Exploitation in Clinical Research

Alan Wertheimer
Professor Emeritus of Political Science
University of Vermont

Department of Bioethics
Clinical Center
National Institutes of Health

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What Makes Research Ethical

" The overarching objective of clinical research is to develop generalizable understanding of human biology ; subjects who participate are the means to securing such knowledge. By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects."

"Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good."

Non-Exploitation and the NIH Canon

- Social value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Respect for human subjects

Nonetheless . . .

- It is not clear when research is and is not exploitative
- It is not clear whether we should disapprove a research protocol just because it’s exploitative

Exploitation in Research

- Vulnerable populations
  - Impaired
  - Institutionalized
  - Low income
- Less developed countries (off-shoring)
  - Placebo controlled trials when proven effective treatment is available
  - When intervention is likely to be used for benefit of developed countries

Three Examples

- Maternal-Fetal Transmission of HIV
- Surfaxin
- Diabetes Drug

Maternal-Fetal Transmission of HIV

- Efficacy of Long Course Treatment of AZT had been established
- Long Course Treatment was thought to be unfeasible and too expensive in less developed countries
- Researchers wanted to investigate efficacy of Short Course Treatment

Maternal-Fetal Transmission of HIV

- Compared efficacy of Short Course Treatment with no treatment or placebo
- Intentionally withhold established treatment
- Local standard of care: nothing
- Benefit to developing societies

The Surfaxin Trial

- Discovery Laboratories
- Respiratory Distress Syndrome
- Standard Care is Surfactant Therapy
- Cost is $1,000 -- $2,400
- Surfaxin was a “me-too” synthetic surfactant

The Surfaxin Trial

- Discovery Labs wanted to conduct a placebo-controlled trial in South America
- Intentionally withhold standard treatment
- Local standard of care: nothing
- Target Market: Developed societies

Similarities and Differences

- Both studies involved denying some participants the standard of care
- There was a plausible scientific rationale for a placebo controlled trial in the short course trial
  - Given assumption that finding a cheaper albeit probably less effective treatment is of social value
- There was less scientific rationale for a placebo controlled trial in Surfaxin
- Short course trial designed to benefit less developed countries
- Neither study would deny any participant treatment that she would otherwise receive
- Participants could give valid informed consent

Diabetes Drug (hypothetical)

- American pharmaceutical company wants to conduct a trial of a new diabetes medication
- Proposes conducting trial in India where there are many people with diabetes who are “treatment naïve”
- Active-Controlled trial
- If successful, drug will be marketed in developed countries
- Participants are offered post-trial treatment

Exploitation Claims

"If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and therefore, unethical."

Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects, Revised draft, January 2002. (CIOMS)

- Short course trial?
- Surfaxin?
- Diabetes

Exploitation Claims

"Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.” (Lurie and Wolfe)

Three Questions

- Are subjects exploited? What's the basis for saying that?
- Are communities exploited? What's the basis for saying that?
- Should we prohibit a trial on the grounds that it is exploitative?

Concept of Exploitation

- A exploits B when A takes unfair advantage of B.

Exploitation Examples

Nazi Experiment. A, a Nazi medical scientist, wishes to discover how long a person can live in freezing water. He places B, who has been placed in a death camp, in freezing water. B dies within an hour.

Kidneys. A, who is affluent, offers to pay B $25,000 for one of his kidneys for purposes of transplantation. B, who is poor, agrees in order to better provide for his family.

Rescue. B's car is in a snow bank on a rural road late at night. A stops and ascertains that it will take him 2 minutes to pull it out. A offers to pull B's car out of the snow bank for $200.

Exploitation Examples (cont.)

Slavery. C sells B to A as a slave. A forces B to work in the fields for bare subsistence.

Sweatshops. Nike hires unemployed people in Thailand. The employees work long hours for $1 per hour, which is considerably above the average wage in Thailand.

Price gouging. Hurricane Katrina has hit Louisiana. A buys 20 generators from local Home Depots and Loews stores in the D.C. area and drives to Louisiana. He sells them to local residents for three times the price he paid.

Two Types of Exploitation

- Harmful and nonconsensual exploitation
- Mutually advantageous and consensual exploitation

Types of Exploitation

- Harmful and Nonconsensual
  - The exploiter benefits
  - The exploitee is harmed
  - The exploitee does not give valid consent
- Examples
  - Nazi Experiment
  - Kidneys?
  - Slavery

Types of Exploitation

- Mutually Advantageous and Consensual
  - The exploiter benefits
  - The exploitee *also* benefits all things considered
  - The exploitee gives valid consent
- Examples
  - Kidneys (?)
  - Rescue
  - Sweatshop
  - Price gouging

Two Quick Thoughts

- Harmful and Nonconsensual exploitation is a no-brainer
- Mutually advantageous and consensual exploitation is more complicated
  - When is the transaction exploitative?
  - Should we prohibit it?

When is a transaction unfair?

- This is HARD
- Appearances can be deceiving
  - Professional Rescuer gets $200 per rescue, but travels the highway looking for people to help. He averages $20 per hour.
  - Amateur Rescuer is an opportunistic passer-by

When is a transaction unfair?

- Taking advantage of vulnerability
- Cannot be correct
    - Doctors
    - Lawyers
    - Plumbers
    - Director of homeless shelter

When are transactions unfair?

- Disproportionate benefit: When A gains much more than B?
- Seems plausible, but wrong.
  - Fair Surgery
  - Unfair Surgery

An Important Distinction

- A is taking unfair advantage of B
- A is taking advantage of an unfairness to B or, perhaps, B's unfortunate or unjust situation.
  - Unemployed Lawyer: B has been unjustly fired. He was making $150,000. A offers B a job teaching at a community college for $30,000.
  - Unemployed research participant

When are transactions unfair

- We need a theory of fair transactions
- I have one but I’ll spare you
- Takeaway is that before we can say that A is exploiting B, we need some criterion of what it means for A to treat B fairly.

Should we prohibit MACE?

- It depends – but not necessarily
- If interference is worse for the exploitees, then probably not. Not subject "protection."
  - Sweatshop
- If interference is better for exploitees or prevents a "race to the bottom," then probably so
  - Example: minimum wage laws

How interference can help

- Left to their own devices, A would hire B for $5.00 an hour
- The law prevents A from doing so by requiring a minimum wage of $7.50 an hour
- Two possibilities
  - (1) A hires B for $7.50 an hour
  - (2) A refuses to hire B
  - Law is o.k. if (1) is more likely than (2)

In other words

- We need to determine what will happen if we prohibit what we regard as exploitation

- This is an empirical question

Exploitation in Clinical Research

Three questions

- Is a trial exploitative?
  - Maternal-Fetal Transmission Trial?
  - Surfaxin Trial?
  - Diabetes Trial?
- If so, should we refuse to approve it?
- What could we do to make it non-exploitative?

Investigators and Regulators Different Responsibilities

- Investigators have to worry about the ethics of their activities: they should not exploit
- Regulators and IRB members have to worry about the ethics of interfering with research: should they stop investigators from exploiting?

A Right to do Wrong

- We should sometimes allow others to do wrong
  - Free speech
  - Withdrawal from research

Should we insist on Standard of Care Principle

- "in any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method.”

  The Declaration of Helsinki
- Is it ethical to conduct a placebo controlled trial when proven care exists?

Does the standard of care principle help subjects?

- Maybe. Such regulations may prevent a "race to the bottom." Similar to minimum wage laws
- No. researchers may go elsewhere if PCTs such as Surfaxin Trial are disallowed. The "real" Surfaxin Trial
- It is an empirical question as to whether disallowing PCTs helps potential subjects.. (Facts matter!)

Community Benefits

"Unless the interventions being tested will actually be made available to the impoverished *populations t*hat are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gained from the clinical trials for the developed countries' own benefit.” (my emphasis)

Annas and Grodin

Community Benefits

- If it is *not* wrong to ask subjects to participate because they benefit and consent, is it necessary that their fellow citizens benefit? (Diabetes Drug)

Community Benefits

- Does the community suffer a net burden?
  - No, because research brings resources to community
  - Yes, because research uses and diverts local resources and imposes other burdens
- An analogy: film production
- If no, does community have a special claim to additional benefits?

An ethical double standard?

- “Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.” (Lurie and Wolfe)
- Is it necessarily wrong to approve a protocol for nation Y when it would not have been approved for nation X?

An ethical double standard?

- Rotavirus is most common cause of severe diarrhea among infants and children
- Can be prevented through vaccination
- Vaccination can have complications, for example, intussusception
- Is it o.k. to vaccinate children where rotavirus is prevalent thereby accepting complications, but not where it is not prevalent because risks exceed benefits?

An ethical double standard?

- The Surfaxin Trial reconsidered
  - Is it possible that parents in Bolivia would consent to have their infant participate whereas parents in the U.S. would not?
  - Is it possible that the risks to subjects are reasonable in relation to their anticipated benefits in Bolivia but not in the U.S.?

Ethics as Regulation

- Before we adopt principles for the regulation of research, we need to know how they affect behavior
- We can't assume that a regulation is wise just because it has a good end

Another (!) Analogy

- Should FAA require that all children, including children under two, be placed in a child restraint on their own seats?
- Evidence suggests that it is safer for infants on planes

Self-Defeating Regulations: The FAA Example

- Evidence also suggested that the requirement would lead to more infant deaths because some parents would prefer to drive rather than buy an extra ticket .

"Effects and Costs of Requiring Child-Restraint Systems for Young Children Traveling on Commercial Airplanes" Archives Pediatric and Adolescent Medicine, 2003

Will requiring researchers to do more for subjects or communities actually help?

- It might
- But it might not
- We need to find out

Conclusion

- We will not resolve questions as to the justifiability of studies such as ***The Surfaxin Trial*** or ***The Diabetes Trial*** by appeal to the derisive language of exploitation.
- We will resolve them by the rigorous examination of ethical arguments and by the study of the effects of various policies on people's lives.