What Makes Clinical Research Ethical?

Answers

1) Informed consent
2) Compliance with the Ten Commandments
3) IRB review
4) Informed consent and IRB review
5) Compliance with Nuremberg, Helsinki, and Belmont
6) Compliance with 45 CFR 46
7) All of the above

What Is the Common Rule?

Answers

1) The “Golden Rule” for plebeians
2) The rules that are shared among all IRBs
3) The Ten Commandments abridged for clinical researchers
4) The Federal rules regulating conduct of clinical research

Case

- BY is a 46 year old post-menopausal mentally disabled woman with LCIS.
- Caregivers from her "home" with power of attorney for health care decisions, bring her to the clinic for 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 who saw BY 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?

DISCLAIMER

These are my personal views and should not be construed to represent the official views or policies of the National Institutes of Health, Public Health Service, or the Department of Health and Human Services.

Justification for Ethical Guidelines

Why do we need ethical guidelines or requirements for human subjects research?

Justification for Ethical Guidelines

- Historical Reasons
- Ethical Reasons

Historical Justification

- 1747 Lind's evaluation of 6 different interventions on 12 sailors for the treatment of scurvy.

- 1776 Robertson's observations on the comparative efficacy of bark on the treatment of "continuous fever" aboard the Juno.

Historical Justification

- 1847 Semmelweis in Austria uses chlorinated lime to sterilize obstetricians' hands to prevent puerperal fever.

- 1898 Fibiger in Denmark treats every other patient with anti-diphtheria serum to establish suitable controls.

Historical Justification

- 1917 Goldberger conducts a comparative study of diet in two orphanages for treatment of pellegra.

- 1931 First randomization and patient blinding in a trial of gold for TB.

Historical Justification

- 1934 First multi-center trial in Britain evaluating serum treatment of pneumonia in London, Edinburgh and Aberdeen.
- 1938 First placebo control in a trial of cold vaccines.
- 1948 First modern randomized placebo controlled trial of Streptomycin for TB.

Historical Justification

The first recorded mention of consent occurs in a 1767 British law suit

Slater v. Baker & Stapleton in which two physicians were held liable for re-breaking a bone because:

"It appears from the evidence of the surgeons that it was improper to disunite the callous without consent; this is the usage and law of surgeons…"

Historical Justification

- Arguments for the importance of consent in research occurred before 1900.

- 1892 Coley injected patients with cancer to induce artificial erysipelas. He describes how he began treatment with a patient who had a sarcoma and only “after some deliberation he consented” and injections began.

Historical Justification

- 1897 Sanarelli announced he discovered the bacillus of yellow fever and produced yellow fever in 5 patients.

- 1898 Osler condemns Sanarelli:

  "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."

Historical Justification

- 1900 Yellow Fever Board established in USA
- 1901 Walter Reed decides that ethics of research required:
  - Self-experimentation
  - Written agreements with other subjects
  - Payment in gold
  - Restriction to adult subjects
  - Using the phrase “with his full consent” in all journal articles.

Historical Justification

- 1946-49 Nuremberg Trial and formulation of the Nuremberg Code.
- Nuremberg Code contains “certain basic principles [that] must be observed in order to satisfy moral, ethical and legal concepts.”
- The first and longest principle is “The voluntary consent of the human subject is absolutely essential.”

Historical Justification

- The problem with the Nuremberg Code is that informed consent would not have made the Nazi experiments ethical. The Code mistakes the problem.

- The problems are:

  Coerced subjects

  Unfavorable risk-benefit ratio

Historical Justification

- 1964 World Medical Assembly issues the Declaration of Helsinki with 22 recommendations “as a guide to every physician in biomedical research involving human subjects.”

- Revised 5 times since 1964—most recently in 2000.

Historical Justification

- 1966 Beecher's article in The New England Journal delineating 22 examples in which patients "never had the risk satisfactorily explain to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered."

Historical Justification

Beecher's 22 examples included:

- Withholding antibiotics from men with rheumatic fever,
- Injecting live cancer cells into nursing home patients (Jewish Chronic Disease Hospital),
- Transplanting melanoma from daughter to mother who died about a year and half later.

Historical Justification

- Tuskegee

  1932 in Macon County Alabama

  400 syphilitic African-American men and 200 uninfected controls

  USPHS actively tried to prevent men from receiving penicillin

  1969 CDC formally decided to continue the study

Historical Justification

- Tuskegee

  1972 press reports caused DHEW to stop the study.

  In 1972 74 participants were still alive and about 100 subjects had died from syphilis.

Historical Justification

- Tuskegee led to the National Commission which issued the Belmont Report defining 3 ethical principles for research:

  Respect for Persons

  Beneficence

  Justice

- Also led to institutionalization of IRBs.

Ethical Justification

- Clinical research develops generalizable knowledge that improves health or increases understanding.

- People who participate in clinical research are a means to securing that generalizable knowledge.

Ethical Justification

- As means, these people can be exploited, that is be used as a means for the benefits of others.

- Ethical requirements for clinical research are meant to minimize the possibility of exploitation.

Ethical Guidelines

- 1947 Nuremberg Code
- 1964 Declaration of Helsinki
- 1979 Belmont Report
- 1982 CIOMS
- 1991 Common Rule

Ethical Guidelines

- All ethical guidelines developed in response to a problem— “born in scandal”.
- They respond to the controversy and do not provide a systematic ethical framework. Frequently, they are incomplete.
- The guidelines also contradict each other.

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

Collaborative Partnership

- To be ethical clinical research must involve the community in which it occurs.

- This requires:
  - community participation in planning, conducting and overseeing research, and integrating research results into the health system.
  - avoidance of supplanting existing health care services and the sharing rewards with the community.

Collaborative Partnership

- Mechanisms to achieve collaborative partnership can be achieved by:
  - Community advisory boards
  - Patient advocates on scientific advisory boards
  - Advocates for funding of research

Social Value

- To be ethical clinical research must lead to improvements in health or advancement in generalizable knowledge.

- Must consider how the research will improve health of:
  - Participants in the research
  - Community in which research is conducted
  - World

Social Value

- Valueless research includes non-generalizable studies, “me too” studies, and non-disseminated research.

Scientific Validity

- Research must be conducted in a methodologically rigorous manner that is practically feasible.

- To be ethical the research must produce reliable and valid data that can be interpreted.

Scientific Validity

- Invalid research includes underpowered studies, studies with biased endpoints, instruments, or statistical tests, and studies that cannot enroll sufficient subjects.

Fair Subject Selection

- The scientific objectives of the study—not vulnerability or privilege—should guide inclusion criteria and targeted populations.

- Lowering risk and enhancing generalizability can then be considered.

Fair Subject Selection

- Convenient groups should not be selected.
- Groups cannot be excluded without scientific reasons.
- Higher risk is a reason to exclude certain groups.

Fair Subject Selection

- Should not select rich, politically powerful or otherwise well connected people for "promising research" studies.

- Endostatin example.

Favorable Risk-Benefit Ratio

- Clinical research must be conducted in a manner consistent with the standards of clinical practice.

Favorable Risk-Benefit Ratio

- 4 Step Evaluation

  1) Risks identified, assessed and minimized.

  Risks must include:

  Physical —death, disability, infection

  Psychological —depression and anxiety

  Social —discrimination

  Economic —job loss

Favorable Risk-Benefit Ratio

- Evaluate the
  - Likelihood of harm
  - Magnitude of harm

- Identify mechanisms to minimize risks:
  - Additional diagnostic tests
  - Hospitalizations

Favorable Risk-Benefit Ratio

2) Potential benefits to individual participants enhanced.

Consider physical, psychological, social, and economic benefits to the individual

Consider only benefits from research interventions not benefit from added health services or payment that are not necessary to the research goals.

Favorable Risk-Benefit Ratio

- 4 Step Evaluation

  3) If potential benefits to the individual outweigh risks to the individual then proceed.

  4) If risks outweigh benefits to the individual, then evaluate risks against social benefit of knowledge gained.

Independent Review

- Because investigators have multiple legitimate interests, they have potential conflicts of interest. Independent review of the research minimizes these conflicts.

- Independent review also assures society it will not benefit from abuse of subjects.

Informed Consent

- Informed consent ensures individuals decide whether they enroll in research and whether research fits with their own values, interests, and goals.

- For those who cannot consent—such as children and mentally impaired—must be sure research fits with their interests.

Informed Consent

Informed consent consists in 4 elements

- Competence of the subject
- Disclosure of information to the subject
- Understanding or comprehension by the subject
- Voluntariness of the decision

Informed Consent

The Federal regulations require 8 elements be included in each informed consent form.

1) Purpose and duration of participation
2) Risks
3) Alternatives
4) Benefits
5) Confidentiality of records
6) Compensation for injuries
7) Person to contact for answers to questions
8) Voluntariness and right to withdraw

Respect for Human Subjects

The ethical requirements of research do not end with a signed consent document. Also include:

1) Protecting confidentiality
2) Permitting withdrawal
3) Providing new information
4) Monitoring welfare
5) Informing them of what was learned from the research

8 Ethical Requirements

- All 8 requirements are necessary and essential to make clinical research ethical.

- Independent review and informed consent are procedural requirements to ensure certain values are achieved. Other procedures may achieve these values. In some circumstances, independent review and informed consent can be waived.

8 Ethical Requirements

In fulfilling the 8 ethical requirements conflicts can occur.

What is fair in subject selection may increase risks.

What enhances scientific validity may increase risks.

What is necessary to respect enrolled subjects or obtain informed consent may compromise scientific validity.

8 Ethical Requirements

No simple formula for resolving conflicts.

Adjust design to meet the requirements. This is sometimes termed “balancing” or “weighing” or “specifying” the principles.

The important point is to be clear about what is being done and give reasons why.

8 Ethical Requirements

Different approaches may both be ethical.

8 Ethical Requirements

- The expertise necessary to implement these requirements includes:

  Educated and trained investigators

  IRBs with investigators, statisticians, ethicists, and lay people.

8 Ethical Requirements

- All 8 ethical requirements are universal. They do not apply only to the US or Europe. They apply to clinical research everywhere.

- The 8 ethical requirements must be adapted to the local health, economic, cultural and technological circumstances. For instance, disease risk effects risk-benefit evaluation.

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

Case

Is it ethical to enroll a mentally incompetent patient in a Phase III randomized chemo-prevention trial?

Is it ethical to enroll BY in a randomized trial to determine which of two hormonal therapies is better at preventing cancer with the fewest side effects?

Case

- Stress informed consent.

  BY cannot consent. There are many eligible participants in the STAR trial. BY 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. The risk-benefit ratio is positive. She is at least as well off in the trial as in clinical care and will be contributing to scientific knowledge. As long as mentally disabled patients are not being unfairly targeted enroll BY.

Case

- Stress fair subject selection

  To deny BY access to the STAR trail 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.