Bedside to Bench or Bench to Bedside: The Ethics of the Investigator-Participant Relationship

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Ethical & Regulatory Aspects of Clinical Research

National Institutes of Health

Bethesda, MD

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Disclosures

- I have no relevant financial relationships to disclose
- I will not be discussing unapproved uses of medical products
Objectives

1. Describe the historical roots of the investigator-participant relationship

2. Explain the therapeutic orientation to clinical research and its problems

3. Define an ethics of the investigator-participant relationship grounded in the ethics of science and the moral status of persons
Are you involved in the conduct of clinical trials?

Are you involved in the conduct of scientific experiments?
Elements of a rigorous experiment

Clearly state the question or hypothesis

Identify the intervention under study (the causal agent)

Describe the outcomes, along with the methods used to measure them

Specify the experimental conditions, including the materials and controls
An irresponsibly brief history of ethics of human experimentation

Early history focused on (usually healthy) volunteers participating in research without a prospect of direct benefit

Starting in late 1940s, physicians, investigators, & policymakers recognized need for an ethics of research with sick patient-participants

- Especially research with potential to benefit participants
Walter Reed’s yellow fever experiments (1900)

How is yellow fever transmitted?

- Fomites (droplets from infected person)?
- Bite of mosquito (Carlos Finlay)?

Reed intentionally exposed volunteers to bites from carrier mosquitoes

- Observed for signs of disease
- Innovations included consent and payment
The undersigned, Honore Fernandez, being more than twenty-five years of age, native of El Hierro in the province of Ferro, the son of Jose Fernandez and Dominga Laureano, here stated by these presents, being in the enjoyment and exercise of his own free will, and he accords to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon him by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated:

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he considers his life is to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this house, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said determination the greatest care and the most skillful medical service.

It is well known that at the conclusion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in monthly installments, and in case of his contracting yellow fever at any time during his residence in this house, he will receive in addition to that sum a further sum of $100 in monthly installments, upon his recovery and that in case of his death because of this disease, the Commission will present the said sum (two hundred nineteen dollars) to the person to whom the undersigned shall designate at his convenience. The undersigned binds himself not to leave the house or leave the house during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself to sign this paper in duplicate, in the presence of mental home, near Washington, D.C., on the 8th day of November nineteen hundred.

On the part of the Commission:

Walter Reed. 

Honore Fernandez.

signature

The undersigned party.


Mil Med | Reprint & Copyright © Association of Military Surgeons of the U.S.
The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.
**Nuremberg Code (1947)**

Response to atrocities conducted by physician experimenters in the Nazi concentration camps

Code implicitly applies to experiments (performed on volunteers) that lack the prospect of benefit to participants
Experiments at NIH Clinical Center

Clinical Center opened in 1953

- Needed volunteers for experiments
- Found source in conscientious objectors to military service, especially members of peace churches
- Roots in World War II “Guinea Pig Units”
Behind Closed Doors
IRBs and the Making of Ethical Research

Figure 3. Thyroid study on a Mennonite Normal patient at the Clinical Center, 1958. Courtesy of the Mennonite Church USA.

Figure 5. Normal patients enrolled in studies at the NIH Clinical Center, 1958. Courtesy of the Mennonite Church USA.
Increasing consciousness, starting in late 1940s, of the need for an ethics of research involving sick patients

Advent of randomized controlled trials

Regulatory requirement to demonstrate efficacy of new drugs

Declaration of Helsinki
## Why does this matter?

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<tr>
<th>Pure experiments in volunteers</th>
<th>Efficacy trials in sick patient-participants</th>
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<tr>
<td>• No prospect of direct benefit</td>
<td>• Prospect of benefit</td>
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<td>• Clear distinction between clinician-patient and investigator-participant relationship</td>
<td>• Blurs boundary between clinician-patient and investigator-participant relationship</td>
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107 patients with pulmonary TB randomized to streptomycin + bedrest vs. bedrest alone

- 6-month mortality 7% vs. 27%
- “Considerable radiological improvement” in 51% vs. 8%
Regulatory requirement for evidence of drug efficacy

Kefauver-Harris Amendment of 1962 to the Federal Food, Drug, and Cosmetics Act of 1938

- Response to thalidomide tragedy
- Required that “evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts”
- Required that participants give informed consent

https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm
Declaration of Helsinki (orig. 1964)

Promulgated by the World Medical Association

Grounds ethics of research in the ethics of the doctor-patient relationship

- “It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission”

- “The Declaration of Geneva of the World Medical Association binds the doctor with the words, “The health of my patient will be my first consideration”...
An example of the problem

NCI-sponsored randomized clinical trial of different chemotherapy regimens for childhood acute lymphoblastic leukemia

• Embedded in trial: does detection of “minimal residual disease” at various time points predict risk of relapse?
Study timeline

BM = Bone marrow aspirate
Randomized controlled trials pose a particular ethical challenge

In ordinary care...

- clinicians use their clinical judgment when recommending treatment to patients ("personalized care")
- clinicians don’t withhold treatments that they believe might be advantageous to patients
- clinicians don’t use placebos
- clinicians don’t blind themselves & their patients to what the patient is receiving
Randomized clinical trials are “of mice but not men”

“the physician must produce unswervingly the virtues of loyalty and fidelity to his patient” (quoting Leon Kass)

“The role of the scientist is quite different. The clinical scientist is concerned with answering questions—i.e., determining the validity of formally constructed hypotheses”

“[The goal of the RCT] is not to deliver therapy. It’s to answer a scientific question so that the drug can be available for everybody once you’ve established safety and efficacy” (quoting Tony Fauci)
Randomized clinical trials are “of mice but not men”

Conflicts with physicians’ role

- No role for physicians’ imperfect knowledge
- Can’t modify technique based on evolving information
- Limit physicians’ access to emerging data
- Physician cannot simultaneously be a fiduciary for the patient while aiming at knowledge to benefit future patients
- “Techniques appropriate to the laboratory may not be applicable to humans. We must develop and use alternative methods for acquiring clinical knowledge.”
Reconciling the methodology of RCTs with physicians’ obligations to their patients

Charles Fried: physician can ethically participate in an RCT if s/he is personally indifferent between the treatments under study

- Central concern is to preserve personalized care, physician’s fiduciary role
Reconciling the methodology of RCTs with physicians’ obligations to their patients

Benjamin Freedman recognized instability of Fried’s answer to the RCT dilemma

- Argued instead that boundaries of acceptable clinical practice define whether RCT is ethical or not
- “clinical equipoise”
Reconciling the methodology of RCTs with physicians’ obligations to their patients

Logic of Freedman’s argument

- Physicians’ treatment of their patients must remain within the bounds of acceptable medical practice
- The community of expert physicians defines the boundaries of acceptable medical practice
- So long as all treatments within an RCT are consistent with acceptable medical practice, the physician may participate
  - Even if s/he has a personal preference for one treatment over the other
Reconciling the methodology of RCTs with physicians’ obligations to their patients

“There exists...an honest, professional disagreement among expert clinicians about the preferred treatment.”

“At this point...there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested.”

“A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favored treatment is preferred by colleagues whom they consider to be responsible and competent.”
But research and care fundamentally differ...

The Belmont Report (1979)

- “For the most part, the term ‘practice’ refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.”
But research and care fundamentally differ...

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...and so the investigator-participant and clinician-patient relationships must differ too.
Pervasive therapeutic orientation to clinical trials (the conventional view) leads to ethical problems

- Impedes informed consent by promoting therapeutic misconceptions
- Blinds investigators to the inherent conflicts between scientific pursuit and participant protection
- Interferes with investigators’ ability to develop a sense of professional integrity

...and so the investigator-participant and clinician-patient relationships must differ too
...and so the investigator-participant and clinician-patient relationships must differ too

“To avoid exploitation and misplaced trust, an investigator approaching a patient about enrollment in a study should describe his or her own role as primarily that of a scientist in pursuit of knowledge aimed at improving medical care for future patients, rather than as that of a personal physician dedicated to promoting the individual patient’s health. Making the relationship with patient-subjects a partnership in pursuit of science will require positive efforts on the part of physician-investigators to counteract therapeutic misconceptions about clinical trials.”
Being simultaneously a clinician & investigator is hard
Being simultaneously a clinician & investigator is hard

We surveyed 1250 contact individuals associated with clinical trials listed on Centerwatch.com

• Response rate 72%
• How often have you faced various conflicts between protocol requirements and participants’ best medical interests during last 2 years?
  • How did you respond to the conflict?
Being simultaneously a clinician & investigator is hard

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<td>Participant met trial termination criteria, but staying in trial was judged to be in his/her best medical interest</td>
<td>36%</td>
<td>• 9% had kept at least one participant in a trial despite their meeting termination criteria</td>
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Reconceptualizing the investigator-participant relationship

Conventional view starts from the foundation of the clinician-patient relationship, modified (within limits) to fit the demands of research

If the conventional view is wrong, we need a rich, comprehensive alternative framework that specifies the obligations of investigators to their patient-participants
A bench-to-bedside approach

Bench to Bedside

Mapping the Moral Terrain of Clinical Research

by STEVEN JOFFE AND FRANKLIN G. MILLER

Medical research is widely thought to have a fundamentally therapeutic orientation, in spite of the fact that clinical research is thought to be ethically distinct from medical care. We need an entirely new conception of clinical research ethics—one that looks to science instead of the doctor-patient relationship.
A bench-to-bedside approach

Three domains characterize ethical biomedical science

- Goals and objectives
- Internal norms
- Ethical constraints
A bench-to-bedside approach

Goals and objectives

- Add to the stock of valid generalizable knowledge
- Relevant in some way to human health and disease
- $34.4 billion NIH budget request for FY2020 signifies extent of our public commitment to this goal
A bench-to-bedside approach

Internal norms

- Adherence to the scientific method
  - E.g., specify question or hypothesis, intervention under study, experimental materials and conditions, outcomes and methods for measuring them

- Adherence to the norms of scientific integrity
  - Avoid fabrication, falsification, and plagiarism
  - Attribute credit, ensure fairness in peer review, etc.
A bench-to-bedside approach

Ethical constraints

▪ Exist even for the most basic *in vitro* work
  o E.g., safety of research personnel & surrounding communities
  o E.g., ensure beneficent use

▪ Increase in number & rigor as you move from *in vitro* work → research with sentient animals → non-patient volunteers → sick patient-participants
A bench-to-bedside approach: ethical constraints

- In vitro research
- Research with sentient animals
- Healthy human volunteers
- Research with sick patient-participants

Ethical constraints
A bench-to-bedside approach

Ethical constraints on research with sentient animals

- All constraints on in vitro research, plus
- Minimize risk, burden, harm, etc. for animal subjects
  - Reduce number of animals
  - Refine procedures to minimize pain etc
  - Replace, whenever possible, with in vitro models or less sentient animals
- Independent review of research (i.e., IACUCs)
A bench-to-bedside approach

Ethical constraints on research with *healthy human volunteers*

- All constraints on animal research, plus
- Avoid unacceptable levels of risk
- Uphold respect for persons, e.g., informed consent, privacy
- Ensure fairness in subject selection (justice)
- Satisfy ancillary care obligations
- Fairly compensate participants
A bench-to-bedside approach

Ethical constraints on research with sick patient-participants

- All constraints on research with healthy human volunteers, plus
- Minimize risks associated with withholding/deferring therapy
- Maximize potential for direct benefit (consistent with achieving aims of the study)
- Ensure honesty regarding nature of participation in research
- Adopt caring attitude that acknowledges status as ill persons
Virtues of the bench-to-bedside approach

Represents a single comprehensive ethical framework for the full spectrum of biomedical research vs the conventional view, which posits different ethics for animals, human volunteers, and sick patient-participants

• (and fails to recognize any continuity with the ethics of *in vitro* science)
Virtues of the bench-to-bedside approach

Acknowledges that trials are experiments designed to acquire important knowledge

- Avoids erroneous ethical guidance stemming from the conventional view
- Allows clear thinking about placebos, research-specific procedures, and other features of rigorous experiments designed to achieve valid results
Virtues of the bench-to-bedside approach

Clarifies meaning of ethical principles in research vs. clinical care
- e.g., beneficence means different things in the two contexts

Highlights positive as well as negative obligations of investigators
- E.g., maximizing benefits, returning summary results

Promotes ethical honesty & integrity in research
To summarize

Early conceptions of the investigator-participant relationship envision a volunteer in a pure physiology experiment.

Rise of clinical trials conducted in sick individuals led to a therapeutic model rooted in the ethics of the clinician-patient relationship.

Reconceptualizing the investigator-participant relationship as rooted in the ethics of science has many advantages over the therapeutic model.
Thank you!

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