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Is This Study Exploitative?

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The ethics of conducting clinical studies in low-resource (developing) countries are complex. We can start with the Belmont Report principles — respect for persons, beneficence and justice — which are very applicable.[1]

The Declaration of Helsinki, the CIOMS International Ethical Guidelines, and the UNESCO Universal Declaration on Bioethics and Human Rights set forth additional principles and guidelines.[2-4] A fascinating body of work about the topic expands upon these documents.[5-12] Nevertheless, the challenge remains to apply these principles and guidelines to the unique circumstances of each study. Since these documents are guidelines (with limited codification into law), researchers must also determine whether a given study deserves to be treated as an exception.

In this article, we will propose an ethical framework and practical method for addressing questions of exploitation, the primary issue in determining whether a given study is ethical. We will propose a set of questions that researchers can answer to evaluate the ethics of a study and decide whether the study can be conducted in an ethical manner and, if so, how it can be conducted most ethically.

The question — "Is this study ethical?" — is only the starting point in a five-part question:

1. Is the study, as designed, ethical? (If "yes," skip to step 5.)
    2. If the study is not ethical, what are the ethical shortcomings?
        3. Can these ethical shortcomings be addressed? (If "no," the study is unethical.)
            4. If "yes," how should they be addressed to make the study ethical?
                5. Given that the study is ethical, how can it be made most ethical within the practical constraints?

Different people have different ethical views. Two people who share the same ethical principles can look at the facts of a study and reach different conclusions about whether it is ethical. To engage in a meaningful ethical discussion, it is thus necessary to understand how each person's ethical conclusions weigh the ethical principles and evaluate the facts against those principles.

Once a study is deemed "ethical," it is still not really ethical until it can be said that it is the most ethical study that can be conducted under the circumstances. In other words, if only one study is to be conducted, only the most ethical design is really ethical.

There is a wide variety of ethical frameworks. They fall into three main (oversimplified) categories:

- Virtue Theory, championed by Aristotle (born 384 BC), emphasizes character.
- Deontology, championed by Immanuel Kant (born 1724), emphasizes conduct.
- Consequentialism, championed by John Stuart Mill (born 1806), emphasizes consequences.

These three theories do not say the other theories are wrong, only that if one focuses, for example, on good character, then good conduct and good consequences will follow.

This article uses consequentialism, which means that the ethics of study depends entirely on its consequences for the study subjects, the community, the researchers, and everyone else

affected by the study. One advantage of consequentialism is that the results are observable. Consequentialism does not mean that the end is more important than the means, i.e., that study subjects can be exploited for the good of the community. Rather, it means that the end impact on everyone, including the subjects, is what matters. Neither does consequentialism mean that the impact on one person is more or less important than the impact on another person; other ethical principles deal with that issue. However, it does mean that goals need to be established and prioritized.

For purposes of simplification, we make the following assumptions:

- There is one study to be conducted in one country.
- The clinical study has ethical issues, i.e., the ethics are not black and white.
- The researchers are based in a developed country like the U.S.
- The researchers are acting in good faith, attempting to address the ethical issues as best they can.
- The researchers are employed by a company that has obligations to its customers, employees, shareholders, suppliers and the communities in which it operates.
- The researchers are not responsible for the social injustice of poor countries coexisting with rich countries (assuming one believes that this situation constitutes social injustice) but should not create or worsen unjust conditions.
- The bargaining position of the researchers is much stronger than that of the potential study subjects, allowing the researchers to exploit the subjects if they so wish.
- The subjects live in a community with its own cultural values, which take precedence over the researchers' cultural values.
- Other members of the community, e.g., government officials, are fulfilling their responsibilities to the best of their abilities.

We further make the following assumptions about the study subjects:

Exploitation vs. Undue Influence

Exploitation is an especially tricky issue because of its evil twin: undue influence. Undue influence occurs when a study offers — or appears to offer — advantages to a potential subject that cause him or her to enroll in the study against his or her best interests. (The concept "against his or her best interests" raises the specter of paternalism, which is another concern.)

One type of undue influence involves the relationship between the study subject and someone conducting the study, e.g., the investigator who also happens to be the subject's physician. When the physician/investigator encourages or even suggests that the patient becomes a subject, it is natural for the patient to assume that the study will offer health advantages. Another type of undue influence involves more tangible advantages like monetary payments and free medical care.

When we increase the advantages of participating in a study to make it less exploitative, we simultaneously increase the level of undue influence. For example, if we offer to dig a new well for your village, which does not currently have a safe source of clean water, will you feel any pressure to participate in the study?

One way to resolve the issue of exploitation vs. tangible undue influence is to look for a "three bears" balance — neither too hot nor too cold. One problem with this approach is that every potential subject is different. Paying all subjects $100 to participate in a study means that there will be exploitation in some cases and undue influence in others. Paying different amounts to different subjects raises other ethical issues.

- They are vulnerable because of their economic situation.
- Their consent to participate is competent, voluntary and fully informed.
- There is a strong inducement to participate, but there is no coercion, deceit, fraud or manipulation.
- On an *ex ante* basis, they will not be harmed, i.e., they will not be made worse off than if they had not participated in the study. (Many studies, anywhere in the world, like public vaccination programs, harm some participants on an *ex post* basis, but the *ex ante* expectations are that the average subject will not be harmed and the risk for all subjects is acceptable.)

With these assumptions, we can focus on the question of exploitation. To start with, exploitation is not *per se* unethical. In most transactions between two people, there is a mutually advantageous, consensual exploitation of the other party. Further, ulterior motives do not *per se* make exploitation unethical, since consequentialism ignores motive. In fact, both parties might have ulterior motives and still conclude a transaction with mutual satisfaction. For the moment, we will just say that exploitation occurs when a researcher takes *unfair* advantage of a vulnerable study subject. (We have already assumed that the subjects are vulnerable because of their economic situation.) This definition hinges on the word "unfair," so will now focus on what makes exploitation in one study ethical and exploitation in another study unethical.

Enrolling subjects in a study that will harm them (on an *ex ante* basis) is clearly unethical. It is also clearly unethical to coerce, deceive or manipulate their consent. The interesting case occurs when competent subjects are fully informed, uncoerced and willing to participate. Under these circumstances, does exploitation exist and, if so, is it ethical?

First, can exploitation exist between two willing parties? The answer is clearly "yes." For example, imagine you are in a park, choking to death on a bit of food, with nobody in sight. A paramedic comes into view, sees your distress, and offers to save your life in exchange for everything you own. He keeps a legal form with him at all times for just this situation. You might not hesitate in accepting the offer. You sign the form, the paramedic saves your life with the Heimlich maneuver, and you are on your way in five minutes. Both parties were willing participants in the transaction, but there was clearly unethical exploitation. (To address situations like this, when a party signs a contract under duress, a court of law can modify or void the contract.)

Imagine now that you are a citizen of a low-resource country, trying to feed, clothe and house your family on one dollar a day. A respected healthcare professional offers you $100 to participate in a clinical study. Do you really have a decision to make?

Now, let's look at a more realistic clinical study. Imagine that you are the benevolent ruler of Ruritania, a very poor country. Ruritania is so obscure that few people have even seen it on a map. Acme Pharmaceuticals comes to you with the following proposition:

> Acme will conduct a study in your country with 400 neonatal infants on a disease that kills about half of those afflicted. Half the infants will receive the study drug and most will live. However, the other half will receive a placebo and about 100 of them will die. In other words, the study will save the lives of about 100 Ruritanian infants. If you refuse the study, it will be conducted elsewhere, sacrificing the lives of those 100 Ruritanian infants. Medications currently on the market can save all the infants' lives, but they are too expensive for your country. The study could employ an active control, but Acme, if forced to use an active control, would conduct it in the United States for legitimate scientific and business reasons. If the study is successful, the new medication will be far too expensive for Ruritanian citizens, even with the 90% discount that Acme can afford to offer.

As the benevolent ruler of your country, should you approve this study? The government of Bolivia was offered a similar study, for a lung surfactant, and did not approve it. Real Bolivian infants died. Did Bolivia make the right decision? Would it have been ethical for the company to conduct such a study in Bolivia? Bioethicists wrestle with such questions.

Before Acme asks whether it is ethical to conduct the study in Ruritania, it must first ask whether it is ethical to conduct a placebo-controlled study at all. If so, how should it choose the country? In this example, Acme might seek to conduct the study in the low-resource country that will be able to afford the new medication the soonest. Numerous other considerations are relevant and specific to each study.

A fundamental question for Acme is what, if any, obligation does it have to the infants in the study, their parents, and the community — in this case, the other citizens of Ruritania? A persuasive case can be made that it has none whatsoever. Just because Acme is developing a new drug, why is Ruritania *its* problem? Under this reasoning, if Ruritania does not want the study, Acme can look elsewhere until it finds a country that wants to save the lives of 100 infants. Although this reasoning is logical, at least in a capitalist country, it seems somehow wrong.

At the opposite end of the spectrum, a persuasive case can also be made that Acme has deep obligations to the infants, their parents, and other citizens of Ruritania. Are the infants in Ruritania less important than the infants in any other country? Under this reasoning, common human decency requires that any study conducted by Acme in Ruritania must include an active control with the best treatment available anywhere in the world. However, since such a study, for legitimate reasons, will not be conducted in Ruritania, this reasoning costs the lives of 100 Ruritanian infants. Certainly, there are 100 mothers in Ruritania who would gladly agree to a clinical study that offers their infants a better chance of survival. Although this reasoning is logical, at least in a socialist country, it seems somehow wrong.

Clearly, a middle way is required. The "Fair Benefits Framework" states that study subjects and others (e.g., the local community) who bear the burden and risk of a study should share fairly in the benefits, broadly defined, during and after the study. The Framework also states that those bearing the burden and risk should have a large voice in determining what is fair. Further, making the resulting benefits agreements publicly available helps mitigate the asymmetry in bargaining power between researchers and study subjects.[13]

Bioethicists would say that this asymmetry imposes positive duties on the researchers above the level of "buyer beware." In other words, the result of a fair-benefits negotiation might still be exploitative, especially if the published benefits agreements provide an exploitative baseline. However, what are those positive duties? What is "fair"? Two related theories help answer these questions:

- Under the **Good Samaritan theory**, Acme accepts Good Samaritan responsibilities when it conducts the study in Ruritania. As members of a society, we are expected to go a bit out of our way to aid our fellows and not expect compensation in return. The person best placed to help is expected to do so. We should be generous to the weak and vulnerable, thereby reducing social injustice. However, the Good Samaritan is not expected to make personal sacrifices that are "too great." Neither is he or she expected to ignore his or her other moral obligations. Before the study, Acme has no particular responsibilities to the inhabitants of Ruritania, but once it joins the community by starting the study, it must make a decent effort to help the infants, their parents, and the other citizens of Ruritania. The Good Samaritan obligation is strongly reinforced because Acme is not just a passer-by but a beneficiary of the study.

  In the choking example above, the paramedic's behavior is offensive because it would take so little effort to save your life. Asking a poor swimmer to jump into a

rushing river and swim under the ice to rescue a personal enemy is asking too much of a Good Samaritan, but asking a passing paramedic for a quick squeeze is well within the limits.

- Under the **public health theory**, when Acme conducts a study in Ruritania, it becomes part of the country's public health community and shares responsibility for public health. In the choking example above, the paramedic's behavior is especially offensive because he or she is a healthcare professional with obligations above and beyond those of an ordinary person. In the context of public health, clinical researchers can be held to a higher standard than ordinary people because they are healthcare professionals and are best placed to provide such help. However, they should not be held to standards as high as a patient's physician, who is bound by the Hippocratic Oath.

Under these theories, one question that arises is whether Ruritania is the relevant community, or just an arbitrary geographical entity. When we talk about public health, we need to decide who we mean by "the public."

Use of these theories is consistent with the Belmont principles:

- **Respect for persons.** The researchers give study subjects the same respect they give other fellow citizens. The researchers respect their autonomy by not taking advantage of their weakness.
- **Beneficence.** The researchers provide more than the minimum benefits to the subjects.
- **Justice.** The researchers consider fairness in distributing the costs and benefits.

These two theories will not yield universally "correct" results that satisfy everyone. Reasonable people can disagree on what constitutes fairness. However, they are *useful* theories that provide an ethical framework for reasonable people — including potential study subjects and the community — to find common ground.

We said above that exploitation occurs when a researcher takes unfair advantage of a vulnerable study subject. We can now say that "taking unfair advantage" occurs when researchers do not fulfill their Good Samaritan and public health obligations. Acme may not be obligated to take measures that double the cost of the study and jeopardize the survival of the company, but spending, say, an extra 10% does not seem unreasonable under either theory.

This approach addresses a common concern about clinical studies in low-resource countries, that there should be a "fair" distribution of benefits. It is intuitively distasteful to use poor people as the means to develop drugs for rich people. In addition to the risk of physical harm, it is degrading when someone takes advantage of your weakness. "Fair" does not mean "equal." Determining what is "fair" is a subjective judgment, but the principle of fairness requires proportionality. Proportionality has two properties: First, the parties should share in the benefits based on their relative contributions. Second, as the benefits to the study sponsor increase, so should the benefits to the study subjects and community.

Once we accept one or both of these theories, we can move beyond yes/no ethics to measure *how* ethical a study is. We may not be able to agree that a given study is fair to the subjects and community, but we should be able to agree that it is more or less fair than a study with a different design. We can also examine the specifics underlying a difference in opinion about the ethics of a study.

Before continuing, we should discuss "reasonable availability" of the study drug because it is often asked of study sponsors and illustrates the complexities. It seems reasonable for the subjects and community to ask the sponsor to make the study drug available once it is

approved for marketing. However, this request raises numerous issues, including the following:

- Does "reasonable availability" mean eventually registering the drug in the country for marketing, or a lifetime supply of the drug for the study subjects?
- What price, if any, should the sponsor charge?
- Can the community's healthcare infrastructure support distribution and use of the drug?
- If the sponsor provides the drug to the community, will the community deliver it to the right people on the agreed terms, or divert it to privileged citizens or sell it to other countries?
- Where is the drug in the development process?
- What happens if the drug is never marketed?
- Does the sponsor have the ability to make the drug available if it wants to do so? For example, the U.S. National Institutes of Health do not manufacture and market drugs.
- Would a different drug be just as good or even preferable?
- How long will it take for a generic drug company to make the drug available at low cost?

Questions

Both of the above theories require in-depth analysis of a given clinical study in a given community. The following questions can help a study sponsor answer the five-part question asked at the beginning of this article.

The Subjects

1. Who are the subjects?
2. What are their values?
3. Who do they care about? (themselves, their family, their descendents, their friends, other people with the same disease, etc.)
4. Who makes their decisions?
5. On an *ex ante* basis, to what extent will the study benefit the subjects? (study drug, medical care, education, etc.)
6. On an *ex ante* basis, to what extent will the study harm the subjects? (risk of adverse effects, interference with their employment and family life, dignity, etc.)
7. Is this the best population for the study?
   a. How similar is this population to the target market for the drug?
   b. Are there other scientific advantages?
   c. Are there risk or benefit advantages?
   d. How relevant are the study's likely results to the subjects?
   e. How vulnerable are these subjects, in comparison to those elsewhere?

The Community

8. What is the community? (village, country, all low-resource countries, etc.)
9. How do the community's rights compare to the subjects' rights (assuming tradeoffs are required)?

10. What voice should the community have in the process of designing and accepting the study?
11. How does the standard of care in the community compare to that elsewhere?
12. What are the study's benefits to the community? (healthcare needs of the community, heathcare infrastructure improvements (e.g., refrigerators, training), research capacity building for future studies, etc. The benefits can be indirect — a malaria vaccine for rich people in other countries might promote tourism and economic growth in the community.)
13. What are the study's costs to the community? (diversion of healthcare resources from clinical care, interference with other studies that might be more beneficial, social disruption, long-term care of injured subjects, etc.)
14. How relevant are the study's likely results to the community?
15. How does the community's research ethical environment compare to that of other communities? (informed consent, good clinical practice, ethics committees, etc.)

The Study

16. What is the relevant standard of care?
17. Who will primarily benefit from the study results?
18. Is the design of the study constrained by the poor economic circumstances of the subjects being studied? (e.g., simpler tests where there is no electricity)
19. If there is a placebo arm, what is the scientific rationale? (e.g., use of an active control can substantially increase the size of the study to differentiate between the two drugs, thereby exposing more subjects to the experimental drug and delaying the results)
20. If there is a placebo arm, what benefits (e.g., hope, medical care) and costs (e.g., stress, blocking other options) does being in that arm provide?
21. What, if anything, prevents the design of a more ethical study?

The Sponsor and its Positive Duties

22. Who is the study sponsor?
23. What are the study's expected benefits, costs and risks to the study sponsor?
24. Who will benefit if the drug is marketed?
25. Are the intended users of the drug more or less deserving or vulnerable than the study subjects?
26. What do the subjects and community want most? (the study drug, other medications, medical supplies and equipment, healthcare training, clean water, Internet access to health information, future studies that provide more direct benefit, research capacity building, etc.)
27. How do the subjects and community express their wishes, and what is the decision process?
28. To what extent is the study sponsor in a unique position to provide benefits?
29. What is a fair percentage of study costs to dedicate to positive duties?
30. What is the best way for the sponsor to use its resources to aid the subjects and the community?
31. Are there other considerations for the study sponsor?
    a. Is it already a member of the community?
    b. To what extent does the proposed plan conflict with its other moral obligations?
    c. To what extent would it do more than it would if the study were in its home country?

d. What are the benefits, costs and implications to the sponsor of being perceived as a good or bad Samaritan?
e. Has it performed or planned other beneficent acts?
f. Is it complicit in a previous wrong that should be righted?

32. Based on the above, does the proposed plan create undue influence?

Conclusion

Exploitation is a complex issue in clinical research, even with the 13 simplifying assumptions above. Ethics are often not black and white, and require a balancing act to find the most ethical solution.

The above principles, methods and questions apply not just to clinical studies in low-resource countries; they apply to studies on vulnerable populations in any country.

It is important to remember that most of the drugs used today in low-resource countries were originally tested on people in high-resource countries. There have even been a few studies in the U.S. that primarily benefit people in low-resource countries. In conducting studies in low-resource countries, we must make every effort to ensure that the studies are ethical. However, we must not focus so narrowly that we forget that every person on the planet, including future generations, is part of the global community.

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