

# Affairs of State

Jill Wechsler

**New policies aim to guide the growing volume of clinical studies conducted overseas and to address disputes involving placebos and protocols.**

Clinical research has become an international industry, and numerous organizations are expanding policies to protect study participants around the world. The International Conference on Harmonisation has adopted standards for good clinical practice that make it easier for sponsors to conduct studies in other countries to support global registration of new drugs and biologics. Last October (2000), the World Medical Association issued a revised version of the Declaration of Helsinki, which has put international research issues in the spotlight. More recently, the U.S. National Bioethics Advisory Commission published its final report on ethical issues



**Jill Wechsler**

is the Washington editor of Applied Clinical Trials, (301) 656-4634.

in international clinical trials.<sup>1</sup> In the works is an update of 1993 guidelines for the ethical conduct of biomedical research by the Council for International Organizations of Medical Sciences.<sup>2</sup>

These initiatives reflect increased concern about clinical research in areas of the world that previously have played a minor role in biomedical R&D. Driving this trend is growing interest in attacking diseases of developing countries. The worldwide spread of AIDS has raised alarms about the political and economic consequences of unchecked pandemics. The United Nations, the World Bank, western governments, and private foundations are working with the World Health Organization (WHO) to provide millions of dollars to study and develop new treatments for AIDS, malaria, parasitic diseases, and tuberculosis, while also expanding studies in developing countries for conditions more commonly found in industrialized nations.

The biomedical research community also is moving overseas to find more willing participants for the growing volume of clinical studies. An added attraction is patient populations with disease exposure or genetic traits important for research projects. AstraZeneca, for example, is collaborating with a Shanghai university to conduct a large-scale study in China investigating the genetic basis of schizophrenia, which will tap into the university's gene research data bank on psychiatric disease.

Unfortunately, some research authorities fear that U.S. companies seek to launch clinical studies overseas to skirt U.S. subject protection policies. These authorities regard study participants in developing nations as "vulnerable" populations who warrant added protections and oversight.

Discovery Laboratories in New Jersey generated considerable controversy

earlier this year with a proposal to conduct placebo-based studies in Latin America on infants suffering from respiratory distress syndrome. FDA delayed approval of the study until the sponsor dropped the placebo arm and agreed to provide long-term treatment to study participants at the conclusion of the trial. The case raised questions about whether the company was conducting the study in Latin America to evade requirements to use only active controls in Europe or the United States where alternative therapies are available.

To address these concerns, the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) has established an Office of International Activities. The Human Research Subcommittee of the White House Office of Science Technology and Policy has been reactivated and is coordinating the administration's response to the Helsinki declaration. And the Food and Drug Administration (FDA) is monitoring more international clinical trials designed to provide data to support market applications for new medical products.

## International standards

Opposition to the Discovery Labs protocol reflects ongoing debate about the use of placebos in clinical studies. This issue has emerged as a main point of contention between the United States and other nations regarding the revised Helsinki declaration. U.S. authorities consider many aspects of the new declaration positive, including sections that call for special treatment of vulnerable populations, the need for researchers to follow international requirements as well as domestic policies, and the importance of protocol review by institutional review boards (IRBs).

Still, U.S. research officials object to



some parts of the document, explained Dixie Snider, associate director of science at the Centers for Disease Control and Prevention (CDC), at an OHRP meeting last December. He noted that the declaration fails to acknowledge that some situations such as emergency treatment may warrant waiver of informed consent, and that the policy states that all research subjects should be assured of continued access to the best treatment methods provided by a study.

*Many modern therapies are not available in developing countries, which means that the standard of care is often no treatment.*

Although this is a laudable goal, Snider pointed out that it is overly vague and could become a major hurdle for companies seeking to conduct studies overseas.

The most significant problem is the Helsinki provision that calls for all benefits and risks to be tested against “best current prophylactic, diagnostic and therapeutic methods,” that is, active controls instead of placebos. Snider explained that U.S. policymakers say it may be appropriate to use placebos if the protocol presents no added risk to study participants, as when a proven therapy has only marginal value. In many situations, it is unclear what might be the “best” existing treatment, and providing some treatment for a given population may be much better than providing no treatment.

The language also ignores the fact that many experts say placebo controls are needed, at least in some cases, to obtain useful information from a clinical study. Some researchers complain that the placebo provision is impractical because it will rule out research that carries any risk, which is the case with many test therapies. They also fear it will block efforts to develop affordable treatments for developing nations. Others counter that use of placebos too often leads to abuse and encourages sponsors to regard poor countries as “dumping grounds.” The challenge, said Snider, is to block

unethical use of placebos so that researchers can feel comfortable when they use them appropriately.

**Koski defends placebo use.** At a March meeting of the World Medical Association (WMA) in Pretoria, South Africa, OHRP director Greg Koski defended the use of placebos in clinical trials and raised other criticisms of the revised document. Though acknowledging that placebo controls are inappropriate when proven therapies are available, Koski pointed out

that they may be suitable when participants remain at “minimal risk” and when active controls cannot provide reliable information about new treatments. Koski added that many modern therapies are not available in developing countries, which means that “no treatment” often is the standard of care. He observed that one goal of clinical trials is to obtain information as efficiently as possible, and that insistence on active controls may defeat this purpose. Appropriate comparators should be determined on a case-by-case basis, based on the disease being studied, the research question, and the consequences of using placebos instead of active treatment.

Koski also objected to the provision calling for sponsors to assure posttrial access to the “best proven” therapy identified in a trial. He noted that there often is disagreement about what is the best therapy, and that such conclusions may vary by population or geographic area. Another point raised by Koski is that the Helsinki document fails to consider how its provisions would apply to epidemiological and behavioral research and could impose “unnecessary and inappropriate impediments” to broader study areas.

In response, the WMA formed a working group to review the placebo controls provision and other controversial issues. The panel aims to develop revised

language to discuss at the WMA General Assembly in October in New Delhi. Meanwhile, the White House Human Research Subcommittee (HRS) continues to examine how the Helsinki declaration affects U.S. policies and to develop a government-wide response. An immediate task is to formulate some kind of guidance on how IRBs and researchers should deal with these issues while the broader policies remain under review.

### **Ethics panel weighs in**

The National Bioethics Advisory Commission (NBAC) report on international research policies provides another voice in the research ethics debate, emphasizing the importance of maintaining high standards when conducting clinical research in developing nations. Although the commission recommends use of active controls, it leaves room for placebos—provided sponsors justify “alternative designs” to an ethics review panel. Other recommendations address:

**Basic ethical protections.** These include IRB review, risk minimization, compensation to participants for direct injuries, and individual informed consent. These protections should apply to all studies providing data for FDA submissions.

**Host country review.** Ethics reviews should be conducted by review committees in the host country as well as by a U.S. IRB. U.S. review could be waived, however, if a U.S. agency determines that the host IRB provides sufficient protections. The report urges development of policies for identifying when regulatory entities in other countries have sufficiently strong ethics oversight capabilities to make U.S. review unnecessary.

**Host country health needs.** Trials conducted in developing countries should address the health needs of the host country. Researchers and sponsors should consult with the community on study design and implementation.

**Culturally appropriate informed consent.** Researchers should develop “culturally appropriate” ways to disclose information necessary for informed consent. Investigators should be “sensitive” to community customs and requirements, and strive to avoid any coercion or

“undue inducements” for individuals to participate in a study. The same consent process should apply to women as to men, unless local custom calls for supplemental permission from a man, and failure to conduct the research could deny potential benefits to women in the host country.

**Posttrial access to therapy.** Research protocols should address how participants will have access to any proven therapies after the trial is completed. Sponsors should make “reasonable, good-faith efforts” to maintain participant access to proven interventions. A concern is that this provision may prevent U.S. companies from testing, say, an expensive heart drug in a poor nation if patients could not afford the medicine after it is brought to market in the United States.

**Building local capacity.** U.S. government agencies, sponsors, and researchers should assist in building local capacity of ethics review committees and of entities involved in designing and conducting clinical trials in developing countries.

The NBAC report is the result of an 18-month investigation by the panel that generated some 160 “substantive” comments, including 50 from developing countries. The final version appears less restrictive than earlier drafts, an evolution that has prompted public interest groups to criticize it as full of loopholes and likely to lead to exploitation of poor patient populations.

### More to come

An opportunity to gain an overarching consensus on international research policies may lie in the CIOMS (Council for International Organizations of Medical Sciences) effort to update its ethics guidelines. A CIOMS panel has been working on this project for two years and is collecting comments on a revised draft through this month.<sup>2</sup> The CIOMS guidelines spell out more specifically than the Helsinki document how clinical trials should be conducted, with detailed discussion of IRB operations, assessment of risk, information to be provided to study

participants, and emergency exceptions to informed consent. It addresses research involving children, pregnant women, and embryos. In discussing the tricky placebo controls issue, it states that placebos should be excluded when proven therapy is available, but supports placebo use when a comparative study of two treatments “will yield no reliable scientific results.”

As discussion continues on international research ethics, U.S. policymakers will try to walk a fine line between promoting high standards and maintaining incentives for biomedical R&D. In an address to the WMA gathering in Geneva in May, HHS secretary Tommy Thompson praised the organization’s efforts to promote ethical principles in research and to listen to the concerns raised by U.S. institutions regarding “interpretation and application of certain provisions.” Thompson also noted that continuing innovation requires both incentives for investment and protections provided by international agreements on intellectual property, and that public-private partnerships will be critical to improving world health in the future.

Congressional Democrats have raised concerns about ethics in U.S. sponsored international research and have called for hearings on the issue. With Senator Edward Kennedy (Democrat, Massachusetts) taking the helm of the Senate Health, Education, Labor and Pensions (HELP) Committee, the topic is likely to gain more attention.

### References

1. National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, 2 vols. (NBAC, Bethesda, MD, April/May 2001; also available at <http://bioethics.gov/clinical/Vol1.pdf> and <http://bioethics.gov/clinical/Vol2.pdf>).
2. Council for International Organizations of Medical Sciences, *Draft Revision of CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, Geneva, Switzerland, May 2001; also available at [www.cioms.ch/draftguidelines\\_may\\_2001.htm](http://www.cioms.ch/draftguidelines_may_2001.htm)). □