



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

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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.
6. Schulman, KA, Lynn, LA and Eisenberg, JM: Cost-effectiveness of low dose zidovudine therapy for asymptomatic patients with human immunodeficiency virus (HIV) infection. *Annals of Internal Medicine* 1991; 114(9): 798-802.
7. Rutstein, DD: The ethical design of human experiments. *Daedalus* 1969; 98(2): 523-41.
8. Levine, RJ: *Ethics and Regulation of Clinical Research*. New Haven: Yale University Press, 1988, esp. pp. 220 ff.
9. Christakis, NA: The ethical design of an AIDS vaccine trial in Africa. *Hastings Center Report* 1988; 18(3): 31-37, esp. p. 36.
10. Christakis, NA: Responding to a pandemic: International interests in AIDS control. *Daedalus* 1989; 118(2): 113-34.
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, 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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ducted in an LDC is a more complex question. Christakis et al. offer an excellent example for analysis.

Dideoxycytidine (ddC) is currently an investigational drug whose patent is assigned to the U.S. government; preliminary phase I/II trials of ddC have shown activity against HIV but with significant dose-related toxicity (severe peripheral neuropathy).⁴ An LDC researcher has initiated a study to see if ddC is cost effective in a country where zidovudine (AZT) is too expensive. An excellent argument is made that an economic cost-effectiveness comparison of ddC to placebo in an RCT is *not* unethical since in this LDC the cost of AZT is prohibitive and thus the standard of care in the LDC is no better than in the placebo arm. Actually, individuals enrolled in the placebo arm may fare better than those receiving standard care because they would receive more intensive health care monitoring. Important ethical contingencies of the trial are described: There is a requirement that the manufacturer provide ddC to the population if it proves to be clinically active and cost effective. A local review board is in place to evaluate the ethical and clinical justifications of the trial. A clinical trial with a placebo arm that would not be approved in the U.S. is defended as ethically sound given the

economic constraints of the LDC described.

It is true that ethical decision-making in non-Western settings may involve a different risk-versus-benefit analysis of research protocols due to differing economic, environmental, or cultural expectations.⁵ Yet the principle of distributive justice creates an expectation of providing (or offering) the benefits of research (if developed) to those who participated as research subjects – or at least to members of the group from which the subjects were recruited.⁶ Is the AZT arm Christakis et al. describe in a footnote, as requested by the manufacturer, justified if AZT is not an affordable drug to citizens of the LDC once the study is completed? For the individual participating in the study, the group randomized to the AZT arm may benefit by improved survival or quality of life.⁷ Yet this arm, although not harmful to subjects of the study, will presumably benefit the developed world more than this South American country. Are there obligations at the end of the study to provide the unaffordable drug to these research subjects? I would argue that expectations have been created and the manufacturer should provide the unaffordable drug (AZT) to participating subjects

after the study is completed. Certain research protocols involving consenting adults may be unacceptable in some countries and quite defensible in others. Christakis et al. defend a clinical trial in an LDC that would have difficulty being approved in the United States. Yet given the political difficulties of conducting placebo-controlled clinical trials of drugs for the treatment of HIV infection in the United States (even if justified), we will need to be very wary of pharmaceutical corporations turning to Third World countries where large populations with HIV infection can be rapidly recruited. Local IRBs are a relatively new concept to many countries and potentially influenced by a large influx of research monies and technology. Although local host country review of the ethical and clinical justifications of a study are crucial, we must also ensure that the research will be reviewed in the U.S. to determine that it is designed with the intent of developing benefits for the population in which it is being tested.

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References

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2. Assuming AZT does prolong survival; a premise recently questioned for black and Hispanic populations. See Kolata, G: Federal study questions ability of drug AZT to delay AIDS. *New York Times*, 15 February 1991, pp. A1, 22.
3. World Health Organization: *Economic Support for National Health for All Strategies*. Geneva: WHO, 1988.
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5. Barry, M: Sounding Board. Ethical considerations of human investigation in developing countries – the AIDS dilemma. *New England Journal of Medicine* 1988; 319:1083-86.
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CALENDAR

NOVEMBER 20: The Applied Research Ethics National Association (ARENA) will sponsor a one-day meeting featuring a variety of presentations on issues pertinent to IRBs and research administration. ARENA will also hold its general business meeting that day. For additional information contact ARENA/ PRIM&R, 132 Boylston Street, Boston, MA 02116; 617-423-4112, 617-423-1185 (fax).

NOVEMBER 21-22: Public Responsibility in Medicine and Research announces its annual IRB conference entitled *The Evolution of Protecting Human Subjects: From Nuremberg to the Nineties* to be held at the Boston Park Plaza Hotel in Boston, Massachusetts. This year's meeting will coincide with a historical exhibit entitled "The Worth of Human Life: Medicine, Public Health, and Ethics in Germany, 1918-1945," which will be presented at the Boston University Art Gallery. For additional information contact PRIM&R, 132 Boylston Street, Boston, MA 02116; 617-423-4112, 617-423-1185 (fax).

DECEMBER 6-7: The American Society of Law & Medicine will sponsor a conference entitled *Antiprogesterin Drugs: Ethical, Legal, and Medical Issues* to be held at the Hyatt Regency Crystal City in Arlington, Virginia. The conference will address the challenges to achieving FDA approval and distribution of the drug through pharmacists. For a brochure and registration information contact Sharin Paaso, Associate Director, ASL&M, 765 Commonwealth Avenue, 16th Floor, Boston, MA 02215; 617-262-4990, 617-437-7596 (fax).