place to pool the prospective beneficiaries and a mechanism through which to direct the subsidies and ensure coverage. Without the pooling mechanism, subsidies alone will fail.

The Health Insurance Portability and Accountability Act is an attempt to ensure a source of insurance for people and groups by prohibiting their exclusion from insurance coverage on account of preexisting conditions.[10] However, the law assumes the existence of a small-group and individual market for insurance that in fact may not exist in many places. Moreover, it places no restraints on the ability of companies to raise premiums in response to the new law or to leave the individual and small-group market altogether, thereby actually reducing the sources of insurance. Given the price barriers to the purchase of insurance, the absence of any subsidies in the law makes substantial expansions of coverage through the Health Insurance Portability and Accountability Act unlikely.

The need to provide both subsidies and sources of insurance has been addressed more directly in initiatives for children's health insurance. In the budget bills passed separately by the House and the Senate, Congress identified a stream of revenue to pay for expanded coverage for children. However, the mechanism through which the subsidy is delivered provoked a sustained debate over whether new federal and state dollars should be used, on the one hand, to expand Medicaid (an existing guaranteed pool that provides insurance directly) so that more children above the poverty level are covered or, on the other hand, to provide grants to states to establish structures for the purchase of subsidized private insurance.[11] The final budget agreement gives states the choice of expanding Medicaid, subsidizing premiums, or purchasing services directly from providers.[12] How the subsidy is implemented, however, makes a critical difference in determining to what extent people actually obtain insurance coverage — for example, whether there is a pool that administers the subsidy and issues insurance, or whether vouchers are issued for the purchase of private insurance through a variety of sources.

In evaluating the effect of the alternative designs for delivering the subsidies, the Congressional Budget Office estimated that by activating the subsidies through expansions of Medicaid, 1.2 million children per year who would not otherwise be covered would obtain health insurance.[13] Under a loosely structured state-grant program spending the same dollars, 520,000 children per year would obtain insurance not otherwise available to them.[11] Ultimately, the budget agreement included a more structured state-grant program, with some federal controls, through which to direct the subsidies, and the amount of federal spending on the subsidies was substantially increased, resulting in insurance for approximately 2.5 million additional children per year.[12]

The need for a mechanism through which to pool potential beneficiaries and trigger the issuance of insurance is further demonstrated by the historic failure of tax credits for individuals purchasing insurance. Tax-credit arrangements, enacted in 1990, resulted in only extremely limited expansions of coverage. Among other reasons, this happened because of the lack of sources of insurance and the lack of a mechanism through which the issuance of the subsidy could trigger the issuance of insurance.[14] The failure of the tax-credit approach resulted in its repeal in 1993.[14] This experience suggests that a voucher approach to the expansion of coverage would fail similarly.

To make the subsidies for children work, the federal government must ensure the stability and availability of clearly defined sources of insurance that is triggered by the issuance of the subsidy. In addition, the national leadership must recognize that expanding coverage only for children will not close the financing gap in the health care delivery system created by the contraction in employer-based private insurance. Accordingly, Congress will have to expand the subsidies and pooling mechanisms to include adults.

The conflict inherent in the trends toward declining private insurance, combined with the reduced ability of providers to offer uncompensated care, has not yet become explosive. However, such an explosion is clearly foreseeable unless the government intervenes to create an infrastructure capable of absorbing the effects of these trends. With such an infrastructure we can facilitate stable health care financing even as the employer-based system atrophies, and we can provide the institutional mechanism through which universal coverage can eventually be achieved.

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ETHICAL COMPLEXITIES OF CONDUCTING RESEARCH IN DEVELOPING COUNTRIES

ONE of the great challenges in medical research is to conduct clinical trials in developing countries that will lead to therapies that benefit the citizens of these countries. Features of many developing countries — poverty, endemic diseases, and a low level of investment in health care systems — affect both the ease of performing trials and the selection of trials that can benefit the populations of the countries. Trials that make use of impoverished populations to test drugs for use solely in developed countries violate our most basic understanding of ethical behavior. Trials that apply scientific knowledge to interventions that can be used to benefit such populations are appropriate but present their own ethical challenges. How do we balance the ethical premises on which our work is based with the calls for public health partnerships from our colleagues in developing countries?

Some commentators have been critical of research performed in developing countries that might not be found ethically acceptable in developed countries. Specifically, questions have been raised about trials of interventions to prevent maternal–infant transmission of the human immunodeficiency virus (HIV) that have been sponsored by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC).[1,2] Although these commentators raise important issues, they have not adequately considered the purpose and complexity of such trials and the needs of the countries involved. They also allude inappropriately to the infamous Tuskegee study, which did not test an intervention. The Tuskegee study ultimately deprived people of a known, effective, affordable intervention. To claim that countries seeking help in stemming the tide of maternal–infant HIV transmission by seeking usable interventions have followed that path trivializes the suffering of the men in the Tuskegee study and shows a serious lack of understanding of today's trials.

After the Tuskegee study was made public, in the 1970s, a national commission was established to develop principles and guidelines for the protection of research subjects. The new system of protection was described in the Belmont report.[3] Although largely compatible with the World Medical Association's Declaration of Helsinki,[4] the Belmont report articulated three principles: respect for persons (the recognition of the right of persons to exercise autonomy), beneficence (the minimization of risk incurred by research subjects and the maximization of benefits to them and to others), and justice (the principle that therapeutic investigations should not unduly involve persons from groups unlikely to benefit from subsequent applications of the research).

There is an inherent tension among these three principles. Over the years, we have seen the focus of debate shift from concern about the burdens of participation in research (beneficence) to equitable access to clinical trials (justice). Furthermore, the right to exercise autonomy was not always fully available to women, who were excluded from participating in clinical trials perceived as jeopardizing their safety; their exclusion clearly limited their ability to benefit from the research. Similarly, persons in developing countries deserve research that addresses their needs.

How should these principles be applied to research conducted in developing countries? How can we — and they — weigh the benefits and risks? Such research must be developed in concert with the developing countries in which it will be conducted. In the case of the NIH and CDC trials, there has been strong and consistent support and involvement of the scientific and public health communities in the host countries, with local as well as United States–based scientific and ethical reviews and the same requirements for informed consent that would exist if the work were performed in the United States. But there is more to this partnership. Interventions that could be expected to be made available in the United States might be well beyond the financial resources of a developing country or exceed the capacity of its health care infrastructure. Might we support a trial in another country that would not be offered in

the United States? Yes, because the burden of disease might make such a study more compelling in that country. Even if there were some risks associated with intervention, such a trial might pass the test of beneficence. Might we elect not to support a trial of an intervention that was beyond the reach of the citizens of the other country? Yes, because that trial would not pass the test of justice.

Trials supported by the NIH and the CDC, which are designed to reduce the transmission of HIV from mothers to infants in developing countries, have been held up by some observers as examples of trials that do not meet ethical standards. We disagree. The debate does not hinge on informed consent, which all the trials have obtained. It hinges instead on whether it is ethical to test interventions against a placebo control when an effective intervention is in use elsewhere in the world. A background paper sets forth our views on this matter more fully.[5] The paper is also available on the World Wide Web (at http://www.nih.gov/news/mathiv/mathiv.htm).

One such effective intervention — known as AIDS Clinical Trials Group protocol 076 — was a major breakthrough in the search for a way to interrupt the transmission of HIV from mother to infant. The regimen tested in the original study, however, was quite intensive for pregnant women and the health care system. Although this regimen has been proved effective, it requires that women undergo HIV testing and receive counseling about their HIV status early in pregnancy, comply with a lengthy oral regimen and with intravenous administration of the relatively expensive antiretroviral drug zidovudine, and refrain from breast-feeding. In addition, the newborn infants must receive six weeks of oral zidovudine, and both mothers and infants must be carefully monitored for adverse effects of the drug. Unfortunately, the burden of maternal–infant transmission of HIV is greatest in countries where women present late for prenatal care, have limited access to HIV testing and counseling, typically deliver their infants in settings not conducive to intravenous drug administration, and depend on breast-feeding to protect their babies from many diseases, only one of which is HIV infection. Furthermore, zidovudine is a powerful drug, and its safety in the populations of developing countries, where the incidences of other diseases, anemia, and malnutrition are higher than in developed countries, is unknown. Therefore, even though the 076 protocol has been shown to be effective in some countries, it is unlikely that it can be successfully exported to many others.

In addition to these hurdles, the wholesale cost of zidovudine in the 076 protocol is estimated to be in excess of $800 per mother and infant, an amount far greater than most developing countries can afford to pay for standard care. For example, in Malawi, the cost of zidovudine alone for the 076 regimen for one HIV-infected woman and her child is more than 600 times the annual per capita allocation for health care.

Various representatives of the ministries of health, communities, and scientists in developing countries have joined with other scientists to call for less complex and less expensive interventions to counteract the staggering impact of maternal–infant transmission of HIV in the developing world. The World Health Organization moved promptly after the release of the results of the 076 protocol, convening a panel of researchers and public health practitioners from around the world. This panel recommended the use of the 076 regimen throughout the industrialized world, where it is feasible, but also called for studies of alternative regimens that could be used in developing countries, observing that the logistical issues and costs precluded the widespread application of the 076 regimen.[6] To this end, the World Health Organization asked UNAIDS, the Joint United Nations Programme on HIV/AIDS, to coordinate international research efforts to develop simpler, less costly interventions.

The scientific community is responding by carrying out trials of several promising regimens that developing countries recognize as candidates for widespread delivery. However, these trials are being criticized by some people because of the use of placebo controls. Why not test these new interventions against the 076 regimen? Why not test them against other interventions that might offer some benefit? These questions were carefully considered in the development of these research projects and in their scientific and ethical review.

An obvious response to the ethical objection to placebo-controlled trials in countries where there is no current intervention is that the assignment to a placebo group does not carry a risk beyond that associated with standard practice, but this response is too simple. An additional response is that a placebo-controlled study usually provides a faster answer with fewer subjects, but the same result might be achieved with more sites or more aggressive enrollment. The most compelling reason to use a placebo-controlled study is that it provides definitive answers to questions about the safety and value of an intervention in the setting in which the study is performed, and these answers are the point of the research. Without clear and firm answers to whether and, if so, how well an intervention works, it is impossible for a country to make a sound judgment about the appropriateness and financial feasibility of providing the intervention.

For example, testing two or more interventions of unknown benefit (as some people have suggested) will not necessarily reveal whether either is better than nothing. Even if one surpasses the other, it may be difficult to judge the extent of the benefit conferred, since the interventions may differ markedly in other ways — for example, cost or toxicity. A placebo-controlled study would supply that answer. Similarly, comparing an intervention of unknown benefit — especially one that is affordable in a developing country — with the only intervention with a known benefit (the 076 regimen) may provide information that is not useful for patients. If the affordable intervention is less effective than the 076 regimen — not an unlikely outcome — this information will be of little use in a country where the more effective regimen is unavailable. Equally important, it will still be unclear whether the affordable intervention is better than nothing and worth the investment of scarce health care dollars. Such studies would fail to meet the goal of determining whether a treatment that could be implemented is worth implementing.

A placebo-controlled trial is not the only way to study a new intervention, but as compared with other approaches, it offers more definitive answers and a clearer view of side effects. This is not a case of treating research subjects as a means to an end, nor does it reflect "a callous disregard of their welfare."[2] Instead, a placebo-controlled trial may be the only way to obtain an answer that is ultimately useful to people in similar circumstances. If we enroll subjects in a study that exposes them to unknown risks and is designed in a way that is unlikely to provide results that are useful to the subjects or others in the population, we have failed the test of beneficence.

Finally, the NIH- and CDC-supported trials have undergone a rigorous process of ethical review, including not only the participation of the public health and scientific communities in the developing countries where the trials are being performed but also the application of the U.S. rules for the protection of human research subjects by relevant institutional review boards in the United States and in the developing countries. Support from local governments has been obtained, and each active study has been and will continue to be reviewed by an independent data and safety monitoring board.

To restate our main points: these studies address an urgent need in the countries in which they are being conducted and have been developed with extensive in-country participation. The studies are being conducted according to widely accepted principles and guidelines in bioethics. And our decisions to support these trials rest heavily on local support and approval. In a letter to the NIH dated May 8, 1997, Edward K. Mbidde, chairman of the AIDS Research Committee of the Uganda Cancer Institute, wrote:

> These are Ugandan studies conducted by Ugandan investigators on Ugandans. Due to lack of resources we have been sponsored by organizations like yours. We are grateful that you have been able to do so. . . . There is a mix up of issues here which needs to be clarified. It is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people.

The scientific and ethical issues concerning studies in developing countries are complex. It is a healthy sign that we are debating these issues so that we can continue to advance our knowledge and our practice. However, it is essential that the debate take place with a full understanding of the nature of the science, the interventions in question, and the local factors that impede or support research and its benefits.

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Editor's note: Letters on this subject will be published in a subsequent issue of the *Journal*, along with the responses of Dr. Angell and Drs. Lurie and Wolfe.

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