Ethical Framework for Randomized Controlled Trials

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Disclaimer

- The views presented are mine and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

Overview

- Discuss the importance of distinguishing clinical trials from medical care
- Present an ethical framework for randomized controlled trials (RCTs)
- Highlight key ethical issues concerning enrolling research subjects with diminished capacity to give informed consent.

The Ethics of Clinical Trials

- A key issue in the ethics of clinical trials is the distinction between clinical trials and medical care.
- This is relevant to controversial topics:
  - Control group selection, especially use of placebos
  - When to stop clinical trials early
  - What counts as informed consent.

Distinction between Research and Medical Care

- Clinical trials are often viewed as a form of medical therapy in a way that confuses the ethics of clinical trials with the ethics of medical care.

- Therapeutic orientation to clinical trials

Therapeutic Orientation

- Investigators are described as physicians and research subjects as patients:
  - Recruitment advertisements
  - Consent documents
  - Articles reporting results of RCTs
- It is frequently claimed that the RCT offers patients optimal or “state of the art” medical care.

Clinical Setting

- Conduct of RCTs in clinical settings reinforces therapeutic orientation:
  - Investigators and members of the research team wear white coats.
  - Research procedures used to answer scientific questions are performed with the same medical technology used in standard medical care.

Ethical Distinction Between Clinical Trials and Medical Care

- RCTs differ from medical care:
  - Purpose
  - Characteristic methods
  - Justification of risks

Purpose of RCTs

- To produce generalizable knowledge about treatment efficacy and safety by controlled experimentation in *groups* of patients with the aim of promoting improved medical care.
- Contrasts fundamentally with goal of medical therapy to provide personal care for *particular* patients.

Characteristic Methods

- RCTs include randomization, blinding, placebos, protocols restricting treatment flexibility, and research procedures to measure study outcomes.
- These methods employed to answer scientific questions are foreign to the ethos of medical care.

Justification of Risks

- RCTs include procedures for scientific purposes that carry risks of discomfort or harm to subjects without a prospect of benefit to them. These are justified by anticipated value of knowledge.
- In medical care, the risks of diagnostic and treatment interventions are justified by potential medical benefits to patients.

Ethical Framework

- Emanuel E, Wendler D, Grady C. What Makes Clinical Research Ethical? JAMA 2000;283:2701-2711.

- Based on Nuremberg Code, Declaration of Helsinki, Belmont Report, US Federal regulations, literature on research ethics.

7 Ethical Requirements

- Scientific/Clinical Value
- Scientific Validity
- Fair Subject Selection
- Favorable Risk-Benefit Ratio
- Independent Review
- Informed Consent
- Respect for Enrolled Subjects

Scientific Value

- Purpose of RCT is to answer a clinically relevant research question.
- If there is no point to answering the question, then the research should not be done.

Scientific Validity

- Various components of RCTs are meant to promote valid, unbiased data:
  - Randomization
  - Control group
  - Blinding
  - Prospective assessment using reliable outcome measures
  - Adequately powered sample

Scientific Validity

- A clinical trial is worthless if it is not well designed to answer a research question.
- Good science is an ethical requirement for RCTs.
- Without adequate value and validity, risks to research subjects can't be justified.

Fair Subject Selection

- Targeting vulnerable populations for clinical research is unfair if it is not necessary to answer valuable scientific questions.
- Restricting access to research without a good reason is also unfair.

Favorable Risk-Benefit Ratio

- Minimizing risks
  - Risks can't be reduced to zero.
  - Risks are to be minimized consistent with answering scientific questions.
- The potential benefits from RCTs must be sufficient to justify risks to participants.

Benefits

- Two types of benefits:
  - Direct medical benefits to subjects
  - Value of knowledge to be gained

Risk-Benefit Assessment

- Are the risks to participants of research interventions outweighed by the potential direct benefits to them?

- Does the knowledge to be gained by the study justify the risks that are not compensated by benefits to subjects?

Independent Review

- To protect subjects from exploitation and harm, clinical research should be conducted only after prospective independent review.

- The task of the IRB is to protect research subjects by applying the other 6 ethical requirements in the review, modification, and approval of protocols.

Informed Consent

- No competent adult should be enrolled in research without informed consent.
- Two basic components:
  - Understanding what research participation involves
  - Voluntary agreement to participate

The Therapeutic Misconception

- A key problem in obtaining informed consent to RCTs is the propensity of patients to confuse treatment in study with routine clinical care.
- Therapeutic misconceptions about the design and conduct of RCTs raise doubts about the adequacy of informed consent.

Respect for Enrolled Subjects

- Protecting privacy and confidentiality
- Monitoring of subjects and stopping trial participation if their health is being compromised
- Informing subjects of study results

Subjects Lacking Ability to Give Informed Consent

- In general, subjects unable to give informed consent should not be enrolled in research unless their participation is necessary to answer important research questions.
- Subjects with cognitive impairments should be carefully assessed to determine if they have capacity to give informed consent.

Surrogate Authorization

- When it is ethically appropriate to enroll subjects unable to give informed consent, informed authorization should be obtained from surrogate decision makers.
- Surrogates should decide in light of values and preferences of subjects.