

New & noteworthy

Updates on activities in the profession

Draft report by National Bioethics Advisory Commission raises new questions

Federal bioethics report could complicate international research

In October 1995, President Bill Clinton established the National Bioethics Advisory Commission (NBAC) to advise all executive branch departments and agencies that conduct, support, or regulate research involving human subjects on public policy issues and other matters related to conducting human research.

In 1999, motivated in part by the outcry over placebo-controlled trials in Africa designed to determine the impact of various antiretroviral modes of therapy on maternal-to-child transmission of the human immunodeficiency virus (HIV), the NBAC initiated a review of international research bioethics. The final report has yet to be released, but the issues raised by the draft report (available at <http://bioethics.gov>) highlight the differences between clinical research conducted within the United States and research carried out by US-based investigators overseas.

Draft report emphasizes posttrial benefits

An important component of the draft report was its emphasis on posttrial benefits. The report notes, "After a clinical trial is concluded, arrangements should be in place to continue to provide to all participants (including members of a control group) any research intervention that proved successful, along with other interventions that were provided to participants during the research, if these participants would not otherwise have access to an established effective treatment. The research protocol should specify how the duration, extent, and financing of this obligation will be explicitly negotiated among the relevant parties in advance. The agreed upon details regarding posttrial treatment must be included in the informed consent process."

This recommendation may be appropriate in the context of a Phase III trial of a new antiretroviral medication, for example, because it would hinder exploitation of foreign populations who cannot afford the new drug. But this recommendation could discourage other important research, such as studies on diseases that are limited to the tropics, including malaria, leishmaniasis, and schistosomiasis. Whereas pharmaceutical companies will sometimes enroll patients from developing countries to evaluate products that will have a market primarily or exclusively in industrialized countries, research into tropical diseases often involves drugs or vaccines that have virtually no market in industrialized nations. Finding industrial partners to help support such projects is already challenging, and any change in policy or regulations that makes industry even less inclined to invest in tropical diseases will further reduce efforts to develop drugs and vaccines for vulnerable populations in developing nations.

Benefits, and not coercion, should motivate participation

The NBAC draft report recommends that "researchers should strive to ensure that individuals participate in research without coercion or undue inducement from community leaders." However, some benefit should—and often does—accrue to those who agree to participate in such studies. For example, in settings where parents have to scramble for the bus or taxi fare to transport their comatose young child to the hospital for treatment of cerebral malaria, the potential benefits of participating in research may overcome any reservations about involving their children in studies. After all, the clean, well-furnished, well-staffed research ward—stocked with all the required medications—stands in stark contrast to the hopelessly overcrowded wards with two or three nurses caring for 50 to 60 children. It has been established that patients in developed countries have better outcomes if they participate in clinical trials (*J Pediatr* 1999;134:130-131). This "inclusion benefit" may be even more pronounced in developing countries, where the disparities in care are even wider than they are in more highly developed nations.

Report supports enhanced capacity building

In recognition of the idea that the presence of US-sponsored research should benefit the host country, the draft NBAC report suggests that "US sponsors and researchers should develop and implement strategies that assist in building local capacity for designing and conducting clinical trials. Identifiable initiatives that assist capacity building should accompany each research project with the ultimate aim of playing a direct role in making host country researchers fuller and more equal



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partners with industrialized country researchers or sponsors."

This kind of burden is not placed on clinical investigators working in the United States. Most investigators working overseas accomplish capacity building by combining resources from disparate sources, such as by seeking training grants to accompany research grants. Although additional institutional support for training and capacity building from sponsors would be welcome, to require this of individual investigators or their sponsors could easily stifle research. Also, such requirements could be insulting to public health officials and others in the developing country. For example, if the US investigator is actually the junior partner—with less capacity—in a collaborative effort with a well-established partner in a developing country, the notion that the US partner would work to develop local capacity could be considered paternalistic and demeaning by scientists and institutions in that developing nation.

NBAC addresses appropriateness of placebo-controlled studies

A thorny issue in many clinical studies carried out in developing countries is that the "standard therapy" used in the United States is



Malaria Project nurses providing patient care on the research ward.



Nurse starting a drip while the mother looks on.

likely to be unaffordable in the host country, and thus would not be used routinely. So, should trials of a new drug be compared with the US standard of care, or with the local standard, which may be no care at all?

The NBAC addresses this question in its draft report with the following recommendation: "In cases in which the only relevant and effective study design would not provide an established, effective treatment, the proposed research protocol should include a justification for using this...design." This implies that placebo-controlled trials are, *a priori*, inferior scientifically or ethically to other designs.

Consider the following example from malaria research: There is a long history of conducting malaria chemoprophylaxis studies in populations that live in malaria-endemic areas. Typically, these populations are continually exposed to malaria, are often chronically infected, and develop immune protection from clinical disease by the time they reach late childhood—though they remain susceptible to asymptomatic infection throughout life. Long-term prophylaxis in these settings is neither practical nor advisable. Such an effort would be extremely expensive in the long run and would

eventually ablate the naturally acquired immunity to malaria that is developed through repeated exposure, thus putting individuals at higher risk of severe malaria should they interrupt or halt prophylaxis. The one group for which malaria prophylaxis is routinely recommended in endemic areas is pregnant women. Because of the difficulties involved in testing new drugs in pregnant women, though, semi-immune older children and adults typically serve as study populations for these drugs.

Malaria chemoprophylaxis studies involve randomly assigning these semi-immune subjects to receive either an antimalarial drug or a placebo for a limited time. Researchers then assess the drug's ability to block infection and disease. The research risks to both groups are minimal, and all subjects benefit from close medical attention during the course of the study—not only for their malaria but for other illnesses as well. Certainly, one could prevent malaria infection in the placebo group with another antimalarial agent, and it is debatable whether a placebo-controlled study is the only relevant and effective study design. However, an equivalence study would greatly increase the study sample size and the cost and will put more people at risk of potential

side effects of the experimental drug. Furthermore, such an approach could easily reduce the likelihood that the study will generate useful information. After all, even if the study drug is less effective than the "established" drug, is it enough better than no prophylaxis to consider further use?

This example differs significantly from the studies that used placebos in testing antiretroviral regimens for blocking mother-to-child transmission of HIV, for the following reasons:

- The disease in question, malaria infection in a semi-immune population, is very low-risk and is easy to cure completely, so the risks to the placebo group are minimal.

- There is relatively little industrial interest in developing antiparasitic drugs, and less funding in general than for research in HIV and acquired immune deficiency syndrome, so study designs that increase cost could cripple studies on parasitic and other types of tropical diseases.

- The benefits of close medical attention for a period of months—which often extend to the subjects' families or even the whole community—clearly outweigh the risks faced by the group receiving the placebo.

Certain ethical issues, such as individual informed consent and

the validity and value of the research itself, are common to clinical research projects around the world. However, there are some questions that are especially challenging for investigators working in developing countries. As noted earlier, these include posttrial benefits, coercion versus benefit, capacity building, and study designs involving placebo-controlled studies. Increasing attention is being directed toward these questions. Open dialogue involving all participants will help to create new guidelines and principles that enhance the conduct of clinical research in developing countries, without unduly hampering such efforts.

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