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Ethics of International Research: What Does Responsiveness Mean?

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International research is essential to understanding and ultimately controlling emerging and long-standing infectious diseases. Yet, such research, when sponsored by developed-world entities (both public and private) and conducted in the developing world, is beset with inherent and complex ethical issues. An overarching ethical concern is the possible exploitation of vulnerable individuals or populations through research. Avoiding exploitation, usually understood as an unfair distribution of benefits, may be more of a challenge in international than in domestic research because of background disparities in health, health resources, and power between developed and developing countries [1-3].

Basic Research Protections

The fundamental ethical concerns in international research are similar to those that arise in clinical research done anywhere. In all clinical research, people are asked to assume risk and inconvenience in the interest of advancing health-related knowledge that may benefit individuals and society as a whole. As a result these individuals may be susceptible to exploitation and harm. Codes of research ethics, regulations, laws, and norms that guide clinical research have been promulgated to minimize the possibility of exploitation by carefully protecting participant rights and welfare. Thorough independent review to assure the rigor of the research question and design, assessment of potential risks in relation to benefits and attention to minimizing risk, fair subject selection, and informed consent are widely recognized provisions for protecting research subjects [4-6].

Reasons for Concern

So why the concern about the ethics of international research? After all, such research advances understanding of prevention, diagnoses, and treatment of prevalent and devastating diseases including HIV, tuberculosis, malaria, schistosomiasis, and others; this information is vital for the health of people in developing countries, as well as for global health. First, the growth of international clinical research in recent years has been staggering. Escalating resources have been devoted to studying important global diseases like HIV/AIDS, malaria, and tuberculosis [7]. At the same time, pharmaceutical, biotechnology, and device manufacturers have dramatically increased outsourcing of drug and product research to the developing world, especially to countries in Southeast Asia, Latin America, and Eastern Europe [8]. These developments arouse concern because research participants and populations in

developing countries may be particularly vulnerable to exploitation due to poverty; illiteracy; limited resources, education, and access to health care; and lack of familiarity or experience with research.

Second, some argue that research sponsors conduct studies in the developing world that would be declared unethical in industrialized nations, thus establishing double standards [9]. According to this view, sponsors choose to do research in the developing world because it is less expensive, subject to fewer regulatory constraints, and provides access to large numbers of treatment-naïve patients, thus allowing investigators to get away with meeting lower standards.

Several thoughtful groups have grappled with how to minimize exploitation and the likelihood of double standards in international research [10, 11]. Among their recommendations, each says that clinical research should be responsive to the needs of the host country community and that the host community should benefit from the research. The President's National Bioethics Advisory Commission, for example, recommended in 2001 that, "clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country" [3]. The World Medical Association's 2000 version of the Declaration of Helsinki states, "Medical research is only justified if there is a reasonable likelihood that the populations in which research is carried out stand to benefit from the results of the research" [12]. The UK's Nuffield Council on Bioethics advises national priority-setting for health care research so that it will be, "easier for host countries to ensure that research proposed by external sponsors is appropriate and relevant to its national health care needs" [11]. In their international guidelines, the Council of International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization advises, "before undertaking research in a population or community with limited resources, the sponsor and 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" [11].

Ruth Macklin pointed out in 2001 that behind this apparent agreement about responsiveness and benefit, there are serious controversies and many unanswered questions [13]. After 5 more years of considerable debate and enormous research growth, these questions remain largely unanswered. What does it mean to be responsive to the health care needs of a population? How should populations benefit from research? Clear answers to these questions are critical if research guidelines and requirements are to truly protect against exploitation.

The Question of Responsiveness

The requirement to be responsive suggests that research should address a question that is relevant and important to a host country and that the answer should be of potential benefit to that country. Must research then be limited to investigating a disease or condition highly prevalent in the country from which subjects are to be recruited and one that has been identified by that country as a high priority? Certainly in a country

where malaria is prevalent and a major cause of mortality in children, a study of a less toxic malaria treatment or a strategy for preventing malaria seems responsive to an important health need. By this criterion, a malaria study could be judged more "responsive" than a study of breast cancer or depression. But it doesn't necessarily follow that a study of breast cancer in a developing country would be wrong, unethical, or exploitative. Disease prevalence or burden cannot be the only criterion for defining responsive research.

CIOMS noted that "it is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefits are made available to the population" [11]. Others agree that responsiveness includes assuring that research results or products proven effective are made available to and viable in the host country [12, 14]. Research results certainly should be made widely available in a way that maximizes their value and usefulness. Collaboration with host country researchers, institutions, health policy makers, community groups, and others throughout all stages of research will assure dissemination of results and assimilation of important new knowledge. In the case of research trials that demonstrate the efficacy of a drug or biologic, plans for making those products available and promoting their licensure and affordability may also be important.

But here the devil is in the details, and there appears to be considerable disagreement in determining how this should work. Is the sponsor, the host country government, or some combination with or without assistance from others, responsible for making products available? Does making a proven product "reasonably available" entail offering it for free, at an affordable price, or just assuring that it can be purchased within the country? Is the reasonable availability requirement satisfied by submitting research data to the relevant regulatory agency for licensure, by subsidizing the manufacture or distribution of the product in the host country, by transferring the technology to the developing country, or by something else? Research ethics committees, sponsors, ministries of health, and others who make decisions about the acceptability of research need clarification in order to apply such requirements appropriately and consistently.

Linking Benefits with Responsiveness

Some have argued that the attention to making research products "reasonably available" is misguided. If the goal is to minimize potential exploitation of research participants, benefits are clearly important, but what matters is the level, not the type, of benefit that participants receive [15, 16]. There are many kinds of possible benefits associated with clinical research:

- Therapeutic benefits to study participants
- Useful and generalizable knowledge for the community
- Infrastructure and capacity building
- The addition of needed public health measures
- Training of research and clinical staff
- Ancillary medical benefits to participants or others

- The post-trial benefit of new drugs and other products
- Economic benefits
- Increased business, employment

In an effort to establish a fair level of benefit in every case, the particular type of benefits provided during and after the study for participants or for their community might appropriately depend on the type of research, the needs and background circumstances of the population, and their well-considered preferences.

In one survey, investigators conducting research in developing countries overwhelmingly agreed that the study population should benefit from research, and more than half of those doing intervention studies said that the interventions would be provided to the research population or others after the study for a year or longer [17]. However, more than half of the respondents were conducting observational or descriptive studies—not intervention studies; focusing "responsiveness" on making products available provides no guidance about appropriate benefits for these studies.

If a community of potential participants were to decide that in exchange for research participation what they most needed and wanted were unrelated health benefits such as mass vaccination or a new clinic building, should that be disallowed because it was not a product of the research*?* In one example, community representatives of an Indonesian island lobbied their ethics committee to allow a study of a malaria prevention drug because they wanted the general health care services and treatment for malaria offered by the study that were otherwise unavailable to them. The drug being studied was intended for use by Western tourists visiting regions where malaria is endemic and would not be useful to the island population, according to a presentation by Reidar Lie November 16, 2005 at National Institutes of Health. Is this study responsive to the community's needs? Would it be unethical for the ethics committee to allow this study to go forward?

Responsiveness, especially as a counterbalance to possible exploitation, is inextricable from considerations of the value of a particular research study and the benefits to participants and communities. Answering a question of social, clinical, or scientific value is an ethical requirement for all clinical research [18]. Responsiveness assumes value but then builds upon it. If the goal of responsiveness is to reduce the possibility of exploitation by making the particular research exchange fair in terms of benefits, then benefits should be decided on a study-by-study basis, dependent on the type of research, predicted risks, anticipated benefits to the sponsors and investigators, and needs and preferences of the host community. Checks and balances are needed for this process in the form of transparency and other mechanisms to avoid the possibility that those in a disadvantaged position agree to less than they should. If, on the other hand, responsiveness is meant to refer to broader obligations of global justice, so that sponsors and investigators are limited to conducting clinical research that rectifies background injustices or changes social structures to reduce vulnerability to exploitation, the requirements for researchers and sponsors are very different, and remain unspecified [19].

Conclusions

In the end, perhaps responsiveness in international research is best accomplished not through further specification of responsibilities laid out in international guidelines but through respectful and close partnerships with host country investigators, communities, ethics committees, and policy makers. True partners are aware of, committed to, and respectful of host community values, needs, norms, and social practices. Such partnerships would promote clinical research that is both valuable and designed to answer questions deemed important by those involved, and would engage in negotiation about benefits openly determined to be fair.

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