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An Ethical Model for International Clinical Research

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Exploitation of any population as clinical research subjects for the sole benefit of another population is clearly beyond the pale. Exploitation is inherently unjust. It can exist even with the informed consent and even enthusiasm of the study subject. The acceptability of a clinical study thus requires a third-party ethical review that considers the potential costs, risks and benefits to the study subject and whether the benefits to society justify the impact on the study subject.

Although the Belmont Report did not explicitly apply the principle of justice to clinical research in low-resource (developing) countries, it clearly does apply: "…[W]henever research…leads to the development of therapeutic [drugs], devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."[1]

However, this article will argue that the literal application of this proscription can be interpreted too narrowly, to everyone's disadvantage. Specifically, in some circumstances, ethical studies can be conducted without limiting relevant benefits to "subsequent applications of the research," especially if "subsequent" is interpreted to mean "as soon as the therapy is available to anyone in the world."

Exploitation

Exploitation exists when there is injustice, disrespect and/or harm to the exploited person.[2] For example, paying a healthy subject $50 for a liver biopsy may be unjust if the sample can be sold at a profit of $500, disrespectful if the subject is not informed that the sample is valuable, and harmful because the procedure causes pain and incurs medical risks. When clinical research is conducted in a low-resource country, even well-intentioned people can find themselves accused of exploitation. For example, placebo-controlled trials with serious medical conditions are generally unethical if the subjects otherwise would have access to effective treatment. However, if the local standard of care is "no treatment," the ethics are more complicated. The ethical standard of "relativism" says the best local treatment should be used as the control. The ethical standard of "absolutism" says the best treatment anywhere should be used as the control. Relativism invites exploitation, while absolutism invites ivory-tower unreality; ethical decision-making requires grappling with both perspectives.

A "fair benefits" ethical standard has been proposed.[2] This standard requires that (a) both parties agree to the arrangements and (b) the benefits are fair. This standard makes sense in theory, but requires answers to difficult practical questions for specific situations: Who agrees on behalf of the subjects and their community? Is a legitimate agreement possible if the power in the relationship is one-sided? What constitutes fair benefits? Who decides what is fair?

The Nuremberg Code

The Nuremberg Code, published in 1946, was the first internationally accepted statement of principles for the protection of human subjects.[3] As a reaction to inhuman Nazi experiments on concentration camp prisoners, the Nuremberg Code focuses on protecting clinical

research subjects. Because the Nazi doctors justified exploitative experiments as "for the greater good," i.e., for the benefit of the community, the community's rights are barely mentioned. However, they are referenced in two principles:

> The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature. (Principle 2)
>
> The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment. (Principle 6)

These principles are not meant to suggest any tradeoff between individual rights and community rights. Rather, they provide additional protections for study subjects. Nevertheless, they illustrate the difficulty of protecting the rights of study subjects outside the context of the community.

The Declaration of Helsinki

The World Medical Association's Declaration of Helsinki, first published in 1964, is widely accepted as a guide for ethical conduct of clinical research in low-resource countries.[4] It is highly protective of study subjects:

> In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests. (Paragraph 6) (This statement is unambiguous, but is qualified by the statements below.)

The Declaration applies the above rule very broadly:

> At the conclusion of the study, patients entered into the study are entitled to…share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits. (Paragraph 33) (Note the words "for example.")

The Declaration's concern for the individual extends to the community:

> Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research. (Paragraph 17) (Note that "reasonable likelihood" is a fairly relaxed standard and the benefit is not limited to use of the specific therapy that eventually results from the research.)

The Declaration thus extends the Nuremberg Code. Protection of study subjects is still paramount, but Paragraph 17 is a bit more explicit about the community's interest in clinical research.

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), first published its International Ethical Guidelines for Biomedical Research Involving Human Subjects in 1982.[5] The Guidelines cover ethical review, informed consent, and other protections for individual subjects. The Guidelines also discuss communities much more extensively than does the Declaration of Helsinki, for example:

> Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified. (Guideline 12) (Note that it is the community's "burdens and benefits.")

The Guidelines recognize the interest of the specific community and society in general in clinical research:

> Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community. (Guideline 10)
>
> External sponsors are ethically obliged to ensure the availability of…services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned. (Guideline 21)
>
> Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained. (Guideline 8)

The Guidelines recognize that capacity building is an important benefit to a community:

> Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research. (Guideline 20)

Protection of study subjects is still paramount, but the Guidelines are much more explicit about the community's interest in clinical research than are the Nuremburg Code and the Declaration of Helsinki. The Guidelines' concern for the community has two effects: First, it expands the sponsor's ethical obligations beyond study subjects. Second, while the subjects' interests are crucial, the community's interests are also important. Thus, some balancing of individual and community interests may be appropriate in some circumstances.

There has been a clear trend in ethical guidelines away from the idea that the subject's rights are all that matter in clinical research. As community rights are asserted more fully, it is hard to avoid the implication that individual and community rights must be weighed and balanced. In the Nuremberg Code, the camel's nose entered the tent. Since then, the eyes have peeked in. Perhaps more of the camel will eventually follow.

Ethical Model

As discussed above, research ethics place a high priority on the welfare of the individual subject.[6-11] For example, the Declaration of Helsinki can be interpreted to prohibit research on people who are unlikely to have access to a study's therapy when it is marketed. Taking this interpretation to the extreme, demands have sometimes been placed on study sponsors

to provide free therapy to study subjects for life. Such requirements can make clinical trials impossible for both practical and economic reasons.

Governmental regulations and international ethical guidelines are based on a particular ethical model of the world:

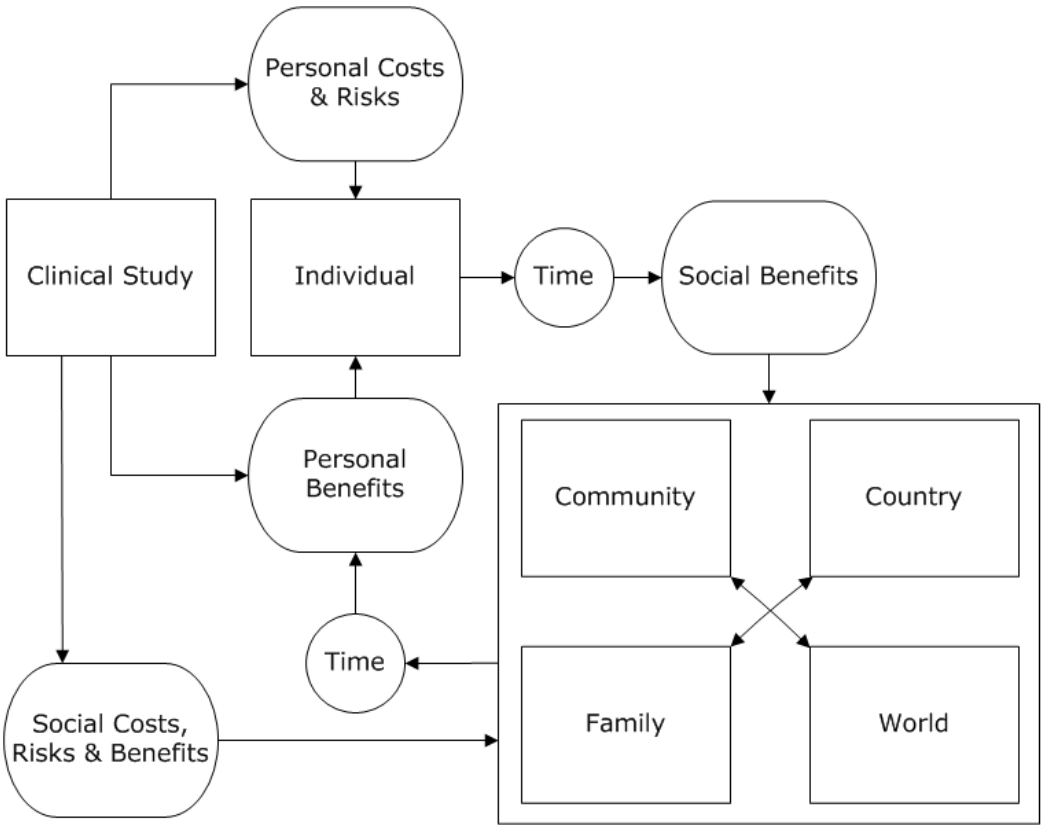
- Clinical research studies impose costs and risks on the individual subject, perhaps offset by benefits to the subject.
- The expected ratio of cost and risk versus benefits for the subject must be small (preferably less than one), with a very low risk of serious negative consequences.
- The study must offer a realistic promise of significant benefits for society.

This ethical model thus raises two related but separate ethical questions:

- Is the cost and risk versus benefits ratio for the subject acceptable, ignoring any potential social benefits?
- Do the benefits to the subject's family, community, country and world justify the impact on the study subject?

The ethical model in Figure 1 describes how a clinical study imposes personal costs, risks and benefits on a study subject, which, over time, provide social benefits. Figure 1 includes a feedback loop of social benefits to the subject; since the subject is a member of society, he or she may also share in the social benefits. The model also includes direct costs, risks and benefits to society, such as the possibility of increasing or decreasing the risk of infection from the study subject. The arrows in the model are theoretical; a specific study and subject are required to know what the various costs, risks and benefits might be.

Figure 1. Ethical Model for Cost and Risk Versus Benefits



The feedback of social benefits to a study subject can take many forms. For example, imagine an HIV/AIDS drug study that does not happen to improve a study subject's health or provide any other direct benefit to the subject. However, the study does eventually lead to the marketing of Drug A, which effectively manages the disease in 80% of treated people. Imagine, further, that Drug A costs $1 billion to develop and $10,000 per treatment to produce, so Company A charges $30,000 per treatment. Unfortunately, the study subject cannot afford it. Nor is Company A willing to give a $30,000 treatment gratis to thousands of study subjects, who remain chronically ill with the disease. It thus appears that the study subject receives no benefit for participating in the study. However, consideration of the feedback loop reveals:

- Fifteen years later, Drug A is off-patent and much cheaper to produce. Company B produces Drug B, a generic version that costs only $10 per treatment. If the subject is still alive, he pays for the treatment and returns to health. Or, perhaps, if he is not alive, his child, who has also contracted HIV/AIDS, pays for the treatment and returns to health. Or perhaps a philanthropic organization provides the drug at no charge through its free clinics, which also offer other free treatment for other ailments.
- Based on the success of the study, Company C discovers that an off-patent drug, Drug C, has some treatment benefit for HIV/AIDS. As a result, the health of many people improves, with significant impact on the standard of living in the subject's country. Even though Drug C does not directly help the subject, his higher standard of living includes access to better healthcare.
- With its profits from Drug A, Company A invests in research on other drugs, some of which eventually reach the study subject and his family and community.

These examples may seem farfetched, but how many cynics predicted that Merck would donate free supplies of ivermectin to treat 70 million people annually in Africa and Latin America, essentially wiping out river blindness? If Merck conducts a study of another drug, has the ethical balance shifted for the 40,000 people whose sight it helps save each year?

The role of time, both future and past, in the model is important. The potential for future benefit is obvious, but what about the past? The study subject may have access to drugs that were developed with the help of thousands of study subjects in the developed world at a cost of billions of dollars over the previous decades. The study subject did not participate in any of those studies or pay any of those dollars, but now receives the benefits. Is it not unreasonable for society to expect its members to "throw something back in the pot"?

The flow of social benefits from a specific study back to the subject may be dilute, but the model accommodates much broader social benefits unrelated to the study. Some of these benefits may relate to other medical treatments, and some may contribute more generally to quality of life. Some may even have negative consequences, e.g., keeping the army of an exploitative government healthy.

Limiting relevant benefits to the specific medical treatment that results from a study is a very limited perspective. Limiting information often results in poorer decisions. Exploitation of study subjects is clearly unacceptable, but some weight should be placed on a broader perspective if society is to have the opportunity to deliver broader benefits to the subject.

The tradeoff between individual and community rights is a central ethical question in all societies. At one extreme, only the direct personal benefits within the scope of a specific clinical study should be considered. The risk here is that everyone suffers because study subjects do not contribute "their fair share" to society. At the other extreme, all social benefits should be considered. The risk here is that study subjects are exploited "for the greater good."

Clinical research ethics strongly protect study subjects. "The greater good" carries little weight. However, in some cultures, the individual is not the important unit. The priority is on the family, community or country, or even a different person, such as a child. How many parents would participate in a dangerous clinical trial that might benefit their children, who have inherited their genetic disease? Current clinical research ethics do not adequately address such questions. Although most or all countries place a high priority on the welfare of children, their role as eventual beneficiaries is largely ignored in determining whether a clinical study with adults is ethical.

Conclusion

"The greater good" does not justify exploitation of study subjects. However, a short-term, narrow view of the ethical tradeoffs in a clinical trial can place too much weight on the direct impact on the study subject and deprive society of significant benefits, which the subject may share. A rising tide lifts all boats, albeit not if a study throws the subject overboard. The same principle applies to more general social benefits, just not as directly. By looking at the bigger picture, we can better balance individual and community rights for everyone, to everyone's advantage. Unfortunately, comparing the direct impacts of participating in a study to all the indirect impacts through society is very difficult. The comparison is easier if we limit it to first- and perhaps second-order healthcare impacts. The challenge is great, but given the importance of health to society and the immense investments — of every kind — in clinical research, it is well worth the trouble to try.

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