

BIOMEDICAL RESEARCH ETHICS IN DEVELOPING COUNTRIES: APPLYING GLOBAL GUIDELINES TO LOCAL CONTEXTS

Shauna Mullally

Department of Systems and Computer Engineering, Carleton University, Ottawa, ON

Abstract — Biomedical research in developing countries is increasing due to technological advancements and a renewed international focus on the health of the world's poor. The ethics of this research are complex, and engineers working in international health research need a solid understanding of these complexities. Global ethical guidelines outlined in the World Medical Association's (WMA) Declaration of Helsinki provide a framework for the policies of national and institutional ethics review boards (ERBs). The evaluation provided by these boards guides the challenging process of applying global guidelines to local contexts in developing countries. In this setting the potential for exploitation rooted in the vulnerabilities of research participants is high. Three case studies of clinical trial research expose these vulnerabilities and demonstrate how nuanced ethical evaluation can be. Capacity building of ERBs in developing countries is an essential step towards promoting more ethical research in the developing world.

1. INTRODUCTION

This paper presents the global ethics guidelines that govern this research, and the ERBs that implement the guidelines. It exposes the challenges of applying the guidelines to developing countries and the vulnerable nature of research participation. Three case studies are presented to demonstrate the complexities of ethical evaluation, and recommendations for improvements are made.

Most research in developing countries is sponsored and performed by institutions and corporations from wealthier countries. This requires researchers from one country to apply ethical research guidelines in a very different social, cultural, political and economic context from their own, which is quite challenging. Not all research is equally beneficial to the host country. A study to ascertain the prevalence of disease in a community as an initial step towards treating it differs greatly from a clinical trial that tests a new intervention on a population which is unable to afford it and unlikely to benefit from its commercialization. Clear ethical guidelines that protect

the rights of research participants and ensure they do not bear great risk but receive little benefit are absolutely essential.

2. GLOBAL RESEARCH ETHICS GUIDELINES

The WMA's Declaration of Helsinki is the international guideline for biomedical research on human subjects. The WMA developed the Declaration in 1964 and it has been amended five times, most recently in 2000 [1]. Core principles for ethical research are outlined in the Declaration of Helsinki: safety, informed consent, confidentiality, scientific validity, special consideration for vulnerable populations, minima standard of care, and the imposition of minimal harm. Ethics organizations the world over derive their ethics policies and regulations from the Declaration of Helsinki. [2]

Two paragraphs added to the Declaration of Helsinki in the 2000 amendment are of particular importance to research in the developing world. Paragraphs 29 and 30 were precipitated by debate in the international community about the ethics of this research, particularly the controversy surrounding the ethics of maternal-fetal HIV transmission trials in Sub-Saharan Africa in the 1990s [3]. These trials are presented as a case study in this paper. Paragraph 29 states:

"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." [2]

This is also known as clinical equipoise; that a new intervention is tested against the *best-known* standard of care [4]. Certain trials in developing countries had attempted to assess the efficacy of a new intervention against the *best-available* standard of care in that setting, which was often nothing. Supporters of this paragraph argue that it ensures developing countries are not "cherry picked" for their low standards of care [4]. Critics argue that best-known standard of care can't be implemented realistically in the developing

world and it therefore deters sponsors from pursuing important research [5]. Paragraph 30 states:

“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.” [2]

This paragraph has also fiercely divided the international research community. Supporters of it argue that it ensures a more fair distribution of risks and benefits between trial participants and sponsors, which is often biased towards sponsors. Critics argue that it inhibits research by placing a large financial burden on the sponsor [1], [6].

3. APPLYING THE GUIDELINES

International and national biomedical research organizations – such as the Council for International Organizations of Medical Sciences (CIOMS) and the Canadian Institute for Health Research (CIHR) – derive their research ethics regulations and policies from the Declaration. Institutional ERBs are governed by these regulations, and derive their rules and policies from them. Implementation of the guidelines at each level will vary as they are adapted to the appropriate context, but the underlying ethical principles should not.

3.1 Ethics Review Boards

In accordance with the Declaration of Helsinki and many national laws, research proposals must be approved by the ERBs (also called research ethics committees) of the sponsoring organization(s) and the host. For example an American pharmaceutical company seeking to trial a vaccine in West Africa must receive approval from the national ethics committees of each West African nation involved in the trial in addition to the U.S. Food and Drug Administration (FDA).

ERBs serve three vital purposes: providing a review that minimizes conflicts of interest, protecting research participants by evaluating risks, benefits and informed consent, and avoiding exploitation of individuals and populations [7]. Strong, independent ERBs in developing countries are fundamental to the ethical pursuit of research. They exist to provide an independent, culturally relevant review of proposals.

Yet ERBs in developing countries are often weak and under-resourced, if they exist at all. One study found that 97% of African ERBs had inadequate training in ethics and HIV vaccine trials, and 80% had inadequate training in health research ethics [7]. The World Health Organization (WHO) African Regional

Office found that 36% of their member countries had no ERB at all [8]. Further, many studies have documented differences and disagreements between host and sponsor reviews [9]. This is an immense problem. When national ERBs are weak if they exist at all and the contextualization of ethics guidelines in developing communities is challenging, disadvantaged populations become extremely vulnerable to exploitation by foreign researchers.

3.2 Contextualizing the Guidelines

Applying the ethical principles outlined in the Declaration of Helsinki to a field research setting in a developing community is quite challenging. *Most* study participants are vulnerable populations in this context; a huge power differential exists between a Western researcher and an illiterate African farmer.

The literature surrounding the application of these principles in this context is very rich [10], [11]. Obtaining valid informed consent from populations with low literacy levels, different cultural traditions, or a context of inequities is quite challenging. One study found that written informed consent was not used in 40% of recent studies. The researchers recommended more flexible ways of documenting consent for the participant population, and 84% of them agreed that a mechanism to measure understanding should be incorporated into study proposals to enhance the validity of informed consent [12]. Confidentiality and reporting of results are also quite challenging in the field setting, where communal living is common and stigmatized results such as HIV status should be handled with exceptional care [13].

Underlying all of these principles is the potential for exploitation based on the nature of research. Exploitation is rooted in vulnerabilities, and characterized by an unfair distribution of risks and benefits. The literature on ethics and exploitation in this context is vast. In [4], Carse and Little identify vulnerabilities that are particularly acute in clinical trial research: asymmetries of expertise, tendencies of deference to medical authority, exposure of one's body (or the body of one's child), and therapeutic misconception¹. The U.S. National Bioethics Committee (NBAC) recommends classifying research on a 'risks and benefits' continuum as a starting point for evaluating its ethicality. At one end of the spectrum lies research that has no practical relevance to the health needs of the host country but is important to the foreign sponsor or researcher; at the other end is research that is directly relevant to the health concerns

¹ Therapeutic misconception arises when research participants misinterpret the result of study participation as being therapeutic.

of the host country but is irrelevant to the foreign sponsor or researcher [14]. These paradigms present an excellent basis for ethical evaluation of research.

4. CASE STUDIES

Three case studies of clinical trial research expose the complexities of evaluating ethicality and the exploitive potential of clinical research.

4.1 Surfaxin Trial in Bolivia

In 2001, Discovery Labs, a U.S. based pharmaceutical company, proposed a clinical trial of a synthetic surfactant, Surfaxin, in Bolivia. Surfactant is used to treat respiratory illnesses such as infant respiratory distress syndrome (IRDS), and while many animal-derived surfactants exist in the U.S. market, Surfaxin was the first synthetic surfactant to be trialed. The proposed study was to be carried out on 650 premature infants suffering from IRDS in Bolivian hospitals [15]. Half of the infants were to receive mechanical ventilation and Surfaxin as treatment, the other half were to receive only mechanical ventilation (a placebo). The study was to be carried out in hospitals in Bolivia that did not provide surfactant treatment due to poor funding. Discovery Labs justified the Bolivian study with the need to rush Surfaxin onto the market in the wake of the mad cow crisis. They petitioned the U.S. Food and Drug Administration (FDA) for approval of the proposal. It replied, "conduct of a placebo controlled surfactant trial for premature infants with IRDS is considered unethical in the USA." [16]

How does this case measure up ethically? First, the proposal lacks clinical equipoise. Discovery Labs proposed testing Surfaxin against mechanical ventilation because it was the best existing standard of care *in Bolivian hospitals* however it should be tested against surfactant therapy. Paragraph 29 is not satisfied. This failure to provide the best-known standard of care to participants during the study could have been justified had the overall, final benefit of the study been to those participating in it [4], but this was not the case. Second, trial participants were not offered the best-proven standard of care after the trial. Paragraph 30 is not satisfied either. Third, concerns about participant coercion exist. Bolivian parents with infants suffering from IRDS and poor treatment options are a vulnerable population who would likely choose to participate in the study out of desperation. Fourth, this case falls at one end of the risk and benefit spectrum and is therefore clearly exploitive; sick Bolivian infants and their families would bear a risk for the benefit of Discovery Labs and infants in wealthier nations. The U.S. NBAC ruled the Surfaxin proposal impermissible

based on its ethical guidelines, and it was rejected. [NBAC Chapter]

4.2 Havrix Trial in Thailand

In 1990, Smith Kline Beecham Biologicals (SKBB) collaborated with the Walter Reed Army Institution of Research and Thailand's Ministry of Health (MoH) to clinically trial Havrix, their hepatitis A vaccine. The trial was a randomized, double blind Phase III study involving 40, 000 Thai children. Thailand was chosen for its population's high hepatitis A infection rate, and because transmission rates were high enough in rural areas to assess vaccine efficacy. Research infrastructure was also in place in the country due to U.S. Army research facilities. SKBB did not commit to making Havrix widely available in Thailand, but participants did receive the vaccine upon study completion [17].

Was this research ethical? The country was chosen for scientifically valid reasons; it wasn't "cherry picked" for loose ethics standards or minimal standard of care. Havrix was also the first hepatitis A vaccine. Paragraph 29 is therefore satisfied because study participants were being offered the best available standard of care. Paragraph 30 is also satisfied. Study participants were offered the best-proven standard of care after the trial. The distribution of risks and benefits is questionable. Study participants benefited from the research but the larger Thai population didn't as it was too expensive for the MoH's national immunization program and SKBB did not offer a subsidized price. Many bioethicists have evaluated this trial [4], including the participants of the 2001 Conference on Ethical Aspects of Research in Developing Countries using the fair benefits framework [17]. Most agree that while it wasn't very beneficial for the host country population, it was not an example of extreme exploitation.

4.3 Short-Course AZT Trials in Sub-Saharan Africa

The short-course AZT trials in Sub-Saharan Africa generated one of the most intense international controversies in research ethics history, providing the impetus for the Declaration of Helsinki revisions. A large randomized trial of women in the U.S. and France in 1994 showed that an AZT regime, a costly 3-part prophylactic regime, reduced mother-to-child (MTC) transmission of HIV from 25% to 8% [3]. Following the publication of the results, most developed countries adopted the regime for HIV-infected women. It was recognized that this intervention was well beyond the financial and technical capacity of Sub-Saharan Africa, where the epidemic was most vicious. The regime cost between

\$800 and \$1000, and required three separate administrations of AZT: orally to pregnant women weeks before birth, intravenously during labour and delivery and via syrup to infants for 6 weeks following the birth [3]. A strong case was put forward for finding a cheaper and more appropriate intervention for the developing world. The WHO and the United Nations AIDS Agency responded by coordinating randomized, placebo-controlled trials across the continent. By 1997, fifteen different studies had been identified [18]. The majority of these trials attempted to determine the efficacy of administering AZT in the final phase of labour (i.e. short course) to reduce MTC transmission.

Were these trials ethical? This was hotly debated, both in the scientific community and the public at large. Concerns were raised over informed consent, and the ethics of informing women they had HIV in the absence of proper care [3]. Clinical equipoise was not satisfied, and the use of a placebo (i.e. no therapy) when a more effective intervention existed was widely criticized [19-21]. Therefore Paragraph 29 was not satisfied. However the 'public health justification' clause was satisfied because the host population was the ultimate beneficiary. Nor was Paragraph 30 uniformly satisfied across trials. These are very valid concerns about how the trials were carried out. Yet the "local context" argument is strong in this case. The purpose of the research was to find an intervention that was appropriate for Sub-Saharan Africa, where the average per capita health expenditure at the time was \$3 per year [3]. Considering the full AZT regime costs between \$800 and \$1000 dollars, wouldn't it have more ethically egregious to *not* search for a cheaper and more relevant regime for Sub-Saharan Africans?

5. RECOMMENDATIONS

What can be done to improve research ethics in the developing world? The first and most fundamental recommendation is to build the capacity of national and institutional ERBs. One study of twelve African ERBs concluded that training, funding, independence and political commitment were the elements most needed to strengthen capacity [7]. Some research also suggests capacity building of local ERBs by foreign sponsor committees be built into studies. The second recommendation is to strengthen the ethics guidelines of institutions in the developed world that pursue this research. They have a greater capacity now to incorporate more ethically rigorous policies into their research. The third recommendation is more rigorous training for field researchers, from both developed and developing countries, on the application of ethical principles in the field. The reality is that protocols can

be forgotten in the field and the integrity of field researchers is paramount. The fourth and final recommendation is for greater ethics education for all involved in this research, including engineers. We owe developing country research participants nothing less.

REFERENCES

- [1] J. Blackmer and H. Haddad, "The Declaration of Helsinki: an update of paragraph 30", Canadian Medical Association Journal, vol. 173 (9), pp. 1052-1053, 2005.
- [2] World Medical Association, "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects", WMA Document 17.C. Available: <http://www.wma.net/e/policy/b3.htm>
- [3] P. De Zulueta, "Placebo-controlled trials and HIV-infected pregnant women in developing countries. Ethical imperialism or unethical exploitation?", Bioethics, vol. 15 (4), pp.289-311, 2001.
- [4] A. Carse and M. Little, "Exploitation and the Enterprise of Medical Research", [unpublished document], presented at Carleton University, October 6th, 2005.
- [5] World Medical Association, "WMA work group seeks further advice on Declaration of Helsinki", Press Release, Jan. 30th 2004. Available: http://www.wma.net/e/press/2004_2.htm
- [6] C. Cox MacPherson, "Research sponsor duties to developing world host nations; the ongoing WMA discussion of possible revisions to the 2000 Declaration of Helsinki (paragraph 30)", Developing World Bioethics, vol. 4 (2), pp. 173-175, 2004.
- [7] N. Kass et al., "The structure and function of research ethics committees in Africa: a case study", PLoS Medicine, vol. 4 (1), pp. 26-30, 2007.
- [8] J.Kirigia, C. Wambebe, and A. Baba-Moussa, "Status of national research bioethics committees in the WHO African region", BMC Medical Ethics, vol. 6 (10), 2005.
- [9] A. Hyder et al., "Ethical review of health research: a perspective from developing country researchers", vol. 30, pp. 68-72, 2004.
- [10] A. Frimpong-Mansoh, "Culture and voluntary informed consent in African health care systems", Developing World Bioethics, vol. 0 (0), pp. 0 [online], 2007.
- [11] S. Newton and J. Appiah-Poku, "The perspectives of researchers on obtaining informed consent in developing countries", Developing World Bioethics, vol. 7 (1), pp. 19-24, 2007.
- [12] A. Hyder and S. Wali, "Informed consent and collaborative research: perspectives from the developing world", Developing World Bioethics, vol. 6 (1), pp. 33-40, 2006.
- [13] G. Pappas and A. Hyder, "Exploring ethical considerations for the use of biological and physiological markers in population-based surveys in less developed countries", Global Health, vol. 1 (16), 2005.
- [14] National Bioethics Advisory Committee (NBAC), "Ethical Considerations in the Design and Conduct of International Clinical Trials", NBAC Report, Oct. 31st, 2001.
- [15] F. Charatan, "Surfactant trial in Latin American infants criticized", British Medical Journal, 322:575, 2001.
- [16] R. Arneson, "Broadly Utilitarian Theories of Exploitation and Multi-National Clinical Research", Princeton University Press, Princeton, 2007.
- [17] M. El Setouhy et al., "Moral standards for research in developing countries from "reasonable availability" to "fair benefits", Hastings Center Report, vol. 34 (3), pp. 17-27, 2004.
- [18] M. Lurie and S. Wolfe, "Unethical trials of interventions to reduce perinatal transmission of human immunodeficiency virus in developing countries", NEJM, vol. 337, pp. 853-856, 1997.
- [19] R. Crouch and J. Arras, "AZT trials and tribulations", Hastings Centre Report, vol. 28 (6), pp. 26-34, 1998.
- [20] J. Cohen, "Ethics of AZT studies in poorer countries attacked", Science, vol. 276 (5315), pp. 1022, 1997.
- [21] J. MacIntyre et al., "AZT trials to reduce perinatal HIV transmission: a debate about science, ethics and resources", Reproductive Health Matters, vol. 6 (11), pp. 129-144, 1998.