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18. Perhaps this is what Wittgenstein had in mind when he observed in *Philosophical Investigations* that "the human body is the best picture of the human soul."
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22. Long, et al.: *The Access Report*.
23. *Ibid.* The idea of "institutional discrimination" is analogous to the phenomenon of institutional racism, whereby discrimination occurs because of biases and prejudices that exist within the system, as opposed to the bigotry of an individual or group.
24. See *Deciding to Enter an AIDS/HIV Drug Trial*. New York: AIDS Treatment Registry, 1989.

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CASE STUDY

Clinical AIDS Research that Evaluates Cost Effectiveness in the Developing World

by Nicholas A. Christakis, Lorna A. Lynn,
and Aduato Castelo

A researcher in a South American country wants to evaluate the economic impact of antiretroviral therapy from the perspective of his developing society. He proposes a large randomized clinical trial (RCT) that will compare dideoxycytidine (ddC) with placebo, not only to assess the relative effectiveness of this antiretroviral agent in prolonging survival and improving the quality of life of patients with HIV infection, but also to determine if an investment by his government in antiretroviral therapy might ultimately prove cost saving to society.¹

For his government, zidovudine appears prohibitively expensive. The government, however, currently does provide hospital-based care (not including zidovudine) for patients with HIV infection once the inevitable and debilitating complications of opportunistic infections develop. A major goal of this RCT is to conduct an economic analysis to determine if, in fact, purchasing antiretroviral therapy would prove to be a prudent investment for the government because of the additional years of relative health and productivity that such therapy may provide. All patients in the study will receive usual medical care, including supportive care and frequent medical evaluations.

Public health officials in this country have indicated that data showing potential cost savings could influence policies, which at the present time do not provide any antiretroviral therapies for the increasing numbers of patients with HIV infection. The manufacturers of the pharmaceutical have shown strong initial interest in funding this study. The researcher's home institution has evaluated the ethical

and clinical justification of the proposal and has given its approval.

Is it ethical in this setting to conduct a placebo-controlled trial when a drug that is known to prolong survival exists? Is it acceptable to design a clinical study to answer an economic question?

In the U.S., RCTs are conducted to determine if a drug is effective for the treatment of a given condition; evidence provided by such trials is instrumental in winning FDA approval for marketing of the drug. Therefore, in a sense, the point of an RCT is to determine whether a drug should be made available to the public. The case at hand is a variation on this theme. It is of no real benefit to people with AIDS in a poor, developing society to be told that there is a drug for their condition, but that it is out of their reach because of resource constraints. Results of the proposed RCT will determine whether ddC will be made available to the public.

The mere existence of an expensive or of a relatively cost-ineffective drug elsewhere constitutes only theoretical availability to patients in the developing world. The very need to conduct research such as the present case illustrates the point that a drug shown to be effective in the developed world meets only the first standard that determines availability in the developing world, where drugs must also meet the standards of affordability, and, more precisely, cost effectiveness. The latter refers to the net cost required to obtain a given benefit from medical care. Cost-effectiveness analyses must be undertaken from a specific perspective, usually that of the patient, the health care provider, a private third-party payor, or a government. Such an analysis is distinct from cost-benefit analysis in that no assessment of whether the cost is "worth" the benefit is made.²

Questions of medical economics, such as those of cost effectiveness or resource allocation, are of critical importance in much of the develop-

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ing countries, bioethical decision-making is potentially powerfully constrained by the fact that healthcare resources are often severely limited.³ Cost alone is frequently an important factor in determining which drugs many countries place on their formularies.⁴ In most South American countries, the vast majority of patients cannot pay for AIDS drugs with their own funds. Moreover, private insurers in South America typically specifically exclude from coverage infectious diseases of all types, including AIDS; hence zidovudine is presently not covered. The national governments therefore bear the financial burden for such medication. The proposed ddC-placebo trial thus promises to provide crucial information that the government needs in determining how to spend its scarce health care funds. Indeed, data provided by the trial will determine which drug, if any, the government elects to make available to its people.

Hence, comparison of ddC to placebo is *not* unethical if the cost of zidovudine is beyond what the government could possibly afford. If zidovudine is known to be too expensive—or too cost ineffective—for a given society to purchase at all, for the purposes of the ethical design of a research study it is as if zidovudine did not exist. It is possible, in other words, that the government of a developing country may decide that antiretroviral therapy of one type or another (e.g., ddC, zidovudine, etc.) is not more cost effective than simple supportive care. This is a legitimate concern in a setting of scarce resources.⁵

We recognize that this stance invites possible discrimination by the government against certain classes of patients. Certainly cost effectiveness alone is *not* the only way a government formulary should be developed. Other considerations, such as equity, disease severity, and disease prevalence, are also important. Our point here is simply that cost and cost effectiveness are clearly legitimate concerns and—sadly in the developing world—must sometimes be prospectively evaluated. Indeed, from the perspective of a developing society, it is hard to justify huge expenditures on drugs for a given condition when there are other, more readily treatable conditions for which affordable and cost-effective therapy is available.

Simple cost finding alone, however, may be misleading. This was

the case for zidovudine treatment for patients with asymptomatic HIV infection in the United States. Although there was an initial outcry in the popular press about the “unfair” high price of zidovudine, health economists have shown that zidovudine therapy is actually more cost effective in terms of cost per year of life gained than many therapies commonly provided in the developed world, such as treatment for high blood cholesterol or screening mammography.⁶

To justify the use of ddC as the study drug in this developing world study, two criteria must thus be met. One is that there must be some expectation that ddC will be clinically effective. This has been met in the present case. Indeed, a number of phase I trials have been completed and phase II trials are under way in the developed world (all of which compare ddC to zidovudine or provide alternating doses of ddC and zidovudine). The other criterion is that sufficient pricing data must be available prior to the outset of the study to permit the expectation that ddC would indeed be more cost effective than zidovudine. That is, there must be honest reason to believe that ddC might be more cost effective when compared to placebo *and more cost effective than zidovudine*. Insufficient data have been provided in this case to determine whether this second expectation has been met.

In the present case, the RCT is specifically designed to control for cost effectiveness of antiretroviral therapy by having a placebo group. This feature of the study design is necessitated by the goal of answering an economic question. Provided this does not come at the expense of *harming* patients, we believe this is acceptable. In other words, it is essential that in studies such as the present case, there be no *a priori* reason to expect that ddC will be worse for patients, clinically speaking, than placebo (indeed, there should be some reason to expect that it will be better than or at least equivalent to placebo). Patients should not knowingly be harmed. Moreover, if we accept the premise that an RCT to answer an economic question is necessary and appropriate, then we must permit the study to be designed in a way that affords an answer to the question. It would clearly be unethical to subject research subjects to risk at all if the study were poorly designed.⁷

Trials evaluating the efficacy of

ddC in the United States would ordinarily not include a placebo arm. Zidovudine has been shown to prolong survival of patients with AIDS or ARC and to delay the onset of AIDS or ARC in certain patients with asymptomatic HIV infection. Because zidovudine is presently available to all patients in the United States for whom it is indicated, a trial of a new antiretroviral agent that would deny the opportunity for the survival advantage of zidovudine over placebo is unethical.⁸ In developing nations that do not, because of expense, provide zidovudine to any patients, however, a trial designed to evaluate ddC against placebo is not unethical.

There are two final ethical expectations that we believe must be met in conducting this study. First, the study should receive the approval of a local body that reviews the ethical design of clinical research. One problem with this type of trial is that it sets the stage for possible abuse of developing world citizens in research studies. This is clearly unacceptable. It is hoped that local review might mitigate this possibility. Second, a contingency of this trial must be a prior commitment by the drug manufacturer and the sponsoring government to provide ddC to the population should it prove to be clinically active and cost effective.⁹

This case serves to illustrate the increasing complexity of bioethical decisionmaking as cultural barriers are breached by an expanding Western medicine. Despite the appeal and prominence of non-Western medical systems, Western biomedicine has become the only truly cosmopolitan system of medicine. This has found several expressions, including the increased movement of Western researchers into non-Western settings and the increased role played by international pharmaceutical concerns.¹⁰ Ethical decisionmaking in non-Western settings and the existence of disparate ethical standards are appropriately receiving increasing attention as medical research becomes more international.

Ethical rules are fashioned by a particular group within a particular cultural tradition and under particular environmental and economic constraints. The ethical expectations regarding research with human subjects may therefore be expected to vary from society to society. Not surprisingly, there is defensible variability in ethical

norms.¹¹ We believe that certain research protocols involving consenting adults that are unacceptable in some countries may be acceptable in others. The AIDS pandemic especially has called into question basing research ethics—wherever the research might be conducted—on Western ideals alone.¹² The present case illustrates that ethical decisionmaking is powerfully influenced by local disease patterns, local values, and local economies. From this cross-cultural perspective, clinical research that does not harm patients, that provides a meaningful benefit to them, and that is aimed at obtaining economic data that will determine drug availability is acceptable and indeed necessary.

References

1. This simple, two-arm study was ultimately replaced—at the behest of the manufacturer of ddC—by a more complex, three-arm study involving ddC, placebo, and zidovudine. At the time of publication, however, the manufacturer had decided not to participate in this trial.
2. For a comprehensive review, see Eisenberg, J: Clinical economics: A guide to the economic analysis of clinical practices. *JAMA* 1989; 262(20): 2879-86.
3. The cost effectiveness of various treatments for various diseases will, of course, vary in different countries owing to a number of factors. For example, a study of the treatment of end-stage renal disease in Brazil, where dialysis patients account for 0.008% of the population but consume 1.6% of the total health care budget, revealed that hemodialysis was more cost effective than peritoneal dialysis, partially because of the re-use of hemodialyzers in Brazil. See, Sesso, R et al.: Cost-effectiveness analysis of the treatment of end-stage renal disease in Brazil. *International Journal of Technology Assessment in Health Care* 1990; 6: 107-114.
4. Regarding the role of cost in the selection of drugs in the developing world, see, for example, Patel, MS: Drug costs in developing countries and policies to reduce them. *World Development* 1983; 11(3): 195-204; Barker, C: The Mozambique pharmaceutical policy. *The Lancet*, 1 October 1983, pp. 780-82. That drug cost is of concern in the developed as well as the developing world is aptly illustrated by the furor created when an Italian study of thrombolysis in coronary arteries revealed no difference between TPA (at \$2,200 per treatment) and streptokinase (at \$186); (Study says \$42,200 heart drug is no better than a \$76 one. *New York Times*, 9 March 1990, p. 1.)
5. Of course, a strong argument could be made to shift new resources into the health care sector, i.e., to expand the resource base. But this approach "solves" the ethical problem by avoiding it.
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11. See, Barry, M: Ethical considerations of human investigation in developing countries: The AIDS dilemma. *NEJM* 1988; 319(16): 1083-86; Newton, LH: Ethical imperialism and informed consent. *IRB: A Review of Human Subjects Research* 1990; 12(3): 10-11; Hall, AJ: Public health trials in West Africa: Logistics and ethics. *IRB: A Review of Human Subjects Research* 1989; 11(5): 8-10.
12. Christakis, NA: The ethical design of an AIDS vaccine trial.

Ethical Dilemmas with Economic Studies in Less-Developed Countries: AIDS Research Trials

by Michele Barry

Christakis et al. describe a randomized clinical trial (RCT) within a developing South American country comparing dideoxycytidine (ddC) to placebo in patients infected with human immunodeficiency virus (HIV).¹ They question whether it is ethical to conduct a placebo-controlled trial when there is a drug known to improve quality of life and possibly prolong survival for patients with HIV,² and they also query whether it is acceptable to design a clinical study solely to answer economic questions in a less developed country (LDC). I would add a third question: Should U.S.-funded research, which would never be approved in the United States, be conducted in an LDC? If so, under what circumstances and with what safeguards should it be conducted?

HIV infection is a devastating health problem not only taxing the resources of the developed world, but also overwhelming the health care systems of developing countries. The World Health Organization and individual countries are constantly reassessing economic priorities for health delivery in settings of scarce resources.³ Christakis's question of the acceptability of clinical studies to answer economic questions is a nonquestion as such studies are a necessity to make rational decisions for countries with limited health care dollars. However, if the end-point of

a study in an LDC is a measure of cost effectiveness rather than one of effectiveness per se (as is the usual endpoint in RCTs in more developed countries), certain novel technical issues become relevant to whether the trial is ethical. In particular, given its endpoint, the proposed ddC trial would need to meet the following criteria:

1. Sufficient data are obtained by the study to allow an economic cost-effectiveness analysis for the LDC (e.g., productive work years gained per unit cost; health care costs deferred per unit cost, etc.). Such data are often difficult to obtain in certain populations in LDCs.
2. Given the scarce resources of an LDC, estimates of possible cost effectiveness based on prior data regarding the drug must be conducted *before* the trial to determine if there is a reasonable chance that the drug will be as cost effective as other priority health care allocations for an LDC (eg, tuberculosis programs, vaccine campaigns, primary health care clinics, etc.).

If these two criteria are not satisfied, the trial would not have a reasonable chance of leading the LDC to decide to use ddC; hence the results of the trial could not help HIV-infected persons in the LDC. In fact, the trial would be of use only to developed societies and hence would offer no benefit to compensate for the risk to citizens of LDCs.

The issue of whether a U.S.-funded study that would not be approved in the U.S. should be con-

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