ETHICS OF PLACEBO-CONTROLLED TRIALS IN DEVELOPING COUNTRIES: THE SEARCH FOR STANDARDS AND SOLUTIONS

ALEXANDER SIMMONDS

Accelerating globalization over the last half-century has granted developing countries steadily increasing access to the medicines and healthcare practices of the first world. As the market for medications has expanded, however, so too has the pool of prospective subjects for clinical trials—and pharmaceutical researchers have leapt to take advantage of them (Glickman 816). The resulting surge in human-subject trials taking place in developing countries (especially those of Eastern Europe and Africa) has generated considerable concern among ethicists, medical professionals, and social commentators. They warn of the potential of first-world medical researchers to exploit the rights of vulnerable participants given the wide disparities that exist in education and healthcare between these countries and those of the developed world (Killen et al. 214). In particular, controversy has centered on the ethics of using a placebo control-group in which one group of participants receives a placebo (pharmaceutically inert substance) for their illness despite the existence of a medication shown to be therapeutically successful (Lau 192). In other words, researchers deny a group of subjects access to the best known treatment. Recent revisions to the Declaration of Helsinki, published by the World Medical Association and widely regarded as the governing document for research involving human subjects (Angell, "Ethics of Clinical Research" 847), have fueled a debate (that is poorly publicized outside of the medical community) on the role of the placebo in clinical trials in developing countries.

In this debate, as in all debates of medical ethics, we lay people have what Robert M. Veatch, Professor of Medical Ethics at Georgetown University, describes as a "critical role." It is we who must select and revise "an ethical theory and other components of an evaluative framework" (4) to apply to clinical research. By examining some of the complex issues involved in discussions of globalized clinical trials, we can develop an informed perspective on which to base such important decisions. This essay first outlines the main issues in this particular debate (the use of the placebo, and the concept of the standard of care), and then focuses on one series of clinical trials in particular, which will enable us to draw out the main ethical conflicts around which the debate centers. In that critical role of the lay person, I ultimately argue that placebo use is unethical when alternative trial methods exist that do not breach a harmonized code of ethics for international clinical research.

The placebo, a pharmaceutically inert substance (typically a sugar pill), is the clinical researcher's analogue to the scientist's control experiment. To prove a new treatment effective above and beyond the psychological results of a simple belief in the drug's

ability to cure, a researcher will compare the experimental treatment's results for an illness with those obtained from the placebo. The placebo-controlled trial "is widely regarded as the gold standard for testing the efficacy of new treatments" (Miller 707) and its use is based on the ethical concept of *equipoise*. Equipoise is "a genuine state of uncertainty about which of the two treatments of a clinical trial has a better efficacy" (Lau 194), and is considered a necessary condition if a clinical trial will use placebos. When there is no known effective treatment, a new drug might produce better, worse, or the same results as no treatment (the placebo) and so there is no ethical conflict in trials where this equipoise is present. If, on the other hand, a therapeutic treatment already exists, then equipoise is no longer present and the trial becomes subject to conflicting ethical standpoints. Whilst "regulatory standards and codes of ethics differ in their guidance concerning placebo-controlled trials when standard, effective treatments exist" (Miller 708), the current (2008) revision of the Declaration of Helsinki states in Provision 32 that "effectiveness of a new intervention must be tested against those of the best current proven intervention" (World Medical Association 2008).

The Declaration of Helsinki argues that all research participants should be entitled to a "standard of care," a term which the medical community borrows from tort law, and is defined as the "degree of attentiveness, caution, and prudence that a reasonable person in the circumstances would exercise" (USLegal). In medical practice, achieving the standard of care has come to mean that physicians must prescribe their patients the best available treatment in fulfilling their obligation to provide the best possible care for that patient. As new drugs are proven more effective for any given illness, the standard of care for that illness increases accordingly. When physicians acting as clinical researchers fail to offer the standard of care by offering a placebo instead, they break their commitment to their patients by denying them the right to proven treatment (Miller 709); in deceiving them about what their treatment actually is (or rather, isn't) they fail to uphold their patients' right to be fully informed.

An example of research that has highlighted the ethical tension between the use of the placebo and the standard of care is the series of clinical trials that took place in Africa, predominantly in the later 1990s, that examined interventions designed to prevent perinatal (mother-child) transmission of HIV. These trials occurred after the landmark 1994 publication of the AIDS Clinical Trials Group (ACTG) Study 076, a randomized, controlled trial that showed that the antiretroviral drug zidovudine "reduced mother-to-infant transmission [of HIV] by approximately two-thirds, with minimal short-term toxic effects" (National Institutes of Health). In developed countries, the zidovudine treatment thus became (and remains today) the minimum standard of care for HIV-positive pregnant women (Buckley 250). Crucially, however, the potential of the drug in developing countries and especially in sub-Saharan Africa remains unrealized "primarily because of the drug's exorbitant cost" (Lurie and Wolfe 853). The controversial trials, involving over 17,000 women, were all attempting to

develop an equally efficient and yet cheaper substitute for zidovudine, so that a more universally available treatment might be found. It is not the worthiness of this goal, but rather the method by which these trials determined the relative efficacy of different treatments that has stimulated debate: as placebo-controlled trials, they necessarily incorporated control groups of mothers deliberately given no effective treatment *despite the existence of therapeutically proven treatment*.

Although it may be true that these women would not have received any treatment had they not been involved in the trial, it is equally true that "investigators assume broad responsibility for the welfare of the subjects they enroll in their studies" (Angell, "Investigators' Responsibilities" 969) and, from a lay person's perspective, the apparent disregard on the part of the researchers for the best interests of all their human subjects seems unethical. Investigators, however, have upheld the view that research in developing countries should be held to different standards from those which govern research in the developed world. In defending their research, their arguments necessarily center around the problem for which a universal notion of the standard of care presents. Many have asserted that investigators have no obligation to provide better care for human subjects than that which "is generally available in the community from which the subjects are drawn" (Angell, "Investigators' Responsibilities" 967). This distinction, given that "hospital and clinic infrastructure, treatment choices, and quality of care vary widely from country to country" (Glickman 819) implies that the standard of care is different in every country and legitimizes placebo-controlled trials in developing countries on the grounds that the standard of care in these countries is typically no better than a placebo. In support of this view, Dr. Nicholas Meda, an epidemiologist from Burkina Faso, stated at a conference of European medical ethicists in 2002 that "in communities where there is no access to treatment of any sort, the concept of best available treatment (as defined by rich countries) is meaningless" (Richards 796).

This idea of a varying standard of care is further justified when one takes into account not only the different availability of treatment in the developing world, but also the vastly different interests these regions have in ongoing clinical research. Thus it is argued that "health research in poor countries should be designed and conducted pragmatically, taking into account local health needs and priorities" (Richards 796). This argument follows the same logic as the World Health Organization panel that approved the controversial zidovudine trials, stating "placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens" (World Health Organization), and emphasizing the need for a rapid solution for the HIV epidemic. Strict interpretation of the Declaration of Helsinki could potentially make research too expensive to carry out, and thus stifle efforts to improve treatment options for devastating illnesses such as HIV/AIDS or tuberculosis. In the broader interest of society, therefore, placebo control groups are

ethically acceptable, particularly given the huge potential benefits that research may bring for the developing world.

What these rationalizations reveal, as doctors Peter Lurie and Sidney Wolfe of the Public Citizen's Health Research Group (a political lobby group based in Washington) have pointed out, is a "fundamental misunderstanding of the concept of the standard of care" (Lurie and Wolfe 854). The concept of a standard of care is based on the most advanced medicine available to benefit humanity, not on the economic ability or inability of those in developing countries to afford the prices set by drug manufacturers. If the standard of care is accepted to vary between the developed and the developing world, or between one country and another, then why should they not also vary within a country or even a single city? The acceptance of an inconsistent standard of care inevitably leads to inconsistent standards for research. As the regulatory environment surrounding the use of human subjects in clinical trials becomes increasingly bureaucratic and expensive (Glickman 817), the incentive to use as research subjects those with the least access to health care increases. Just as weak labor laws encourage a "race to the bottom" by prompting firms to seek to outsource production to countries with the lowest wages, weak ethical oversight of clinical trials lead to a "race to the bottom" by rewarding drug companies for exploiting human subjects in developing countries with cheap research. What follows is that "the abominable state of health care in [developing] countries can be used to justify studies that could never pass ethical muster" in the developed world (Lurie and Wolfe 855).

Here, the perspective of the lay person—independent of any particular vested interest in medical research—becomes vitally important. The most pressing issue should not be one of medical technicality, but one of Veatch's "ethical frameworks": how valuable does the lay person find an irreducible ethical code for clinical research, and how strongly does the lay person believe in a universal standard of care? If we apply a standard of ethics that is based on the economic circumstances of a region, then we might accept that those in a poor neighborhood are less entitled to treatment than those in a richer neighborhood. An ethical framework that rejects this relativism must also uphold a universal standard of care. Indeed, one of the primary reasons why ethical codes for medicine (such as that which requires physicians to treat their patients to the best of their ability) place such a strong emphasis on the universality of their application is to combat the temptation for medical researchers to subordinate their subjects' welfare to that of medical progress. With the most altruistic of intentions (e.g., reducing the expense of HIV/AIDS medication), researchers might "find themselves slipping across a line that prohibits treating human subjects as a means to an end" (Angell, "Ethics of Clinical Research" 847).

Yet one could ask why the use of human subjects as a means to an end is ethically prohibited. Who gets to define the boundaries of what is (and is not) ethical for clinical research on humans? Currently, ethicists of the developed world in organizations such as the WHO and the WMA have the most influence, leading at least one, Dr. Ruth

Macklin, a professor of bioethics at the Albert Einstein College of Medicine, to use the term "ethical imperialism" (188) to criticize developed countries for imposing their ethical frameworks on developing nations. Whilst first-world nations might be justified in setting guidelines for trials and scientists in their own "developed" world, research originating in, and carried out by, scientists from Africa, Latin America, or Eastern Europe should be guided by the universal "principle of justice that says: 'Treat like cases alike and different cases differently'" (210).

The idea here is that those working in the developing world should have greater flexibility to define ethical frameworks relative to their own cultural and healthcare needs. The problem with this method, a problem which undermines the framework insisting on a universal standard of care, is in distinguishing how two cases are alike or different. Proponents of the zidovudine trials believed that they were different from similar trials in developed countries because they were founded on inherently different risk-benefit opportunities (i.e., the potential to stem an epidemic such as HIV) and cultural motives on behalf of the researchers. Opponents believed that regardless of who was carrying out the research, the trials were like any other trial involving human subjects and thus governed by the Declaration of Helsinki's ethical requirements. Ultimately, we must recognize that "to get beyond relativism is not to embrace ethical imperialism" (Macklin 273). Upholding the sanctity of the human being, as acknowledged in the ethical and medical precepts of the developed world and embodied in the concept of a universal standard of care, means that research should accommodate the cultural and healthcare needs of the developing world.

Finally, those who attempt to skirt around the fundamental ethical quandary of placebo-controlled trials by suggesting that the greater responsibility of researchers is not for their individual human subjects but for the greater needs of society ignore the existence of viable alternatives. Research need not be stifled simply because placebo-controlled groups are deemed unethical in cases where effective treatment exists. Indeed, from a scientific perspective, active-controlled trials (in which a new medication is compared to the existing standard of care)—provided that reasonable doubt exists amongst researchers as to the relative efficacy of the two drugs—avoid the ethical problems of a placebo and enable research that meets the requirements of equipoise. As zidovudine and other drugs with high retail value are "usually made available free of charge by the manufacturer for use in clinical trials" (Lurie and Wolfe 854), excessive cost is not a compelling objection. Active-controlled trials therefore have the advantage of being both ethically acceptable and, for the multi-billion-dollar pharmaceutical industry in which each of the largest twenty companies alone invested over one billion dollars into research in 2007 (Med Ad), economically feasible. Furthermore, there is a growing consensus within the sphere of clinical research that active-controlled trials are "scientifically preferable" (Weijer 306) to placebo-controlled studies. Instead of seeking to determine whether the experimental treatment is "better than nothing," clinical trials should test whether it is superior to or equivalent

in efficacy to standard treatment which already has been proven effective (Rothman and Michels 849).

The active-controlled trial emerges as a solution compatible with both the need for trials with massive potential benefits for society to be carried out in developing countries, and the ethical framework that we as lay persons must impose on medical research wherever that research might take place. Ultimately the greatest problem is summed up by Dr. Peter Piot, former Executive Director of the Joint United Nations Programme on HIV/AIDS, in a letter to the editor of the *New England Journal of Medicine*: "The real double standard lies not in the way trials are being conducted, but in the inequity in access to medicines in different countries." Whilst there is little that lay persons can do to solve that particular issue in the immediate future, a continued discussion about implementation and enforcement of an appropriate ethical framework governing clinical trials in developing countries lies entirely within our grasp.

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