

Introduction: Why Exploitation?

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Introduction

The first effective intervention that could dramatically reduce the risk that an HIV-infected woman would pass the virus to her baby was discovered in 1994.¹ The intervention was tested in the AIDS Clinical Trial Group (ACTG) Study 076 and came to be known in the medical community as “the 076 regimen.” This regimen was both costly and complicated, involving large quantities of AZT (the trade name for the drug zidovudine) administered in an elaborate schedule. A pregnant HIV-infected woman receiving the 076 regimen was required to begin treatment in the second trimester of pregnancy, so that she would receive the drug for a minimum of twelve weeks. During this time, she took oral AZT five times a day. During labor the woman received intravenous AZT; and for six weeks after delivery the woman’s newborn received oral AZT four times a day. A woman following the regimen was not allowed to breast-feed.² In 1994, the average cost for the full regimen was \$1,000 (U.S.) per woman.³

Despite the regimen’s cost and complexity, the discovery was a huge breakthrough. The 076 regimen reduced the rate of maternal-fetal HIV transmission by 70 percent, from a baseline rate of 25 percent to a rate of 8 percent.⁴ Within a few months of these findings, the U.S. Public Health Service recommended that the 076 regimen be recognized as the new standard of care for HIV-infected pregnant women.⁵

This discovery meant little, however, to most HIV-infected pregnant women, since the vast majority of these women live in developing countries.⁶ The annual health budget of these countries is approximately \$10 per person.⁷ In some cases, available funding is even lower. For example,

in Uganda, the annual health expenditure in the mid-1990s was estimated to be under \$3 per person per year.⁸ So a treatment regimen that cost \$1,000 per person was not—and still is not—even on the list of remote possibilities. Beyond cost, delivery of the 076 regimen was not practically feasible in many developing countries—or regions of countries. Most women in such areas do not present for prenatal care until much further along in pregnancy than required by the twelve weeks of the original regimen. In many places, there are no facilities for giving intravenous AZT. Most births occur at home. Finally, most women have no choice but to breast-feed their newborns, since they are unable to afford baby formula and/or unable to obtain safe drinking water to mix with the formula.⁹

Nevertheless, the urgent need for some solution to the problem of maternal-fetal HIV transmission in developing countries, particularly in Africa, was widely recognized. In the mid-1990s, approximately 1,000 HIV-infected babies were being born each day.¹⁰ And to this day, women in the developing world “infected through heterosexual sex, are the fastest growing group with HIV infection, and infected women are the principle source of infected children.”¹¹

In June 1994, the World Health Organization held a meeting to discuss strategies for discovering an effective and affordable approach to the problem of maternal-fetal HIV transmission in developing countries. At that meeting, it was concluded that the best approach was to do randomized controlled trials (RCTs) of shorter and simpler regimens of AZT versus placebo controls.¹² Consequently, sixteen trials were designed and approved to be conducted in eleven countries: Burkina Faso, the Dominican Republic, Ethiopia, Ivory Coast, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, and Zimbabwe.¹³ Of these sixteen trials, fifteen used placebo controls, of which nine were funded by the National Institutes of Health (NIH) and the Centers for Disease Control (CDC), with five funded by governments other than the United States and one by the Joint United Nations Programme on HIV/AIDS (UNAIDS).

It was the fact that fifteen of these trials utilized a placebo control that first spurred ethical criticism. Controversy erupted into public awareness in 1997, when two researchers from the Public Citizen’s Health Research Group, Peter Lurie and Sidney Wolfe, wrote a letter to the

U.S. secretary of health and human services, Donna Shalala, and followed up with a commentary in the *New England Journal of Medicine*.¹⁴ In both the letter and the commentary, they condemned the NIH- and CDC-sponsored trials as unethical. Simultaneously, Marcia Angell, the executive editor of the *New England Journal of Medicine*, published an editorial strongly supporting Lurie and Wolfe's position and comparing the AZT trials to the infamous Tuskegee studies of untreated syphilis in poor African American men in rural Alabama.¹⁵ These articles sparked an intense and often heated public discussion of the ethical status of placebo-controlled trials in developing countries.

From the very beginning, opinions were deeply divided over these trials. Two members of the *New England Journal of Medicine* editorial board, both of whom were experts on HIV and HIV research, resigned over Marcia Angell's editorial.¹⁶ Harold Varmus, then director of NIH, and David Satcher, then director of CDC, wrote a reply defending the trials as ethical and arguing that the use of placebos was justified by the complexities of the situations in the countries under study and by the urgent needs of these countries.¹⁷ Two prominent bioethics journals—*Bioethics* and the *Hastings Center Report*—devoted whole issues to the debate, with prominent bioethicists writing articles on both sides of the case.¹⁸ From then right up until now, the medical and bioethical literature has been inundated with discussion of the case.

When controversy first erupted, discussion of the ethical problems was confused. Many different arguments were conflated, without clear distinctions being made. With the passage of time and deeper reflection, however, the concerns of ethicists have resolved themselves into three major categories—all of which have relevance far beyond the original maternal-fetal transmission studies that sparked the debate.

Standard of Care and the Ethics of Study Design

Critics of the original AZT trials argued that these trials revealed the application of a morally insidious double standard, since they used placebo controls despite the fact that researchers would not have been allowed *for ethical reasons* to run a placebo trial of AZT in the developed world.¹⁹ After 1994 the 076 regimen was the standard of care in developed

countries. This meant that using placebo controls in further transmission studies in (for example) the United States would be unethical, since one significant norm of developed world research ethics requires that in most cases placebo controls not be used once some form of effective therapy exists for the illness or condition being studied. The critics argued that if placebo controls were unethical in developed countries such as the United States, Canada, or the countries of Western Europe, then they must also be unethical in developing countries such as Zimbabwe and Uganda. The criticism was that the choice of placebo controls revealed a lowering of ethical standards, which in turn reflected a lack of equal concern for the welfare of these subjects.

The critics were correct to point out that developed world researchers generally do not use placebo controls once some form of effective treatment exists for the condition or illness being studied.²⁰ There are, however, recognized exceptions to this rule as, for example, when participants are unlikely to suffer any long-term ill effects from receiving placebo. Still, at the time, critics felt that none of the standard exceptions applied to the AZT perinatal transmission trials.

In addition, some critics cited a provision in the Declaration of Helsinki to justify their objections. This provision, while supporting their favored conclusion in the AZT case, is also very strong. It does not, for example, recognize even the standard exceptions to the rule against placebo use mentioned above. This provision states: "In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method."²¹ Those critics (such as Lurie, Wolfe, and Angell) who relied most heavily on this provision of Helsinki, felt that once the 076 regimen was proven effective in 1994, every patient in a subsequent research trial should be assured of receiving 076 or a better treatment.

On the other side, defenders of the trials emphasized that placebo controls offered the best way of answering a question that was itself largely dictated by the poor economic circumstances of those being studied. Thus for them, the ethical question was: Could features of the economic and health delivery situation in developing countries justify departure from the norm? Economic constraints were clearly perceived as irrelevant by the critics. But defenders felt that this view was too rigid. They felt that, in this case at least, the answer to the above question was yes.

Defenders pointed out that different trial designs are used to answer different types of questions. The economic constraints such countries face mean that their governments need answers to questions that people in developed countries, with access to the 076 regimen, do not. Only by using placebo controls, it was argued, could information that would actually be useful to the populations being studied be generated. Hence, defenders argued that talk of “double standards” was out of place in discussions of the perinatal trials. It is precisely because all is *not equal* between developing countries and developed countries—because 076 is not affordable there, because women in these settings arrive for care only at the point of delivery, and because intravenous methods of delivery are not feasible in these settings—that it was deemed necessary to find a regimen both cheaper and simpler to administer.

Perhaps most significantly, researchers were open from the beginning to the idea that what they were searching for *was a less effective, but still somewhat effective regimen*.²² If indeed shorter courses of AZT were likely to be less effective than the 076 regimen, then only a placebo trial could answer the question of *how much more effective than nothing* the alternative regimen was. And this information would, in turn, be key to health policy decision making posttrial.

It is important to emphasize that the defenders of this trial did not think that the importance of a particular research question could justify *just any* treatment of subjects.²³ Rather, they felt that it could justify the use of placebo in these particular settings, given that these people *would otherwise receive no treatment at all*. They clearly recognized that, with these designs, some participants would not benefit as much as they might have, had they been in an active-controlled trial. But they felt that this was morally acceptable as long as (1) using placebo controls was necessary in order to gain the knowledge sought, and (2) no participant was made worse off by participating in the trial than she otherwise would have been.

Controversy over study design also led to controversy over the Declaration of Helsinki. Defenders of the AZT trial noted that requiring that *every* trial participant receive the “best proven therapy” was deeply problematic. If interpreted literally it actually precluded *any* randomized trial—even an active-controlled trial—once an effective therapy was available. After all, testing the 076 regimen against any newer treatment would have meant depriving the participants receiving the new treatment

of “the best proven” treatment, for only the 076 regimen was the *best proven* treatment—the new one was not proven.

However, even if interpreted simply as a requirement *on what control group members must receive*, as many people appear to have interpreted it, the requirement was thought to rule out far too many perfectly acceptable trials.²⁴ In 2000, after extended international discussion, the declaration was modified but in a way that ultimately reasserted the original strong position.²⁵ Since then, however, various other significant health policy groups, including UNAIDS, Council for International Organizations of Medical Sciences (CIOMS), the Nuffield Council, and the National Bioethics Advisory Commission (NBAC), have rejected the Helsinki “best proven” requirement, and some have argued that the strong Helsinki view has now emerged as the minority view.²⁶ However, the debate over what guidelines should replace the “best proven” guideline continues.

The debate just described—which has come to be known as “the standard of care debate”—is one about the *ethics of study design*. It is important to remember this because developing world research raises more questions about ethical study design than just the questions about placebo use described earlier. The particular needs of the developing world challenge the received wisdom about ethical study design on a number of fronts, and it is important that we not let the placebo issue blind us to these other real problems. For example, there are many diagnostic and therapeutic interventions that could be used in research studies, and which for various reasons researchers might wish to use, that are *less effective* than standard interventions employed in developed countries. For instance, in the developed world, response to antiretroviral drugs is measured in terms of CD4 counts or viral loads. But would it be unethical—would it reveal the presence of an objectionable double standard—to use weight gain or other simpler tests in developing countries where the lack of equipment, reliable electricity, and money makes using these laboratory tests difficult or impossible?

In a slightly different vein, although most of the debate has focused on the way in which placebo use in trials like the AZT trials challenges traditional interpretations of the standard of care rule, there are critics who have insisted that such designs pose just as much of a challenge to other traditional rules of ethical study design such as the principle of clinical equipoise.²⁷ All these varied problems about study design de-

serve attention in the context of considering which practices are exploitative and which ones are not.

Informed Consent

The second frequent concern voiced about developing world research is that informed consent suffers in these contexts, sometimes to the point of nonexistence. Informed consent is almost universally recognized as a necessary requirement of ethical research. Certainly detailed informed consent is required for all research receiving U.S. government funding, and it is also required for all test results submitted to the Food and Drug Administration (FDA) for approval of a new drug. But critics worry that it will be unusually difficult to obtain meaningful consent from poor, uneducated subjects unfamiliar with the concept of research.

One concern played up by the media is that researchers are not adequately motivated to tackle what is assumed to be an impressively difficult task. In the extreme case, they may even be tempted, once they find themselves far from any oversight bodies, to forgo informed consent altogether.²⁸ Most parties agree that *if* this occurred it would indeed be problematic. However, there is very little evidence that such extreme behavior is widespread.

More subtle questions arise when we ask whether the consents that are obtained in such settings are really valid. One concern is about *understanding*: perhaps no matter what researchers do, uneducated subjects simply will not be able to grasp what is being presented to them. A different concern is about *voluntariness*. Some critics have claimed that it is impossible for subjects to give truly free consent in such settings. So, for example, one finds claims such as the following:

I'd argue you can't do studies ethically in a country where there is no basic health care. You can tell a person there that this is research, but they hear they have a chance to get care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?²⁹

It is difficult to avoid coercing subjects in most settings where clinical investigation in the developing world is conducted. African subjects with relatively little understanding of medical aspects

of research participation, indisposed toward resisting the suggestions of Western doctors, perhaps operating under the mistaken notion that they are being treated, and possibly receiving some ancillary benefits from participation in research, are very susceptible to coercion.³⁰

Ultimately, critics have asked “whether a Third World villager who knows little about modern medicine can give informed consent in a way comparable to a Western patient?”³¹

Defenders of these studies counter, in response to the first worry, that being poor and having few health care options does not make a person stupid or unable to understand explanations of clinical research. Indeed, they note that to survive in Africa often requires a great deal of savvy and a keen sense of one’s interests and how to realize them. They also note that there are woefully limited empirical data suggesting that research participants in African countries have systematically lower understanding as compared with research participants from developed countries. In *both* developing and developed countries, what little data there are suggest that research participants often fail to understand what *randomization* really amounts to. This suggests that full understanding is hard to achieve *in every setting*. Nonetheless, the data also suggest that subjects often have a relatively good appreciation of the risks and benefits of a study.³²

Finally, it is pointed out (in response to the second worry) that merely possessing few good options does not undermine the voluntariness of choice. People often confront few options, but nevertheless act voluntarily and autonomously. For instance, individuals who need heart or liver transplants confront a bleak set of options. Yet no one thinks—or should think—that opting for a solid organ transplant is an involuntary or coerced choice.

Reasonable Availability and Fair Compensation

The third common concern about developing world research is that it is unfair to the study participants in particular and to the host communities in general, since in many cases drugs or interventions developed as

a result of the research will not be available to either group posttrial because of prohibitive costs.³³ The claim here is that the poor are being used to develop drugs for the rich and that this is itself inherently unethical. Generally, critics have referred to this set of problems as “the problem of reasonable availability,” though in fairness there are really *several* issues here as opposed to one. One question is about what is owed to *populations or communities*. The other is about what is owed to *trial participants* once the trial is over. Moreover, labeling the problem as a problem of “reasonable availability” prejudices the question of *what* is owed to communities and participants by implying that what is owed must necessarily be reasonable access to drugs developed through the trial. However, it is possible, as we shall see, to recognize that something is owed, and yet argue that what is owed need not be access to drugs.

The issue of *community* benefit emerged early on as a result of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993), published by CIOMS.³⁴ This document argued:

As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins.³⁵

This ethical requirement was reiterated in CIOMS’s 2002 revision.³⁶

In light of this requirement in the CIOMS guidelines, many criticized the AZT trials because the sponsors did not *guarantee* inhabitants of the countries the AZT posttrial, even if it was proven effective. For instance, Annas and Grodin argued that while the research questions may have been framed with the health needs of developing countries in mind, not nearly enough had been done to guarantee that these populations would receive the drugs actually being tested if they proved effective.³⁷ Although the trials examined cheaper regimens, there was no pretrial plan agreed to by all involved that laid out how a successful treatment, should one be developed, would be implemented in the host countries. There was no binding commitment from the manufacturer of AZT to make it available at affordable prices, and in most cases the fifty-dollar cost of the short-course AZT regimen would still be unaffordable.

Furthermore, given the poor health care infrastructure of these countries, there was no plan for how to actually distribute the medications. They argued that without binding agreements in place ahead of time, there was no real assurance of reasonable availability, making the AZT trials unethical. In a related article Glantz, Annas, and colleagues summed up their view as follows: “In order for research to be ethically conducted [in developing countries] it must offer the potential of actual benefit to the inhabitants of that developing country. . . . For underdeveloped communities to derive potential benefit from research, they must have access to the fruits of such research.”³⁸ In 2002, the chair and executive director of the United States’ NBAC adopted a similar line: “If the intervention being tested is not likely to be affordable in the host country or if the health care infrastructure cannot support its proper distribution and use, it is unethical to ask persons in that country to participate in the research, since they will not enjoy any of its potential benefits.”³⁹

Critics of the reasonable availability requirement have noted that, as it stands, it is incredibly vague. How is “community” to be defined? Must drugs be provided to every sick member of the host country, or does community not extend as far as national boundaries? And for how long must drugs be provided, particularly if it is clear that the host country will not be able to assume that cost anytime in the near future?

Other critics have gone further and argued that reasonable availability should not be seen as an ethical requirement of research in developing countries.⁴⁰ What *is* a requirement is that the host community actually benefit fairly from the conduct and/or results of research. But providing medication posttrial is *not* the only way the community might reap benefits. The important point is to assess the overall net benefits for the community of participating in the research as opposed to focusing exclusively on one particular type of benefit—access to the tested drug.

Moreover, defenders of the view that reasonable availability is not an ethical requirement have pointed out that such a policy makes more sense for various additional reasons. No single trial ever proves or disproves the effectiveness of an intervention. Usually multiple trials are required to persuade the medical community about the effectiveness of drugs and other treatments. Thus, guaranteeing access after only one trial is unrealistic. Furthermore, implementing any particular intervention, even in developed countries, is a haphazard process at best. Adoption of a new drug or technology is not like switching on a light

that can occur by an agreement or government fiat. Diffusion of drugs and interventions is a complex social phenomenon that is not under the control of a single sponsor.

Finally, even though all parties appear to agree that benefits (of some sort) must be offered, it is not at all clear why all the responsibility for supplying benefits should rest with *the sponsor* of the research. In many cases, the sponsor, such as the NIH or CDC in the United States, or the Medical Research Council of the United Kingdom (MRC), is legally required to focus on research and not health care implementation. Hence such agencies are legally barred from assuming responsibility for posttrial drug distribution. Many other parties might have ethical obligations for implementing an intervention proven effective by these sponsors, including the host country's government, international aid organizations, or governments in developed countries other than the sponsoring government. So it remains unclear why CIOMS singled out research *sponsors* as being the key ones responsible for assuring reasonable availability.

In addition to concerns about communities, there are also concerns about participants. In particular, what is owed posttrial to participants who are placed on a drug during a study and who benefit from it? For example, in the AZT trials, should someone have undertaken to make AZT available posttrial to the women who participated, and to those children who contracted the virus? This is a particularly charged question in the case of HIV/AIDS trials because antiretroviral treatments are both incredibly beneficial and incredibly expensive. Furthermore, they need to be taken continuously—for the rest of the patient's life—if they are to be effective. There is now an emerging consensus in the international community that such care must be offered, but as with the issue of community benefit, deep questions remain about who exactly is to provide it.⁴¹ Once again, the fact that agencies like NIH are not able, under their mandate, to provide long-term care, makes the question particularly difficult.⁴²

Exploitation: The Common Thread

What do worries about standard of care and other aspects of study design, informed consent, and reasonable availability and/or fair benefits all have in common? Exploitation. Underlying each is the worry that

poor research participants in developing countries are exploited by research trials sponsored and conducted by developing countries. The real ethical violation of using placebos, or not getting valid consent, or not providing drugs proven effective in the trial or sufficient alternative benefits is that it exploits the people in these developing countries.

The language of exploitation runs throughout the medical literature on these issues.⁴³ To give just a few examples: After decrying the use of placebos in the maternal-fetal AZT transmission trials, Lurie and Wolfe argued that “residents of impoverished, postcolonial countries, the majority of whom are people of color must be protected from potential *exploitation* in research [our italics].”⁴⁴ In her remarks on the same trials, Marcia Angell urged, “Acceptance of this ethical relativism [by which she refers to her opponents’ claim that it is permissible for trials to differ based on local differences] could result in widespread *exploitation* of vulnerable Third World populations [our italics].”⁴⁵

Similarly, Annas and Grodin declared that

unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply *exploiting* them in order to quickly use the knowledge gained from the clinical trials for the developed countries’ own benefit. . . . The central issue in doing research with impoverished populations is *exploitation* [our italics].⁴⁶

However, concerns about exploitation are not limited to clinical research in developing countries. Exploitation is a potential concern in all clinical research. All research “uses” the participants to gain information that, hopefully, will improve the health of others whether directly, or indirectly through additional research. Thus, all research participants are in danger of being exploited. As one South African researcher observed: “The starting point of all clinical trials is the assurance that trial participants will be protected from *exploitation* [our italics].”⁴⁷ In a similar vein it has been claimed that

[t]he overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology; subjects who participate are the means

to securing such knowledge. By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects. Ethical requirements for clinical research aim to minimize the possibility of *exploitation* by ensuring that research subjects are not merely used, but are treated with respect while they contribute to the social good [our italics].⁴⁸

However, characterizing the ethical issue at the heart of clinical research as one of exploitation can be both helpful and problematic. It is helpful because it unifies what have often been diffuse, disjointed, and even incoherent concerns about research in developing countries into what seems to be a single, clear ethical issue. It is problematic because the appearance of simplicity is deceiving. Exploitation is itself a diffuse and unclear ethical concept. Hence we run the danger of substituting a vague pile of concerns for an equally vague label—giving it the patina of coherence but without real clarity.

Why is exploitation itself vague and unclear? The problem stems both from the fact that exploitation can be used in morally loaded and morally neutral ways, and from the fact that we often fail to realize that not all “use” of people, despite sounding bad, is morally problematic.

In the most minimal sense, “to exploit” simply means to *use* something to advantage. A weight lifter exploits his muscles to lift weights, a carpenter exploits his tools to build beautiful chairs, a scientist exploits a quirk of nature to make a new cosmological discovery or synthesize a new molecule. In these common cases, the exploitation is not morally worrisome. Moreover, in this simple nonmoral sense, the word quite *naturally* applies to clinical research because research uses human beings to gain generalizable knowledge.

Despite sounding bad, however, use of people, by itself, need not be morally bad, since competent adults need not be *abused* and may consent to being used. Indeed, consent to fair use is what happens in ethical research. A more morally loaded sense of the term, according to which exploitation involves using those who are *vulnerable*, also turns out, when we press on it, to be a description that applies to much ethically justified clinical research on sick people. The problem here is that the notion of “vulnerability,” like the notion of “use,” is merely a marker for moral concern and not a sure sign of moral infringement. Although

it sounds bad to say that we “use those who are vulnerable,” it is possible to use those who are vulnerable without taking unfair or inappropriate advantage of their vulnerability. For example, an employer who hires extremely poor workers desperate for a job, and who pays them a decent, livable wage is using those who are vulnerable but without taking unfair or inappropriate advantage of their vulnerability.

Clearly, confusion and misunderstanding can easily arise here. The morally worrisome connotation of exploitation is related to use. But how? That is the tricky question at the heart of most discussions of exploitation. We must address these questions head-on if we are to gain an understanding of current problems in the ethics of clinical research. Specifying what constitutes exploitation is critical not only for correctly labeling a situation or relationship but also for devising the appropriate remedy. Unless we know what the problem is, it is very hard to know what the right solution is. Often the wrong solution will just exacerbate the problem.

The Origin of This Volume and a View of What’s Ahead

The essays in this collection emerged from the recognition by members of the Department of Clinical Bioethics of the National Institutes of Health of the centrality of, but also the challenges surrounding, the concept of exploitation. In the spring of 2002 members of the department first convened a seminar series on exploitation and its relationship to research practices in developing countries. This volume of essays is the product of that seminar series, either directly (certain of the essays were written for that series by guest speakers) or indirectly (because the series stimulated additional reflection on the part of individual attendees of the seminar).

Because so much ink has already been devoted to the maternal-fetal HIV transmission studies, and because consequently positions have become entrenched without much openness to deeper reflection, we decided to organize the essays around two different cases that raise many of the important and charged contextual issues in fresh clothes.

The Surfaxin case involves a proposed research study on a new surfactant, a drug sprayed into the lungs of premature infants to increase

the pliability of the air sacs and ease breathing. While many natural and synthetic surfactants were already on the market, the pharmaceutical company developing the drug wished to sponsor a randomized controlled study using a placebo, to be conducted in four Latin American countries. The Havrix case, on the other hand, involved the randomized controlled trial of a hepatitis A vaccine in northern Thailand sponsored by the U.S. Army in conjunction with a pharmaceutical company. In this case, the control intervention was not a placebo but a hepatitis B vaccine. Detailed case descriptions are included in this volume, and the authors comment to some degree on one or both of these cases.

Importantly, neither of the two trials we have selected involved HIV/AIDS, and neither trial was conducted in Africa. However, one involved the use of placebos in critically ill infants despite the fact that a known effective intervention already existed. Both trials involved poor participants in developing countries, with researchers coming from the United States. In neither case was it expected that the trial drugs, if proven effective, would be made available any time soon to participants or their communities, though in both cases other types of benefits were offered by the sponsors. One was a government-sponsored study, the other sponsored by a pharmaceutical company.

In addition to the two case studies and the essays that follow, this volume also contains a chapter entitled “Research Ethics, Developing Countries, and Exploitation: A Primer.” It has been our aim from the start to make this volume as accessible as possible to people from different disciplines: physicians, clinical researchers, health policy analysts, philosophers, bioethicists, public health students and professors, and health lawyers. Hence, the first half of that chapter provides an introduction to the fundamental concepts of research ethics and the special issues that arise when they are applied to a developing world setting. These include informed consent, randomized controlled trials (RCTs), standard of care, clinical equipoise, and so on. This section is intended for readers who are familiar with ethical theory but less familiar with the peculiar concerns of clinical research. The second half of the chapter provides an overview of the concept of exploitation to help orient those less familiar with philosophy to the various ways in which philosophers have approached the topic. This section will briefly introduce readers to the history of the concept (in particular, its Marxist meaning), as well as

provide an introduction to the contemporary non-Marxist conceptions that figure in these essays. The section lays out the central questions about exploitation that remain open for debate.

We hope this volume raises the quality of thought and public deliberation on exploitation by elucidating what really constitutes exploitation and what can be done to mitigate it, all in the context of real situations that confront policy makers, ethicists, government and corporate officials, the media, and the public.

Notes

1. Edward M. Connor et al. "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment," *New England Journal of Medicine* 331 (1994): 1173–80.

2. *Id.*

3. Christine Grady, "Science in the Service of Healing," *Hastings Center Report* 28, no. 6 (1998): 34–38, at 35.

4. Connor et al., *supra* note 1, at 1173.

5. Peter Lurie and Sidney M. Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *New England Journal of Medicine* 337 (1997): 1853–55, at 853.

6. Indeed, 90 percent of all HIV-infected individuals reside in developing countries. These statistics are based on November 2004 figures from the UNAIDS Web site, http://www.unaids.org/en/resources/questions_answers.asp#II (accessed July 24, 2005).

7. Grady, *supra* note 3, at 35.

8. Robert A. Crouch and John D. Arras, "AZT Trials and Tribulations," *Hastings Center Report* 28, no. 6 (1998): 26–34, at 33.

9. *Id.* at 26; Grady, *supra* note 3, at 35.

10. Crouch and Arras, *supra* note 8, at 26.

11. Grady, *supra* note 3, at 35.

12. World Health Organization, *Recommendations from the Meeting on Mother-to-Infant Transmission of HIV by Use of Antiretrovirals* (Geneva: WHO, 1994).

13. Lurie and Wolfe, *supra* note 5, at 853.

14. *Id.*

15. Marcia Angell, "The Ethics of Clinical Research in the Third World," *New England Journal of Medicine* 337 (1997): 847–49.

16. Richard Saltus, "Journal Departures Reflect AIDS Dispute," *Boston Globe*, October 16, 1997, A11.

17. Harold Varmus and David Satcher, "Ethical Complexities of Conducting Research in Developing Countries," *New England Journal of Medicine* 337 (1997): 1003–5.

18. See, e.g., volume 12, issue 4 (1998) of *Bioethics*: David B. Resnik, "The Ethics of HIV Research in Developing Nations," 286–306; Reidar K. Lie, "Ethics of Placebo-Controlled Trials in Developing Countries," 307–11; Udo Schuklenk, "Unethical Perinatal HIV Transmission Trials Establish Bad Precedent," 312–19; Joe Thomas, "Ethical Challenges of HIV Clinical Trials in Developing Countries," 320–27; Carlos del Rio, "Is Ethical Research Feasible in Developed and Developing Countries?" 328–30; see also volume 28, issue 6 (1998) of *Hastings Center Report*: Ezekiel J. Emanuel, "A World of Research Subjects: Introduction," 25; Crouch and Arras, *supra* note 8; Grady, *supra* note 3; Leonard H. Glantz, George J. Annas, Michael A. Grodin, and Wendy K. Mariner, "Research in Developing Countries: Taking 'Benefit' Seriously," 38–42; Carol Levine, "Placebos and HIV: Lessons Learned," 43–48.

19. Lurie and Wolfe, *supra* note 15; Angell, *supra* note 15. The language of "double standards" originates with Lurie and Wolfe.

20. This rule is generally traced to the World Medical Association's (WMA) Declaration of Helsinki, which in turn is a development of the Nuremberg Code, the first formal code of clinical research ethics drawn up in the wake of the Nuremberg trials of the Nazi doctors who conducted horrific human experiments during World War II. However, it is worth noting that although this is a widely recognized norm of medical research, it is not a *binding* rule for much research. It is not, for example, included in the U.S. Federal Code of Regulations (DHHS Title 45, CFR 46) that govern all human subjects research that receives U.S. government funding. Nor is it contained in that part of the U.S. Federal Code (DHHS 21 CFR 50 and 56) that specifies the ethical requirements research must pass if it is to be used to win FDA approval. The current version of Helsinki at the time of this dispute was the one from 1996. However, the relevant passage (paragraph II.3) predates 1996. The 1989 version of the Declaration of Helsinki is reprinted in George J. Annas and Michael A. Grodin, *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992), 339–42.

21. The Declaration of Helsinki, September 1989, par. II.3.

22. Grady, *supra* note 3, at 35.

23. This is significant, because some of the rhetoric surrounding these trials, particularly Marcia Angell's comparison of the AZT trials to the infamous Tuskegee trials of untreated syphilis, implies that defenders have only the most crude types of utilitarian arguments on their side. The suggestion is that these are people for whom no treatment of subjects is ruled out if it will lead to useful medical knowledge. However, that is not the position of most defenders. See Angell, *supra* note 15, at 847.

24. Robert J. Levine, "The 'Best Proven Therapeutic Method' Standard in Clinical Trials in Technologically Developing Countries," *IRB: A Review of Human Subjects Research* 20 (1999): 5–9; Reidar K. Lie, Ezekiel J. Emanuel, Christine Grady, and David Wendler, "The Standard of Care Debate: The Declaration of Helsinki versus the International Consensus Opinion," *Journal of Medical Ethics* 30 (2004): 190–93.

25. For discussion of the proposed revisions, offered before the final changes occurred, see Brennan, "Proposed Revisions to the Declaration of Helsinki—Will They Weaken the Ethical Principles Underlying Human Research?" *New England Journal of Medicine* 341 (1999): 527–30; Robert J. Levine, "The Need to Revise the Declaration of Helsinki," *New England Journal of Medicine* 341 (1999): 531–34; Kenneth J. Rothman, Karin B. Michels, and Michael Baum, "For and Against: Declaration of Helsinki Should Be Strengthened," *British Medical Journal* 321 (2000): 442–45.

26. See, e.g., Joint United Nations Programme on HIV/AIDS (UNAIDS), *Ethical Considerations in HIV Preventative Vaccine Research* (Geneva: UNAIDS, 2000); Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 2002); Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (London: Nuffield Council on Bioethics, 2002); National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda, MD: NBAC, 2001). For the claim that a new consensus has emerged that contradicts Helsinki, see Lie, Emanuel, Grady, and Wendler, *supra* note 24.

27. For discussion of this, see chapter 1 in this volume.

28. See, e.g., Howard W. French, "AIDS Research in Africa: Juggling Risks and Hopes," *New York Times*, October 9, 1997; Sharon LaFraniere, Mary Pat Flaherty, and Joe Stephens, "The Dilemma: Submit or Suffer: The Body Hunters, Article III," *Washington Post*, December 19, 2000.

29. George Annas quoted in LaFraniere, Flaherty, and Stephens, *supra* note 28.

30. Nicholas A. Christakis, "The Ethical Design of an AIDS Vaccine Trial in Africa," *Hastings Center Report* 18, no. 3 (1988): 31–37, at 31.

31. LaFraniere, Flaherty, and Stephens, *supra* note 28.

32. Christine Pace, Christine Grady, and Ezekiel J. Emanuel, "What We Don't Know about Informed Consent," *SciDevNet*, August 28, 2003, www.scidev.net/en/opinions/what-we-dont-know-about-informed-consent.html.

33. See, e.g., Glantz, Annas, Grodin, and Mariner, *supra* note 18; Crouch and Arras, *supra* note 8.

34. The Council for International Organizations of Medical Sciences (CIOMS) is an international nongovernmental organization closely tied to the World Health Organization (WHO) and founded by WHO and the United Nations Educational Scientific and Cultural Organization (UNESCO).

35. The Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 1993), Commentary on Guideline 15, at 45.

36. The Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 2002), Guideline 10, at 32.

37. George J. Annas and Michael A. Grodin, "Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa," *American Journal of Public Health* 88 (1998): 560–63, at 561.

38. Glantz, Annas, Grodin, and Mariner, *supra* note 18, at 39.

39. Harold T. Shapiro and Eric M. Meslin, "Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries," *New England Journal of Medicine* 345 (2001): 139–42, at 139. Also see National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research*, chap. 4.

40. Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, "Fair Benefits for Research in Developing Countries," *Science* 298 (2002): 2133–34; and "Moral Standards for Research in Developing Countries: From 'Reasonable Availability' to 'Fair Benefits,'" *Hastings Center Report* 34, no. 3 (2004): 17–27, reprinted as chapter 9 of this volume.

41. Christine Grady, "The Challenge of Assuring Continued Post-trial Access to Beneficial Treatment," *Yale Journal of Health Policy, Law, and Ethics* 5, no. 1 (2005): 425–35.

42. See, e.g., *NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following Their Completion of NIH-Funded Antiretroviral Treatment Trials in Developing Countries* (Bethesda, MD: National Institutes of Health, Office of Extramural Research, 2005), available at <http://grants.nih.gov/grants/policy/antiretroviral/QandA.htm#Purpose>.

43. Indeed, the examples in the text barely scratch the surface. Other instances in which the issues have been framed in terms of exploitation include Emanuel, *supra* note 18; Glantz, Annas, Grodin, and Mariner, *supra* note 18;

Grady, *supra* note 3; Ronald Bayer, "The Debate over Maternal-Fetal HIV Transmission Prevention Trials in Africa, Asia and the Caribbean: Racist Exploitation or Exploitation of Racism?" *American Journal of Public Health* 88 (1998): 567–70; Salim S. Abdool Karim, "Placebo Controls in HIV Perinatal Transmission Trials: A South African's Viewpoint," *American Journal of Public Health* 88 (1998) 564–66; Isabelle de Zoysa, Christopher J. Elias, and Margaret E. Bentley, "Ethical Challenges in Efficacy Trials of Vaginal Microbicides for HIV Prevention," *American Journal of Public Health* 88 (1998): 571–75; Resnik, *supra* note 18; Lie, *supra* note 18; del Rio, *supra* note 18; Barry R. Bloom, "The Highest Attainable Standard: Ethical Issues in AIDS Vaccines," *Science* 279 (1998): 186–88; Brennan, *supra* note 25; Udo Schuklenk and Richard Ashcroft, "International Research Ethics," *Bioethics* 14, no. 2 (2000): 158–72; Solomon R. Benatar, "Avoiding Exploitation in Clinical Research," *Cambridge Quarterly of Healthcare Ethics* 9 (2000): 562–65; Solomon R. Benatar and Peter M. Singer, "A New Look at International Research Ethics," *British Medical Journal* 321 (2000): 824–26; Mary Pat Flaherty and Doug Struck, "Life by Luck of the Draw: The Body Hunters, Article VI," *Washington Post*, December 22, 2000; Shapiro and Meslin, *supra* note 39; Paquita de Zulueta, "Ethical Imperialism or Unethical Exploitation?" *Bioethics* 15 (2001): 547; Ruth Macklin, "After Helsinki: Unresolved Issues in International Research," *Kennedy Institute of Ethics Journal* 11 (2001): 17–36; Michael Specter, "The Vaccine: Has the Race to Save Africa from AIDS Put Western Science at Odds with Western Ethics?" *New Yorker*, February 3, 2003, 54–65.

44. Lurie and Wolfe, *supra* note 5, at 855.

45. Angell, *supra* note 15, at 848.

46. Annas and Grodin, *supra* note 37.

47. Karim, *supra* note 43, at 565.

48. Ezekiel J. Emanuel, David Wendler, and Christine Grady, "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 283 (2000): 2701–11.