose and duration of treatment, size and nature of sample, outcome measures?
- Is the placebo control justified?
#3: Scientific Validity

- Study, as designed, is likely to be completed (study demands, parking)

- Assessment of feasibility must consider
  - the nature of the disease
  - the community in question
  - the resources available for the study
  - number of potential subjects
#4 Fair Subject Selection

- Fair distribution of risks and potential benefits within and across communities

- Start by assuming everyone is eligible.

- Exclude individuals only when there is a good scientific or ethical reason.
Evaluation

• Certain groups at higher risk?

• Or more likely to benefit?

• Promote access or protect from risks (e.g. adults who cannot consent)_FF

• When is enrollment of children justified?
#5: Favorable Risk-Benefit Ratio

Step #1: **Minimize risks**
- Use qualified research team
- Eliminate duplicative procedures

Step #2: **Enhance potential benefits**
- Maximize scientific information
- Provide clinically relevant information
#5: Favorable Risk-Benefit Ratio

Step #3: **Weigh risks and benefits:** Do the potential benefits to the subjects, if any, justify the risks they face?

Step #4: **If YES:** Risks acceptable

**If NO:** Are the ‘net’ risks acceptable and justified by the social value of the information to be collected?
#6: Independent Review

- Independent Committee needs
  - Scientific, cultural, and ethical expertise
  - Authority to modify or stop the study

- Committee should provide initial and ongoing assurance that ethical principles are met.

How evaluate effectiveness of IRBs?
#7: Informed Consent

- Participants should understand:
  - Their medical and personal situation
  - The purpose, methods, risks, potential benefits, and alternatives to the research

- How much needs to be understood depends on the study in question.
Waiver/Alteration

- The requirements for informed consent may be altered or waived by the IRB when appropriate.

- Alteration may be appropriate when a complete waiver is not (e.g. learning health care).
Incompetent Participants

- Avoid enrolling individuals who are unable to consent

- Have safeguards in place when there is a compelling reason to enroll them:
  - proxy decision maker
  - assent
#8: Respect for Subjects

Respect enrolled subjects
- Ethically sensitive research team
- Understand individuals and community
- Monitor subjects’ welfare
- Right to withdrawal
- Turn subjects into participants: research with rather than on subjects
Application

• There is no recipe that allows investigators to apply the framework in specific cases.

• Instead, judgment is necessary to determine how the principles apply in specific cases. For example, what are valid ways to indicate consent?
Conflicts

• In some cases, two or more principles may conflict.

• For instance, increasing the scientific value of studies can lead to increased risks, whereas reducing risks can reduce the scientific value of the study (e.g. fewer scans or blood draws).
Resolving Conflicts

• In cases of conflict, choices must be made based on the relative importance of the competing considerations in the case.

• How great are the increased risks? How valuable is the added information? Can the subject consent to the risks?
Expertise and Process

The need for judgment in applying and balancing the principles emphasizes the importance of knowledgeable and committed individuals, and an effective process, to ensure clinical research is ethical.
Status

• The 8 requirements are universal. They apply to clinical research everywhere.

• However, the 8 requirements must be adapted to the local health, economic, cultural and technological circumstances.
Research for Pay

• The majority of clinical trials are now sponsored by industry.

• This raises important issues, including investigator conflicts of interest, whether participants’ should share in profits, whether sponsor conflicts undermine accurate reporting of results.
Some Other Current Issues

- Maximum threshold of net risks for competent adults?
- When are trials without consent acceptable?
- Ethical to expose individuals who cannot consent to research risks?
- Ethics of research versus clinical care?
Summary

- Clinical research has great potential to improve health.
- It also raises important ethical challenges.
- The 8 principles provide a framework to help to address these challenges.