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Ethical considerations in international biomedical research

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Abstract

The proliferation of international biomedical research has stimulated growing concern regarding the potential for exploitation of vulnerable populations in low-income countries by research sponsors in high-income countries. Three sets of international guidelines on ethical biomedical research — the WMA Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the UNESCO Universal Declaration on Bioethics and Human Rights — have been generated and yet none are legally binding. The UNESCO Declaration is unique among the three because it was written as an intergovernmental instrument on bioethics, intended to guide the development of novel national ethical policies worldwide, and particularly in developing nations. Policies that emphasize prescribed negotiations between the sponsoring and host countries, the mandatory inclusion of benefit sharing for the host population after completion of the study, and the formation of local Research Ethics Committees to oversee the research from planning through completion are some examples of important steps to be taken. Creation and enforcement of policies such as these will empower developing nations to influence the way in which biomedical research is conducted within their borders and on their citizens.

Key words: bioethics, international biomedical research, benefit sharing, research ethics committee

Introduction

The exploitation of low-income countries (LICs) in biomedical research directed by sponsors in high-income countries (HICs) has become a significant ethical issue in an increasingly global economy, in which national borders no longer present barriers to science, research, and business. The term "exploitation" itself can take on a range of definitions, even within the narrow realm of biomedical research. One simple definition is the unfair distribution of the benefits of biomedical research in the context of international collaborative research (1). In contrast, a more in-depth definition specifies the use of power differentials without consideration of harm to participants, using research participants to obtain knowledge without making the benefits of the research available to the participants or their communities, conducting studies with minimal benefit to the participants and their communities while maximizing financial long-term benefits for the research sponsors, or denying post-trial use of beneficial therapies developed in the trial to the participants (2). However specifically one defines the term, it is clear that the exploitation of vulnerable populations in biomedical research is ethically unacceptable and is of increasing importance on the international stage.

Three international documents have been produced and closely scrutinized that address this issue in addition to the general ethical concerns of biomedical research. The World Medical Association initially developed the *Declaration of Helsinki* in 1964 and has revised it numerous times, most recently in 2008. The Council for International Organizations of Medical Sciences (CIOMS), an international non-governmental organization affiliated with the World Health Organization, subsequently produced a document entitled *International Ethical Guidelines* for *Biomedical Research Involving Human Subjects*, with the specific intent of instructing the effective application of the *Declaration of Helsinki*. The most recent revision of the CIOMS Guidelines occurred in 2002. Finally, the United Nations Educational, Scientific, and Cultural Organization (UNESCO) adopted

the *Universal Declaration on Bioethics and Human Rights* in 2004, which is of particular interest because its goal is specifically to support policy change and encourage new laws in member states that will increase the prevalence of ethical regulation of biomedical research throughout the world. This differs from the *Declaration of Helsinki*, which is predominantly aimed at physicians, and the *CIOMS Guidelines*, which speaks directly to researchers. Each of these documents shares a foundation of three basic ethical principles, which are stated in the CIOMS Guidelines. Namely, these are: respect for persons, beneficence, and justice (3). When considered in relation to each other, the implications of the ethical standards put forth in these documents present a united front for the international biomedical research community to heed.

Key to the engagement in meaningful and ethical research protocols across international borders is the desire and ability to understand and respect differing cultures and the individuals who comprise those cultures. Nussbaum indicates three essential capacities for enabling intelligent dialogue and cooperation between people of disparate cultures in the modern and increasingly global world: the ability to critically examine one's self and one's traditions, the ability to see oneself as connected to all other human beings, and the ability to imagine what it might be like to be in another – very different – person's shoes (4). The ability of researchers to do these things will facilitate consideration of ethical standards in international biomedical research.

Philosophical framework for ethical applications

The ethical issue at stake becomes apparent when one considers the competing viewpoints of researchers seeking to advance the current state of knowledge through their work, and of those who support biomedical research but are wary of the potential to exploit vulnerable populations in the course of such research. It is worth pointing out that these viewpoints are not mutually exclusive; in fact, this is precisely why ethical guidelines are a helpful force in navigating the decisions necessary to mount a productive and ethical research project across international borders. This is supported by Benatar, who describes the wide range of differences in how people view medical research and notes that the extent of the differences is substantial and has practical implications in developing ethical policies for research (2). International biomedical research is inherently more challenging than localized research projects, because the approach must be pluralistic to allow the two (or more) societies involved to interact ethically. Initial approval by a single institutional review board (IRB) or research ethics committee (REC) in the sponsoring country is not sufficient to ensure ethical treatment of study participants in another nation, particularly if the other nation is an LIC. Bowman's explanation of a common criticism of modern bioethics — that it is based solely on Western moral philosophy and Western biomedical perspectives — indicates why this is so. He describes modern bioethics' foundation in science and technology separate from religion, politics, and morality along with its focus on autonomy as evidence that it is predominantly based on Western philosophy, sometimes to the exclusion of other cultures that emphasize values, beliefs, and social structure in decision-making (5). Benatar considers this criticism in depth and proposes a means of approaching bioethical issues in a more pluralistic manner. He points out that there are two critical elements to considering a truly pluralistic ethical framework: first, it is necessary to gain "deeper insights into our own value system and the value systems of others." Second, it is important that we "avoid either uncritically accepting the moral perspectives of all cultures as equally valid, or rejecting them all as invalid" (2, p.576).

Benatar suggests a combination of philosophical frameworks upon which to base ethical decisions. The first describes four forms of social solidarity, or ways of viewing the world. In an individualist society, people are considered independent, looking out for themselves individually amid a network of other ego-focused individuals. In an egalitarian society, people see themselves and each other as entitled to equal opportunity for good lives and equal outcomes. An hierarchical society sees the world as controllable, and people respond to authority that is based upon social position. Finally, in a fatalistic society people generally see the world as unfair and see little possibility to effect any change upon the world around them (2). These categories are meant to be viewed in a two-dimensional grid or continuum, and any given society in the real world will likely encompass characteristics of multiple forms of social solidarity to varying degrees. The importance of this analysis lies in its description of how a population will react to and engage with an externally driven research protocol. Understanding the society in which the research participants live and how they view the world allows external researchers the opportunity to approach the community fairly and ethically without imposing their own value system upon it.

The second framework that Benatar describes focuses on four differing perspectives of ethical dilemmas, which should also be envisioned as a two-dimensional grid, effectively as quadrants. Whereas moral absolutism views ethics as set in stone, absolute and unchanging regardless of the beliefs of an individual, society, or culture, moral relativism considers ethical systems to be relative to the time, place, and culture of the situation (6). Similarly, while reasoned global universalism uses a rational process to develop and justify ethical principles that are meant to apply to all people in all situations, reasoned contextual universalism applies to all people but leaves room to take into account any morally relevant local factors that impact the circumstance (7). Because it considers local contexts in applying rational ethical principles, reasoned contextual universalism should be the goal of any bioethical framework used in international research.

Ethical sharing of the benefits of biomedical research

One of the key aspects of ethical research that employs vulnerable populations, particularly in LICs, is consideration of benefit sharing. Benefit sharing is the continued availability after study completion of any therapy or treatment that is beneficial to participants in the research study, particularly those that may lack reasonable access to the treatment otherwise (8). A disparity exists when research involves the testing of drugs and interventions on participants in LICs for products that will be sold exclusively in HICs (1). These instances serve to widen the gap in global access to health care and health research funding.

The UNESCO *Declaration* states that "benefits resulting from any scientific research and its applications should be shared with society as a whole… in particular with developing countries" and goes on to specify that "special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research" is essential (9). Similarly, the CIOMS *Guidelines* indicate that research conducted in a community with limited resources must be responsive to the health needs and priorities of the community and that "any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community" (10).

In a study of how application of the UNESCO *Declaration* was integrated into national policy in Kenya and South Africa, as developing nations, Langlois found that Kenya has drafted regulations that require treatment provisions to participants if the research results identify treatment benefits and a prior agreement before the start of vaccine trials regarding the availability, affordability, and accessibility of those treatments. Similarly, South Africa requires research proposals to indicate in advance whether there is a foreseeable likelihood that participants will benefit from the products of research and whether the participants will receive long-term therapy after study completion (11).

Benefit sharing goes beyond benefits to the individual study participant. The CIOMS *Guidelines* outline a responsibility of the research sponsor to ensure that their research projects "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" (10). The document goes on to specify that "external sponsors would be expected to employ and…train local individuals to function as investigators, research assistants, or data managers, for example, and to provide…reasonable amounts of financial, educational, and other assistance for capacity-building" (10). The goal, of course, is to create a lasting improvement for the host country that will continue to support the population long after the initial study has concluded.

RECs in both host and sponsoring countries

If ethical guidelines are to be enforced, then there must be oversight in the research community to ensure their application. RECs play a vital role in the advancement of guidelines put forth by the various international declarations. Initial approval by an REC in the sponsoring country ensures that scientific validity and ethical applications of the research are acceptable within the cultural views of the sponsoring country, but this approval alone is not sufficient to speak to the application of the host country's value system. For this reason, the host country must be represented in the planning process and should require approval by its own REC for any study that will involve its citizens as research participants. For example, in the application of the UNESCO *Declaration's* Article 6, which states that community consent of local representatives or leaders may be required in addition to individual informed consent of participants, Kenya established community advisory boards (CABs) to handle the communications and dialogue with researchers in advance of the commencement of

HIV/AIDS vaccine research (11). CABs, if appropriately staffed and if used widely among other societies as well, could serve to represent local populations of LICs in the planning stages of international biomedical research.

A collaborative partnership between the research sponsor and a local CAB could be a productive mechanism to establish and support an ethical relationship between the researchers and research participants. As Lavery indicates, successful collaboration requires meaningful engagement and negotiation between the research sponsor or investigators and the host society (1). This requires representation of host country researchers, institutions, and governments in the negotiations from the start. If a common structure was prescribed for the CAB, each of these groups could be predictably represented. Additionally, if the membership of the CAB was carefully designated, the same committee could also potentially serve as the REC. The CIOMS Guidelines specify that membership of the ethics board should "include physicians, scientists, and other professionals, such as nurses, lawyers, ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community"(10).

Lavery also argues that a cultural shift is required among IRBs and RECs to move away from an intense focus on specific techniques, such as informed consent, that may limit protection from exploitation. Instead, RECs should emphasize planning for the distribution of research benefits and improving the host country's capacity to improve access to care since these actions would likely have a greater impact in reducing exploitation (1). The CAB could take on multiple tasks that would encourage agreement on the ethical framework of the research to be conducted and adherence to international guidelines. First, the CAB could handle negotiations with the research sponsor. These negotiations — regarding research protocols, training, and inclusion of local researchers or assistants as well as plans for post-trial obligations — would include accessibility and affordability of any treatments found to be beneficial through the studies. Local REC approval (perhaps by the CAB) should be required in addition to approval by the sponsoring country IRB/REC before any international biomedical research begins.

Logistically, the question of who will be responsible for structuring and funding the REC approval process remains. Lavery proposes that there is benefit in establishing a dedicated support team that would essentially function as an intermediary or guide through the REC process. The team would be an independent entity, without affiliation to the research sponsor, but could be attached to an international agency whose mandate involves protecting research participants from exploitation (1). The team would facilitate the engagement and negotiations between the research sponsor and host country CAB/REC. The team would be expected to provide "relevant expertise, experiences and, ideally, knowledge of local culture and politics, in lending assistance for research" (1, p.334).

Another important aspect of the clinical research that should include the REC is the ongoing monitoring of research projects once they have been approved and are underway. This typically falls to the Data Monitoring Committee (DMC), established by the research sponsor, which has two main jobs: to ensure the safety and wellbeing of study participants and to oversee that the study follows established protocols and is conducted properly (12). Involving the CAB/REC in the process of monitoring data throughout the course of the study increases the chances that local concerns would be addressed. Friedman points out that while a DMC is made up of professionals and individuals knowledgeable in relevant areas, that "practicing physicians and lay representatives tend to be most responsive to interests of individual subjects" (12, p.7). In an international study, the CAB/REC encompasses local members and has the ability to advise on the localized cultural nuances in an ethically charged situation. All three sets of international guidelines require ongoing monitoring of the continued application of ethical standards by an REC. Planning for this step should also be included in the negotiations between the sponsor and the local CAB/REC.

The CIOMS *Guidelines* specify that the financial responsibility for ethical review falls to the research sponsors. In the commentary on Guideline 2, the document specifies, "sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process" (10). This is an important point, because the ethical considerations of both host country and sponsoring country should carry the highest priority and should be safeguarded from fluctuations in the budgeted funds as a result of political changes that occur from time to time in either the sponsoring or host country. Host countries, particularly LICs, should not be required to fund the CAB/REC, because such funding may be unpredictable and a nation's changing economic status should never endanger the ethical treatment of its citizens.

Conclusions

Three sets of international guidelines on ethical biomedical research — the World Medical Association *Declaration of Helsinki*, the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, and the UNESCO *Universal Declaration on Bioethics and Human Rights* — have been written and while not legally binding, they serve to direct an international effort to develop ethical practices in international research. Unlike its counterparts, the UNESCO Declaration was specifically designed to be an intergovernmental instrument on bioethics, with the intention of guiding policy development in biomedical research ethics, particularly in developing nations. Ideally, the UNESCO *Declaration* will prompt an increasing number of countries to establish national ethical polices on biomedical research. Implementation of the international guidelines is an application of Michel Foucault's concept of bio-power, which can be described as "the taking charge of life, more than the threat of death" and acknowledging that doing so requires "continuous regulatory and corrective mechanisms" (13, p.143-4).

One of the end goals of ethical international biomedical research is to level the playing field and significantly decrease, if not eliminate, the disparity in health care and access to research funding between HICs and LICs. The gap is significant, but, as Benatar points out, the "inability to achieve immediate equity should not be an impediment to making improvements that could spread more widely with time and effort" (2, p.581). Implementing the international guidelines and putting more power in the hands of an LIC to influence the way in which biomedical research is conducted within its borders and on its citizens are aspects of a notable start. Enforcing post-trial obligations and ensuring continual access to treatments and new medicines are two additional steps in the right direction. Together, these steps begin to build a momentum of improvement that will lead to substantial gains in the equitable distribution of research funding and accessible health care.

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Competing interests

The author declares that she has no competing interests.

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