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IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

In This Issue

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IRB review of smallpox vaccine study receives national public scrutiny

Protocol put to the public for review

Once a final decision is made regarding some proposed research involving very young children and an older smallpox vaccine, there could be long-term repercussions for IRBs nationwide. This especially is true now that the entire world can focus a magnifying glass on the IRB approval process with regard to one particular study.

The IRB protocol review process was given unusual public attention in November after the Oct. 31 *Federal Register* notice sought public review and comment on a protocol for administering a smallpox vaccine to children.

Three IRBs had reviewed the same protocol, and while two had approved it, a third IRB narrowly voted against its approval but had made a motion to refer the protocol to the secretary of the Department of Health and Human Services (DHHS) for further action. In response, DHHS has published the study's protocol, 10-page informed consent form, opinions of 10 experts, partial transcripts of notes from IRB meetings on the protocol, and other information about the vaccine and the study. The information is available on the Internet: http://ohrp.osophs.dhhs.gov/dpanel/dpindex.htm.

The proposed study poses some long-term ethical problems, according to some of the experts convened by DHHS to review the protocol and offer public opinions about whether the protocol should be approved.

"I am concerned about the precedent that would be set in allowing this study," wrote **Dale E. Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota in Minneapolis, who was one of the 10 national experts who reviewed the protocol.

"It should be unusual that a substantive risk be allowed to be borne without offsetting personal benefit by someone incapable of being his or her own consent authority," he wrote in a five-page letter to Greg Koski, MD, PhD, former director of the Office of Human Research Protections (OHRP) in Rockville, MD, and David Lepay, MD, PhD, senior advisor for

clinical sciences and director of the Office for Good Clinical Practice at the U.S. Food and Drug Administration (FDA) in Rockville, MD.

Preschool children are particularly vulnerable to potential ethical abuses during clinical research, notes **Mary Faith Marshall**, PhD, professor of medicine and bioethics in the School of Medicine at Kansas University Medical Center, and the chair of the DHHS National Human Research Protections Advisory Committee. She was one of the experts consulted by DHHS.

"The potential for abuse or exploitation increases when subjects cannot make their own assessments of the relative risks and benefits of the proposed research," Marshall wrote to Koski and Lepay. **(See article on smallpox trial consent form, p. 136.)**

"The risk of death based on earlier data is targeted at less than three per million children in this age range," wrote **Rosemary B. Quigley**, JD, MPH, who also is an expert consulted by DHHS. Quigley is a member of the National Institutes of Health (NIH) Director's Council of Public Representatives and is a law clerk to Judge Kermit Lipez, who sits on the United States Court of Appeals for the First Circuit.

"However, a significant proportion of the trial participants will suffer moderate to severe symptoms of headache, fever, fatigue, and rash, with some requiring medical treatment," Quigley adds. "The risk of these experiences is greater than a child would normally encounter."

The study proposes to evaluate the potency, dose, and safety of vaccinia virus vaccine (Dryvax) when administered to children, ages 2 to 5 years. It would be studied in an undiluted formulation and in a 1:5 dilution, with five skin punctures. Forty participants would be recruited between two sites: the University of California-Los Angeles (UCLA) Center for Vaccine Research and the Cincinnati Children's Hospital Medical Center. **(See facts about Dryvax, p. 135.)**

Two California IRBs reviewed the protocol and came to different conclusions. The Kaiser Permanente Southern California IRB decided in favor of the protocol, and the Harbor-UCLA Medical Center IRB voted 6-to-5 against it. The Cincinnati Children's Hospital Medical Center IRB voted to approve the protocol after extensive deliberation.

"It's a tough call because the risks are great," says **Irwin Light**, MD, IRB chair for the Cincinnati Children's Hospital Medical Center IRB.

"We put in stringent procedures for enrollment and recruitment of subjects," he says. "A third party will be involved in the recruitment process and will screen people to make certain they're not responding to some unrealistic hysteria and that they are willing to follow through with precautions."

The proposed smallpox vaccination study is loaded with ethical land mines. The risks are

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In a nutshell: Facts about the Dryvax study

The proposal for the study, titled "A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Responses of DryVax Vaccine Administered to Children 2 to 5 Years of Age," provides the following details:

- A total of 40 children would participate in Los Angeles and Cincinnati.
- Children would be administered a purified and lyophilized product prepared from lymph obtained from the skin of vaccinia-infected calves.
- Dryvax, produced by Wyeth Laboratories, is part of a limited, 15 million-dose stockpile that was prepared 20 years ago, discontinued in 1983, and now is in storage at the Centers for Disease Control and Prevention in Atlanta.
- Two studies have been conducted with the vaccine in adults, including undiluted Dryvax and 1:5, 1:10, and 1:100 vaccine dilutions.
- Some participants experienced systemic signs and symptoms including fever, headache, muscle aches, chills, nausea, fatigue, and rashes at remote sites. More than 2% of the 665 adult subjects with vesicle formation at varying periods after vaccination rated their headaches, muscle aches, and fatigue as severe.
- Serious adverse events were experienced by 12 subjects, including one case of severe headache with nausea lasting between days five and 14 post-vaccination, and a case of erythema around the vaccination site.
- A study of children receiving the smallpox vaccine in the early 1970s focused on primary percutaneous vaccination of 786 children between the ages of 1 and 9 years. Of 148 children who received Dryvax, eight developed satellite lesions, three developed erythema multiforme; and one developed a mild illness with generalized vesicular lesions. ■

severe, while the potential societal and participant benefits are nebulous since smallpox remains eradicated from the world and could not be a threat except in the event of a terrorist attack by an organization that somehow obtained the virus from one of its few remaining sources.

"How do you separate panic from reality?" asks Light, noting that even the history of the protocol dates back to a time of fear over biological warfare.

"Our IRB was told in December of 2001, at the height of the anthrax scare, that this protocol was coming our way and that we needed to review it immediately because a terrorist could attack by the next week," he explains. "We called for an IRB meeting for Dec. 28, and the day before the meeting, the FDA called us to say the protocol was withdrawn."

During those weeks of relentless media coverage of anthrax, the potential smallpox vaccination protocol was announced in Cincinnati media outlets, resulting in parents inundating the IRB with requests to participate in the trial, Light notes.

Since then, the panic and fervor have resided, and since the trial has not yet begun to recruit children, he says he couldn't predict what the interest would be.

A potential analogy could be the swine flu panic and vaccine of the late 1970s in which the government pushed forward public immunization for a flu that never materialized. The vaccine resulted in Guillain-Barre syndrome in some of the immunized, and the infectious diseases community and government lost a great deal of credibility when the potential threat was over, says **John M. Neff**, MD, director for the Center for Children with Special Needs at the Children's Hospital and Regional Medical Center in Seattle.

"I think that's what's bothering everybody," he says. "Is that a threat that's going to materialize or is it anxiety that is getting played out this way."

The threat of smallpox being reintroduced in the world and the United States is a hypothetical unknown, Neff says. "With the potential of war, there's more of an immediacy in these trials."

Another problem with any smallpox vaccine studies is that the nation's health has changed considerably since the 1960s and 1970s when the vaccine last was administered, says **Anthony Robbins**, MD, MPA, professor and chair of the department of family medicine and community health at Tufts University in Boston.

"There are a lot more immunocompromised people out there now than in the past because of the presence of HIV and the many anti-cancer drugs that suppress the immune system," he reports. "It's much more risky now."

Dryvax is a live virus vaccine that is administered by insertions of a needle, causing a blister. Unlike other vaccines, the smallpox vaccine remains present on the person's skin and can be spread to other individuals. Because of this problem, the study's investigators say that it will be necessary to have the children remain out of

school or daycare for 30 days after vaccination.

"So we're talking about risks to both the person who is vaccinated and the risks to others who might come into contact with that vaccinated individual," Robbins says.

"Efforts are being made now to see if a safer vaccine can be produced by changing the virus in a manner that would make it less dangerous to people exposed to it, but so that it still will give protection against smallpox virus," he adds.

Also, the Dryvax trials pose additional ethical considerations since they would include giving some children a diluted vaccine, which may or may not provide any particular child participant with immunity to smallpox. On the other hand, the adult studies have shown that the diluted vaccine provides good protection. Some experts consulted by DHHS have suggested that this information should suffice, and the diluted vaccine should not be studied in children.

Members of the Cincinnati Children's Hospital IRB, in discussing the protocol at a meeting on July 16 were concerned about the 30-day school/daycare prohibition on children participants. They wondered whether this meant that the children would need to be isolated from all contact with other children and/or adults and whether the children's parents could become exposed to the vaccine virus through contact with their children, resulting in their own lost wages.

If the children Dryvax trials are finally approved, there will be very stringent exclusion criteria with more than 15 exclusion details, including a history of atopy, eczema, or other exfoliative skin disorders, immunodeficiency disease, use of immunosuppressive medications, allergies to components of the vaccine, thimerosal, cidofovir, or probenecid, and household members or contacts who are pregnant younger than 12 months old or who have the same skin or immunodeficiency disorders that would result in the exclusion of the actual subject.

Anyone who is pregnant or planning to get pregnant should not be exposed to the vaccine or a vaccinated child because the vaccine is associated with fetal death or miscarriage, Neff says.

One of the challenges for investigators and IRBs is to make certain the potential subjects and their families are carefully screened for all of the exclusion criteria, both through family histories and medical check-ups, he says.

"I wouldn't vaccinate anyone without knowing their HIV status and T-cell count, and I'd do pregnancy tests and pregnancy counseling," Neff says. "I'd be very cautious on that."

With all of the potential hazards and such poorly understood benefits that could be derived from clinical trials in small children, some of the experts and others question why this research should be pursued.

"The truth is I don't know how you do vaccine trials on children ethically," says **Vera Hassner Sharav**, president of the Alliance for Human Research Protection in New York City.

"I understand the danger of smallpox, but I also know that at a declaration of war time you always wind up with a whole lot of things done that use the war as an opportunity to do what you otherwise can't," she remarks. "Some research needs to be slowed down." ■

Lengthy consent form still needs adjustments

Smallpox study consent has significant flaws

The 10-page human subjects consent form proposed for the Dryvax vaccination study of children, ages 2 to 5, has a number of flaws, according to the IRBs and experts who have reviewed the study proposal and consent form.

"The consent form should provide more complete information and avoid language that minimizes the potential risks from this vaccine," says **Neal A. Halsey**, MD, professor of international health and pediatrics at Johns Hopkins University in Baltimore and the director of the Institute for Vaccine Safety of the Bloomberg School of Public Health, also at Johns Hopkins. Halsey's comments about the study and consent form were obtained by the Department of Health and Human Services (DHHS) as part of a public review of the potential study.

The consent form includes a couple of pages of risks and discomforts that could result from the vaccine and one-third of a page describing benefits that may reasonably be expected.

"The risk of death from smallpox vaccination for children in this age group was estimated to be two for every 1 million first vaccinations," the consent form states.

Under benefits to the child, the consent form lists potential protection against the smallpox virus, in addition to:

• "Your child will continue to receive routine and sick child care from their regular pediatrician

or nurse practitioner."

• "There will be no costs to you or your child for participation in the study."

Rosemary B. Quigley, JD, MPH, one of the 10 experts asked by DHHS to review the protocol and consent form, says in her letter to DHHS that this statement should be removed because there could be costs, such as withdrawing the child from daycare and paying for baby-sitting or from the loss of work pay.

Under benefits to humanity, the consent form states:

• "Participation in this study may provide benefits to society in the search for a method for giving Dryvax vaccine safely and effectively so that the greatest number of individuals may receive protection against smallpox."

• "These benefits may not happen and unexpected side effects may also develop."

The consent form also states that if a child participant is injured because of the research, emergency medical care will be available. "The care will not necessarily be free of charge. Financial compensation for any injury from this research is not available," the consent form adds.

Halsey's letter to DHHS notes that the consent form makes no mention of the fact that one-third of adults who received Dryvax had sufficient discomfort and inability to use their arm so that they missed school or work. "On the consent form there is a notation of central nervous system 'infection' at the bottom of page six, but there is no mention that severe persistent neurologic sequelae are common in children who develop post-vaccinial encephalitis," he wrote. "There is no known effective therapy for post-vaccinial encephalitis."

Parents and guardians should be shown photographs of some of the more common skin rashes that occur in children, as part of the consent process, Halsey adds.

Further, he points out that the "Dear Parent" letter was inaccurate in stating that the routine Dryvax immunization was stopped in 1971 because the world was declared free of smallpox.

"Routine immunization against smallpox was stopped because of the serious adverse events associated with smallpox vaccine and the very low risk of exposure to smallpox," Halsey states. "The last case of naturally occurring smallpox occurred in 1977, and the world was not declared free of smallpox until 1980."

The IRB at Kaiser Permanente Southern California, which was one of three IRBs to review the protocol, suggested that the consent form contain an additional exclusion of children who have a propensity to bite.

The Cincinnati Children's Hospital Medical Center IRB, which like the Kaiser IRB has reviewed and approved the protocol, suggested that investigators use a more formal screening process to determine how rational parents are and to rule out significant psychological issues, according to the IRB's minutes from a review meeting held in July.

"You have to make sure you are dealing with someone who will make a rational choice and also make sure you are dealing with a family who can control the possible exposure of contacts," the minutes read. "If you are dealing with a family that deals in chaos, this may not be possible." ■

Shift in philosophy was outgoing director's goal

Initiatives were a collaborative effort, he says

When the Office for Human Research Protections (OHRP) was created in 2000, **Greg Koski**, MD, PhD, was appointed its first director. At the time, he outlined plans to strengthen and overhaul existing human research protections programs.

"The time has come for us to take a new approach," he said in the fall of 2000 to the U.S. House of Representatives, Committee on Veterans Affairs (VA), Subcommittee on Oversight and Investigations hearing on VA medical research. The new approach he referred to was an ideology shift, from one of mere compliance with governmental regulations to one where those involved are focused on responsible conduct.

"Compliance in itself doesn't protect anyone," he said in a May 2001 interview with University of Southern California Health Sciences campus publication. "Every individual has to understand what his or her responsibilities are. The protection of subjects in not just an administrative process, hoops we have to go through. It is the foundation of what we do," he concluded.

In an interview with *IRB Advisor*, Koski talks about the initiatives launched, the impact the philosophical shift has had, and the success realized during his time as OHRP director.

When he came to OHRP, he was well aware of the challenges that he would face. Criticism of the human subject protections efforts had been detailed over the years in a series of reports released from

the Office of the Inspector General dating back to 1982. He points out what he saw as a primary flaw in protection efforts: reliance on IRBs alone to identify research protocols that harmed subjects.

"It seemed to me that what we had was a system that was well conceived but not well executed," he says. "The system that was set up that relied on IRBs and informed consent became what many view as barriers to doing research."

Koski says he and others in the community at the regulatory level see protection as a shared responsibility with everyone — IRBs, researchers, even the subjects — playing a vital role. To that end, he launched a program for remodeling the existing system. "In a general way, the overall approach had to be a shift in philosophy from a system of compliance to a system focused on preventing harm," he says.

Quality improvement is a major push

One of the first projects undertaken was the overhaul of the assurance process. According to Koski, it has been simplified dramatically. Additionally, there are plans to make the process electronic, which will allow OHRP to collect data on IRBs that can be used in future evaluations and benchmarking studies.

Simplifying that process has allowed the office to redirect resources, Koski says. "We expanded town meetings, sponsored conferences and displays at professional meetings, and expanded education activities."

Additionally, OHRP has increased not-for-cause evaluations. "The government has a responsibility to the public to provide oversight," he says. But, he points out, his aim was not to police IRBs, rather it was to offer technical support to assist them.

OHRP also launched phase I of a quality improvement program. Phase I asks IRBs to complete a self-assessment designed to measure the board's level of compliance with federal regulations. "The most important part is self-assessment — looking at yourself." Koski points out.

The assessment is evaluated by OHRP staff, who then provide feedback in the form of a site visit, videoconference, or letter. The program is voluntary and feedback is designed to help IRBs make improvements. **(For more information on the quality improvement initiative, see *IRB Advisor*, May 2002, p. 54.)**

According to Koski, the program has been well received. "It has continued to grow," he reports. "It is collaborative rather than confrontational, which is why it has been so well received."

Koski is encouraged by the positive response. "The only option is to go back to no controls or back to policing, which will negatively affect research." His goal is to encourage the community to stay focused on preventing harm and research safety.

Most participants are requesting a site visit, he says. To date, OHRP has visited 21 sites and participated in one videoconference. The goal for 2003 is 10 site visits and an occasional 50 letter or videoconference consultations each month.

"We have a regulatory responsibility, then it gets us to a better place," says Koski, referring to phases II, in which best practices will be shared, and III, in which institution-based quality improvement programs will be advanced. "The pilot mode of QI actually provides methodologies for measuring the performance of institutional review boards and their ability to do substantive review of research protocol," he says.

An important element of all of the initiatives launched in the last two years is the ability to collect data. "Many of the new programs — IRB registration, quality improvement — provide an opportunity to collect very useful date on the system and how it works," Koski says. "You can't improve performance if you can't measure it. Auditing standards don't measure performance."

Koski points out that all of the initiatives have been collaborations among all the governmental agencies, from the Food and Drug Administration (FDA) to the VA. Additionally, he noted a concerted effort from the research community to take steps to improve human subjects protections programs without federal prompting. For example, the Association of American Medical Colleges developed conflict-of-interest guidelines, the Association of Clinical Research Professionals pioneered training programs for investigators, and the Association for the Accreditation of Human Research Protection Programs and the National Committee for Quality Assurance have established voluntary accreditation programs for IRBs.

"They are a sign of a willingness of the entire research community to take that charge — taking responsibility rather than have government do it for them. The reason we get regulations is either people won't do what they're supposed to or they want to do what they're not supposed to do."

In the works is a new handbook for investigators and IRB sponsors. A first draft of the electronic handbook should be available during the first quarter of 2003.

Koski is moving back to Boston and will

assume his previous position as an associate professor at Harvard Medical School. Additionally, he'll join the Harvard-based Institutes for Health Policy as a senior scientist. "The past two years have been among the most demanding and most rewarding," he says. "I've had an extraordinary opportunity to witness dramatic changes and play a part in them." ■

SPOTLIGHT ON COMPLIANCE

New legislation will change human research oversight

Two bills call for more stringent guidelines

By **J. Mark Waxman**, JD
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The continuing publicity surrounding both ever increasing public financial support for clinical research and claims of improper human research activities has led to calls for additional oversight of the clinical research enterprise. Two bills — H.R. 4697 and S.3060 — introduced this year illustrate important, but fundamentally different, approaches to the oversight environment.

• **H.R. 4697** — "The Human Research Subject Protections Act of 2002," introduced May 9, 2002, by Rep. Diana DeGette (I-CO), is designed to accomplish a variety of goals. First, the statute seeks to create a set of standardized guidelines that would be used by all federal entities involved in human subject research. A key thrust of this mandate, echoed in S.3060, is "harmonization" or standardization of rules governing issues such conflicts of interest, attestation requirements by clinical investigators, and provisions related to emergency interventions.

Second, there is a clarification of the definition of "human subject research" as clinical research that is conducted with the "direct involvement" of human subjects. Specifically excluded are the collection, analysis, or abstraction of data not gathered for research or investigation with human subjects, which includes business, health, marketing, or education records.

Third, there would be specific statutory definitions of key terms and processes. Among the most important are those with respect to informed consent and conflicts of interest. The law would mandate that the informed consent process include a consent form, which contains an acknowledgement that seven categories of information, as well as any additional categories that may be required by the Department of Health and Human Services Secretary, have been explained in writing. The categories are:

A. the purpose of the research;

B. the potential risks and benefits of being a subject in the research;

C. if relevant, the difference between research and therapeutic treatment;

D. the right to cease participation at any time;

E. the identity of the sponsors of the research;

F. any conflict of interest that the investigators have in the research;

G. as applicable to the research, the medical tests and procedures that may be necessary as part of the research, and the extent to which their costs will be paid by the sponsor or someone else.

The rules with respect to obtaining the necessary consent will be set forth in regulations, which will include information about contacting the Office for Human Research Protections (OHRP), an agency whose role will be spelled out by the statute, to submit questions.

Conflicts of interest are addressed directly in provisions discussing the role of the IRB. These provisions make it clear that the IRB, the investigator, and the institution served by the IRB will be required to address both actual conflicts of interest, as well as interests that create the appearance of a conflict of interest. The statute would specifically mandate that the institution review actual or apparent conflicts, and seek to reduce or eliminate them, as well as oversee them in appropriate cases.

Fourth, providing further impetus to a growing movement, the proposal envisions that IRBs and the related institutions may be voluntarily accredited by nongovernmental entities recognized by the secretary. This formal recognition of the desirability of accreditation of a clinical enterprise would appear to be a clear signal that more than governmental oversight is envisioned — even though the approach being taken in H.R. 4697 is voluntary as opposed to mandatory.

Fifth, recognizing that the changes desired to enhance the clinical research process will take time

and effort, the statute would mandate that those receiving grants provide for a program of education for investigators and board members. To support this mandate, grants will be made to create model education programs, including best practices.

Finally, to assist with the costs of the overall compliance effort, the costs associated with mandated activities would be treated as direct, as opposed to indirect, costs.

• **S.3060** — "The Research Revitalization Act of 2002," introduced Oct. 4, 2002, by Sen. Edward M. Kennedy (D-MA), seeks to be both more comprehensive and more regulatory in nature than H.R. 4697. While the goals are the same, the means are clearly more aggressively stated.

S.3060 articulates that its desired reach is to all research conducted within the United States. In this regard, the legislation would mandate all such research be conducted in accordance with "Ethical Principles" specifically included by the statute. Those principles, in general, are the standards for approval to be followed by IRBs under either bill.

In the case of S.3060, the voluntary accreditation approach is made mandatory. Within six years of its adoption, IRBs would be required to be accredited by OHRP or an approved accrediting entity. The basis for accreditation would include requirements that board members have appropriate: a) expertise, experience, and education; b) insulation from conflicts; and c) established adequate review processes.

The bill addresses research in countries outside the United States. OHRP, in consultation with the Secretary of State, will be required to publish a list of countries in which research oversight is similar to the United States. In those countries research may be conducted, provided an ethics review board in that country will review it. In cases where there is research involving greater than minimal risk in countries not on the published list, review of the effort must be by an ethics review committee of that country (if it exists) and an accredited IRB.

S.3060 specifically requires regulatory activity in a wide variety of areas. Some will be helpful in hopefully in providing clear rules to IRBs and institutions on what is allowable and what is not. For example, in the area of clinical trial subject compensation, there might be a regulation that says payment may be made to a subject up to "$X" per visit during a clinical trial, as opposed to a general regulation that says payments must be consistent with a goal to protect subjects against coercion or duress. Additionally, there also would likely be a regulation to address payments for recruiting subjects, specifically, the amounts and conditions under which payments may be made. Another mandated area is specific regulation of the appropriate use of placebos in research.

As is the case with H.R. 4697, there is a great deal of emphasis on avoiding conflicts of interest. This proposal addresses institutional as well as investigator conflicts, and particularly where there is receipt of "significant income" from an interested entity — defined as an expectation of more than $10,000 in a 12-month period.

While it is not possible to know the form of any final bill coming out the Congress at this point, the messages being conveyed are clear. First, it will become highly desirable, if not mandatory, for IRBs to put themselves in a position to be accredited. This means that creating an auditable trail of documentation necessary to show compliance with existing regulatory requirements is becoming more important.

Second, if research participants, including industry, desire to maintain a voluntary, as opposed to a much more mandatory or regulatory environment, they will need to become more actively involved in the legislative process.

Third, it simply should not matter to anyone whether federal law, in terms of the approval processes to be applied, governs research.

Finally, the Association of American Medical Colleges reports, as well as others, and these legislative proposals, provide a very clear message that conflict-of-interest oversight and disclosure are high-priority items. Institutions and their related IRBs would do well to make this an area of focus. ■

Poor countries may not benefit from research

Organization updates international guidelines

Recently updated guidelines for human subjects biomedical research highlight the international research community's concerns that studies conducted in poor nations may give too little attention to the health and well-being of participants who have few options and fewer medical resources.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects, developed by the Council for International Organizations of Medical Sciences (CIOMS) of Geneva, have been extensively revised and updated since the last

version was published in 1993.

The changes, published in October 2002, highlight how the research community has changed in the past decade, says **Juhana E. Idanpaan-Heikkila**, PhD, MD, secretary-general for CIOMS.

"Since 1993, we see more and more new challenges and these huge changes in international research," Idanpaan-Heikkila says. "More and more clinical research is taking place in resource-poor countries with very little tradition and experience in research."

This often means the nations lack well-organized oversight institutions for clinical trials, and they may not have ethics committees, he says.

"They may not be experienced in dealing with very complicated scientific issues, and the research sponsors are more and more anxious to go to these countries because they don't need to be on waiting lists for trials," Idanpaan-Heikkila says. "The case certainly is different in western nations today where most institutions are overloaded with research activities."

Plus, the world has seen an emergence of new and older deadly diseases, such as the HIV/AIDS epidemic in sub-Saharan Africa and tuberculosis following on its heels. These epidemics have created a need for new medications and treatments, all of which are being studied among populations in both the industrialized world and in resource poor nations, he says.

One of the ethical issues that arose has to do with how unbalanced the health options are for clinical trial participants in poor nations. If they are enrolled in a clinical study they may receive cutting edge medical treatment, but if they are not they may receive no treatment at all.

"In western countries people are already getting something, and so you have to change and manipulate existing treatments," Idanpaan-Heikkila says.

However, in poor nations, the study participants may have no treatment to which to return once the study concludes.

Also, there is the issue of whether this research holds any realistic potential benefit for the public in poor nations. For example, suppose a new antiretroviral drug is being studied to treat HIV. Even if this drug proves to have very potent activity against the virus and eventually is brought to the international market, how likely is it that the general public of a nation as poor as Zambia will be able to purchase and distribute the drug to its HIV-infected population when even aspirin often proves too expensive for general use?

"Does this research really benefit these countries, and what remains after the study when the scientist collects instruments and goes home?" Idanpaan-Heikkila asks.

So one of the ethical challenges of international research is deciding how to make a balanced evaluation of the research from both the sponsor's and the host nation's perspectives, he says.

"These countries are very happy to receive these studies and not the least because of the experience, training, and money they bring," he notes. "All of this has caused new problems."

These issues have led to CIOMS adding a new first guideline of the "Ethical justification and scientific validity of biomedical research involving human subjects" and to the organization extending the third guideline, which is "Ethical review of externally sponsored research." **(See CIOMS guidelines, p. 142.)**

"Our guidelines clearly are saying that it's not enough if the sponsoring country does its best in ethics evaluation because they don't know local circumstances," Idanpaan-Heikkila says. "They don't know if the study addresses the health needs of that country or not, so therefore it has to be a double evaluation with the sponsoring country doing this and the host country doing something, too."

Researchers and IRBs need to address some unique issues regarding research in poor nations, and these include deciding in advance whether and how long treatment will be provided research participants after the trial ends, if the treatment is apparently safe and apparently effective, Idanpaan-Heikkila says.

"I think it's not ethically right to start people on treatment for six months and then leave and let them die," he says. "You have to provide treatment, and the first option is to have it organized in advance that they may continue on this medication."

Also, placebo studies pose ethical dilemmas that need to be resolved in advance because this is an issue that never has received a full consensus of opinion and standard for care. The guidelines suggest that when there is no treatment for a certain disease, then the comparison of the investigational treatment and placebo may be appropriate, and the same may be true in the case of trials in which the subjects have a mild condition.

However, although placebo trials require fewer subjects to be enrolled in a study, this may or may not be a good reason for using a placebo study arm, Idanpaan-Heikkila says.

"If you use placebo you can cut down on the

number of people you need for a study by nine-tenths," he says. "So instead of 600, you may need 60 people; and so now the IRB may view any unnecessary exposure to risky treatment to be dangerous, so it will require the study to limit to a minimum the number of people required."

On the other hand, a particular disease may have an acceptable treatment that is available, and investigators will want to study a treatment they believe to be more efficacious. In this case, it may be unethical to compare the potentially better therapy with a placebo, when the comparison could be between the new therapy and the existing therapy, Idanpaan-Heikkila says.

CIOMS has tried to address all of these complicated issues, and the organization has added more requirements and recommendations for how informed consent should be obtained, he adds.

"We also have tried to extend guidelines regarding vulnerable groups in research, including pregnant women, children, immigrants, nomads, people in nursing homes, military service people, medical students, nurses, and members of hierarchical groups," Idanpaan-Heikkila says. ■

Here are CIOMS research guidelines in a nutshell

Many are new or revised

The Council for International Organizations of Medical Sciences (CIOMS) published in October 2002 its revised and updated International Ethical Guidelines for Biomedical Research Involving Human Subjects. Here is a brief look at the new and revised guidelines:

1. Ethical justification and scientific validity of biomedical research involving human subjects.

Sponsors and investigators need to ensure that all of the investigators and others involved in a study are qualified by education and experience to perform competently, and these qualifications need to be reviewed by a scientific and ethical review committees.

2. Ethical review committees.

Review committees must be independent and have no financial dependence on the research. Investigators need to obtain their approval, and the committee should review new studies and monitor studies that have already been approved.

Also, these review committees need to be local and invite the views of people representing patients with the diseases or impairments being studied.

3. Ethical review of externally sponsored research.

Reviews of research protocols should be as stringent in examining ethical and scientific standards for studies conducted in a host country as they are for the sponsoring country, and the health authorities of the host country should be involved in ensuring that the proposed research is responsive to the public's health needs.

4. Individual informed consent.

Prospective subjects or their legally authorized representatives will need to provide voluntary informed consent for all biomedical research involving humans. The consent process should include language and comprehension provisions and be subject to renewal during the course of a study.

A special consideration needs to be made to accommodate cultural concerns. In some communities, the investigator may need to obtain permission from a community leader or council before approaching prospective subjects and obtaining their individual consent.

5. Obtaining informed consent: Essential information for prospective research subjects.

6. Obtaining informed consent: Obligations of sponsors and investigators.

Investigators need to ensure the adequacy of informed consent, be capable of answering all of subjects' questions, and provide counseling when appropriate.

7. Inducement to participate.

While reimbursement for travel and expenses are permitted, medical care may be provided at no charge, and payments may be made to subjects, these payments should not be so large as to induce prospective subjects to consent against their better judgment.

8. Benefits and risks of study participation.

9. Special limitations on risk when research involves individuals who are not capable of giving informed consent.

The risks from research interventions that do not hold out the prospect of direct benefit for the individual who is not capable of giving informed consent should not be more likely or greater than the risk attached to routine medical or psychological examination of such persons.

10. Research in populations and communities with limited resources.

11. Choice of control in clinical trials.

12. Equitable distribution of burdens and benefits in the selection of groups of subjects in research.

13. Research involving vulnerable people.

Investigators need special justification for inviting vulnerable people to serve as research subjects.

14. Research involving children.

15. Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent.

16. Women as research participants.

Women of reproductive age should not be excluded from research, but a thorough discussion of the risks in the event of pregnancy should be discussed.

17. Pregnant women as research participants.

18. Safeguarding confidentiality.

Investigators should inform subjects of the limits in their ability to safeguard confidentiality and of the possible adverse social consequences of breaches of confidentiality.

19. Right of injured subjects to treatment and compensation.

Research subjects who suffer injury due to their participation in a study should receive free medical treatment and other assistance that would compensate them equitably for any resultant impairment, disability, or handicap, and their dependents are entitled to compensation in the event of the subject's death.

20. Strengthening capacity for ethical and scientific review and biomedical research.

21. Ethical obligation of external sponsors to provide health care services.

External sponsors are ethically obliged to ensure that the host country has health care services essential to the safe conduct of the research, treatment for subjects who suffer an injury resulting from the research, and a commitment that the sponsor will make a beneficial intervention or product, developed as a result of the research, reasonably available to the host country's population. ■

White House wants embryos protected

New committee to make recommendations

A new federal advisory panel that will provide ethical guidance for researchers engaged in studies involving human subjects has been charged by the Bush administration to consider human embryos to be human subjects, deserving of the same protections currently afforded fetuses, children, and adults.

The committee will not have the ability to enact legislation. It can only recommend changes to the Department of Health and Human Services (DHHS), which would then choose whether to go through the legislative or rule-making process to enact a change in policy.

However, depending on whom the administration selects to sit on the committee, it could be the start of a process that could result in greater restrictions on embryo research at some fertility clinics, universities, and research labs, experts told *The Washington Post* Oct. 30.

"I'm very concerned that this addition [of the word 'embryos'] will serve to seriously politicize the reconstituted committee," said **Robert R. Rich**, executive associate dean of research at Emory University School of Medicine in Atlanta and a member of the now-defunct National Human Research Protections Advisory Committee.

"Embryos are not included as human research subjects, according to [current federal regulations]. It will be impossible to gain consensus around this issue if appointees to the new committee represent both sides of this very contentious issue, since it is governed by emotions and beliefs and is really not amenable to rational or scientific discourse," he said.

The National Human Research Protections Advisory Committee was formed at the direction of President Clinton to recommend new protections for human volunteers in research trials following several scandals in which people

COMING IN FUTURE MONTHS

- IRBs, institutions receive guidance on conflicts of interest
- Study shows a too-cozy relationship between study sponsors and institutions
- Exempt vs. nonexempt protocols
- IRB accreditation

participating in research trials were harmed. Following the change in administration, President Bush allowed the committee's mandate to expire and announced the formation of a new committee, the Secretary's Advisory Committee on Human Research Protections, which now will advise DHHS on similar matters. At press time, no committee members had been appointed. ■

CE/CME objectives

The CE/CME objectives for *IRB Advisor* are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- understand the regulatory qualifications regarding human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research;
- apply the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- have an understanding of the potential for conflict of financial interests involving human subject research;
- understand reporting adverse events during research. ■

CME*questions*

CME subscribers: *Please use the enclosed Scantron to submit your answers for the July-December 2002 CME test and return the Scantron and CME survey in the enclosed envelope.*

21. Which of the following is an ethical reason why an IRB might not approve the proposed Dryvax (smallpox vaccine) study for children, ages 2 to 5?
A. The smallpox vaccine is known to have significant and serious risks.
B. Children, unable to provide their own informed consent to research, require greater protection by IRBs and others overseeing studies.
C. There is only a very small chance that the children who participate in the study will derive any direct benefit because the risk of a bioterrorism attack involving smallpox is indeterminable.
D. All of the above

22. The Council for International Organizations of Medical Sciences published in October, 2002, its revised and updated International Ethical Guidelines for Biomedical Research Involving Human Subjects. Which of the following is one of the chief changes that the council recommends?
A. That all research conducted in poor nations requires informed consent
B. That all research conducted by wealthy pharmaceutical companies provides lifetime medical care to host-nation participants of experimental drug trials
C. That countries sponsoring biomedical research in poor nations assist and ensure that the host nations provide well-organized local oversight of the clinical trials
D. All of the above

23. S.3060, "The Research Revitalization Act of 2002," proposes which of the following:
A. Accreditation of IRBs would be mandatory.
B. Accreditation of IRBs would be voluntary.
C. Accreditation would be mandatory for institutions receiving federal funds.
D. There is no provision related to accreditation in the bill.

24. H.R. 4697, "The Human Research Subjects Protections Act of 2002," would require written definitions of:
A. Any conflicts of interest that investigators have in the research
B. The identity of the sponsors
C. The potential risks and benefits of being a subject in the research
D. All of the above

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