IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

DECEMBER 2003
VOL. 3, NO. 12 • (pages 133-144)

New HHS research committee plans to clarify and define some regulations

Initial focus on accreditation, children

IRBs and the research community soon may have new guidance in defining and clarifying some of the gray areas in regulations of human subject protection.

The Department of Health and Human Services (HHS) created the Secretary's Advisory Committee on Human Research Protections (SACHRP) to replace the National Human Research Protections Advisory Committee.

"We have been charged by Secretary Tommy Thompson in a charter to advise him on protection of human subjects with particular emphasis on special populations," says **Ernest Prentice**, PhD, SACHRP chair, and the associate vice chancellor for academic affairs at the University of Nebraska Medical Center of Omaha.

SACHRP has ex-officio members from various federal agencies, including the National Institutes of Health (NIH), the Department of Justice, the Food and Drug Administration (FDA), the Department of Education, and others, he notes.

"So we're getting input from all official branches," Prentice says. "That means NIH can advise the committee about their concerns, and we can address them."

HHS has asked the committee to provide guidance on research that involves the following populations and issues:

- special populations, such as neonates and children, prisoners, and the decisionally impaired;
- pregnant women, embryos, and fetuses;
- individuals and populations in international studies;
- populations in which there are individually identifiable samples, data, or information;
- investigator conflicts of interest.

The committee's responsibilities also include the review of ongoing work and activities of the Office of Human Research Protections (OHRP), including a review of assurance systems, minimal research risk standards,

the granting of waivers, OHRP's educational programs, and the monitoring of IRBs and institutions that sponsor research.

"That's a fairly broad charter, and obviously we can't tackle all of those issues simultaneously," Prentice says. "So we have chosen to identify some initial challenges and tasks that we're going to work on as a committee."

SACHRP has formed three subcommittees to further examine the areas of IRB and research institution accreditation, research protections for children under the regulation Subpart D, and research involving prisoners.

"We've also appointed individual members of the committee to spearhead discussion on some issues, including adverse event reporting, litigation, and international research," Prentice says.

When the subcommittees complete their reports and the full committee has discussed and accepted these reports, the committee will give its final report to HHS, and it may form several different subcommittees, he notes.

"I'm optimistic the work of the committee will result in significant products, will assist in ensuring appropriate protection of human subjects, and, at the same time, will facilitate important research," Prentice says.

For him and other leaders in the research community, a big concern is the public's loss of trust in human subjects research.

"It's very important that we maintain the public's trust in clinical research so they know their rights come first, and that they know there is a staffed IRB that will work with investigators to ensure appropriate protection, and that they know the institution is committed to this endeavor," Prentice says.

Accreditation a hot issue

Here is a thumbnail look at the issues being addressed by SACHRP's subcommittees:

- **IRB accreditation:** "As a committee, we want to look at ways to motivate institutions and look at the impact of accreditation and whether or not the federal government ought to be involved in certifying accreditations," Prentice notes.

"We think as a committee that [human subjects research] accreditation is something that's long overdue," he says. "They've had animal research accreditation since the 1960s, so it's incredible that we've chosen to accredit animal research and only now look at human research accreditation."

The accreditation subcommittee is looking at the pluses and minuses of accreditation and the issue of whether the federal government should be in the business of encouraging accreditation, says **Thomas L. Adams**, CAE, a member of SACHRP and the accreditation subcommittee. Adams also is the chief executive officer of the

IRB Advisor (ISSN 1535-2064) is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to **IRB Advisor**, P.O. Box 740059, Atlanta, GA 30374.

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Subscription rates: U.S.A., one year (12 issues), $399. With CME: $399 Outside U.S., add $30 per year, total prepaid in U.S. funds. Two to nine additional copies, $314 per year; 10 to 20 additional copies, $279 per year. For more than 20, call customer service for special handling. **Back issues**, when available, are $55 each. (GST registration number R128870672.)

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Alexandria, VA-based Association of Clinical Research Professionals (ACRP), an 18,000-member association that provides training and education for people involved in clinical research.

Specifically, the subcommittee will assess existing impediments to accreditation and identify ways to reduce impediments and, perhaps, enhance inducements, he says.

"As a general rule, I personally believe accreditation is a good thing," Adams adds.

"The types of things we're looking at are not necessarily covered under the current rules and regulations, but may further be fleshed out by either a legislative or regulatory initiative in the future," he says.

The two nongovernment organizations that currently provide accreditation services for IRBs will have an opportunity to meet with the subcommittee to explain how the programs are working, Adams says.

"Accreditation is an important way to ensure patient protections," he notes, adding that another part of the trend toward ensuring quality in human subjects research is certification.

ACRP provides certification for research professionals and has just begun a program for principal investigators, Adams says.

More information about the certification program can be found on the organization's web site at www.acrpnet.org.

Focus on risks

• **Research involving children:** SACHRP and a subcommittee focusing on the Subpart D regulations will advise HHS on appropriate interpretation of the regulations that apply to additional protection of children, Prentice reports.

This is an area that has caused some confusion among IRBs for 20 years, and the issue is further problematic when the FDA's parallel regulations are considered, he adds.

The subcommittee will work on defining some of the terminology that has troubled IRBs and investigators over the years, says **Celia B. Fisher**, PhD, a SACHRP co-chair of the pediatric research subcommittee. Fisher also is the Marie Ward Doty university chair and the director of the Center for Ethics Education at Fordham University in Bronx, NY.

For one thing, the subcommittee will attempt to provide guidance for what constitutes minimal risk in research that involves children, she notes.

"In the federal guidelines, minimal risk is defined in terms of the everyday experiences of the child," Fisher says. "And one of the issues that has been confounding IRBs and investigators is whether everyday experiences should be defined relative to the healthy child or the vulnerable child."

Minimal risk needs to be thoroughly examined from all angles, including psychological and social-behavioral, she says.

An example would be a social-behavioral research that asks children in a school setting about depression, suicide, trauma, sexual activity, or drug use, Fisher adds.

"This is where IRBs are having tremendous difficulty figuring out whether this is minimal risk, or whether this is in some sense risky just to read the question and ask for answers," she says.

For biological research, a blood draw might be viewed as minimal risk, but if the child is a hemophiliac, it no longer can be considered a minimal risk, Fisher adds.

"At the same time the federal guidelines and recommendations can't absolutely define this issue because every child's population is different," she says. "So what needs to be done is to provide guidelines for how to assess whether a research design presents minimal or greater than minimal risk."

Another clarification involves when the regulations permit pediatric research that is a minor increase over minimal risk with no direct benefits, Fisher says.

"You are allowed to do this research if it has direct relevance to the child's condition," she notes. "But defining the child's condition can be very confusing."

For example, is being a child a condition in itself or does "condition" only refer to illness? Also, is a child's poverty a condition? Is minority status a condition? Or if the child has been abused is that a condition? Fisher asks.

"It's very difficult to narrow the definition because there may be instances where simply being a child is important to doing the research," she says.

The subcommittee also will address the controversies involving 407 reviews of which the most notable review this past year involved the proposed pediatric smallpox clinical trials, Fisher says. **(See story on 407 reviews, p. 136.)**

Clinical trials of vaccines to prevent illness are examples of studies where it's necessary to have children as subjects, she explains.

"But there are other times where you do not want to simply use children because you want to

test [a drug or device] that will be largely used by adults," Fisher adds.

• **Research involving prisoners:** SACHRP and the prisoner research subcommittee will address the Subpart C regulations to determine whether additional protections are appropriate for protecting prisoners involved in research, Prentice says.

The regulations were issued more than 20 years ago, and a great deal has changed since then, he notes.

"We know that the regulations are very restrictive, and we know that prisoners are often deprived of an opportunity to participate in clinical research because the regulations are so restrictive," Prentice explains. "While we understand that individuals in prison are in a potentially coercive environment, nonetheless, this becomes a matter of justice, and we want to make sure the research is appropriate for the times." ■

Committee looking at 407 review process

Case in point: Pediatric smallpox vaccine

IRBs and research institutions may have some disagreement and confusion over when it's appropriate to send a pediatric research proposal to the Department of Health and Human Services (HHS) for a 407 review.

While it was extremely rare for IRBs to request 407 reviews in the past, since 2000, these request have become more common, which is one of the reasons the issue is being addressed by the Secretary's Advisory Committee on Human Research Protection (SACHRP), says **Ernest Prentice**, PhD, chair of SACHRP and the associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha.

In the HHS regulations the Subpart D defines four categories of research involving children, and these fall under 404, 405, 406, and 407. They are based on the level of risk associated with the research and whether there is any direct subject benefit, he explains.

As the risk increases in the absence of direct subject benefit to the child participating in the research, the regulations become more stringent for the approval of the research, Prentice says.

"If the IRB cannot approve an HHS-funded research under 404-406 regulations, then it must be reviewed by an expert panel at HHS," he notes. "This expert panel must review the entire protocol and make a recommendation to the [HHS] secretary of whether or not the protocol should be funded by the federal government."

SACHRP's pediatric research subcommittee is examining the 407 review process and plans to make recommendations that will help to improve it, says **Celia B. Fisher**, PhD, a SACHRP co-chair of the pediatric research subcommittee. Fisher also is the Marie Ward Doty university chair and the director of the Center for Ethics Education at Fordham University in Bronx, NY.

"One of the issues right now is that IRBs appear to be unclear about the kind of information and the kind of requirement that they need to go through before they even send a protocol to the Office of Human Research Protections [OHRP] as a 407 review case," she says.

"This is very important because what some of them don't seem to understand is they need to justify why it's a 407 review case, and they have to do that through making the argument on paper of why it's not a 404, not a 405, and not a 406," Fisher explains. "And they need to say why they think it's ethical to do the study and why they would approve it under 407 if they had the authority."

Instead, what has been happening lately is that IRBs have sent protocols to OHRP for a 407 review if they don't know what else to do with it, she notes.

"And that's not really what the requirements are, so one of the things SACHRP wants to do is clarify what the responsibility of the IRB is," Fisher says.

The point is to neither encourage nor discourage 407 reviews, but to use them appropriately, she says.

"If you discourage them, then IRBs may be either disapproving important research or approving research at the 405 or 406 level that should be reviewed as a 407," Fisher explains.

"So if you make the procedure too hard or arduous or unclear, then you're going to be discouraging IRBs from even attempting to go there," she adds. "And on the other hand, if it's unclear what a 407 review requires, then the 407 review could become a wastepaper basket for the things an IRB doesn't want to handle."

A case study

Perhaps one good example of an appropriate 407 review is the one that was held to assess the

proposed pediatric smallpox vaccination trials, Fisher says.

The proposed clinical trials involved the Dryvax product and were intended to evaluate the potency, dose, and safety of vaccinia virus vaccine when administered to 40 children, ages 2 to 5 years, at the sites of the University of California-Los Angeles (UCLA) Center for Vaccine Research and the Cincinnati Children's Hospital Medical Center. **(See December 2002 issue of *IRB Advisor* for in-depth look at Dryvax pediatric research proposal.)**

The trials were being considered after the Sept. 11 terrorist attacks in New York City at a time when the nation had heightened concern about bioterrorist attacks as it prepared to go to war with Iraq.

It was very difficult to assess the level of risk that smallpox posed to the general population and to the potential children research subjects, Fisher says.

"If smallpox had a high possibility of being introduced into this country, then one would argue that being tested with the vaccine had the potential for some minimal benefit," she says. "If not, then the risks with the vaccine would outweigh the benefits."

On the other hand, the Dryvax vaccine's risks were well known, as it had routinely been given to children and adults decades earlier. While it was considered an acceptable risk during the years when smallpox remained a threat on the global stage, by 21st century standards, some 20-plus years after the smallpox virus had been eradicated, the vaccine was considered a high risk because of its potential adverse effects on individuals with autoimmune diseases, emphysema, pregnancy, and other conditions.

While two IRBs found that the proposed pediatric vaccine trial posed an acceptable risk with potential direct benefits, a third IRB reviewing the same protocol disagreed and asked for a 407 review, Prentice says.

A panel of national experts was asked to submit their opinions about the proposed trial as part of the 407 review, and these papers were made public via the Internet, he says.

The resulting public scrutiny resulted in the Dryvax pediatric trials being canceled, Prentice adds.

But the point is that the IRB that called for the 407 review was appropriate in making this decision, Fisher says.

"I think it's good that there are controversies at the 407 level, which is what the smallpox vaccine proposal was," she says. "In other words, there is permissible research that has small risks to children, and it's so important to the nation that the secretary of Health and Human Services has the ability to approve it after looking at recommendations from various experts."

From an ethical standpoint, there are certain issues that will always create a dilemma, and these are the sorts of research decisions that perhaps should be requested for a 407 review, Fisher adds.

"I don't think the purpose of the 407 review is to limit ethical discourse at the IRB level, but the aim is to have greater consistency in what the ethical issues are and what the terms mean," she says. "You do want to make that debate fair and consistent in research across the country, but right now it's not because the guidelines are not clear, and so they're open to subjective interpretation, and each IRB tries to do its best." ■

Advocates say, 'Give back to community that gives'

Study population should benefit

For more than two centuries, the small communities that make up the Canadian province of Newfoundland and Labrador, on the country's most northeastern coast, were largely isolated from the rest of the world. Over the years, few families moved in or out. More than 90% of the inhabitants of the province, which borders the Gulf of St. Lawrence, can trace their ancestry directly back to England or Ireland.

It is this unique setting that now is drawing genetic researchers from around the globe.

"We have pockets of homogeneity around the province," explains **Daryl Pullman**, PhD, associate professor of medical genetics on the faculty of medicine at Memorial University of Newfoundland. "There are certain communities that have a high incidence of certain kinds of genetic disorders, so they have become very attractive from a genetic research point of view."

Unfortunately for residents, outside researchers rarely have been interested in the welfare of the people they ask to contribute DNA, or the potential impact that participation may have on them. Often, they arrive, collect samples and information, and then depart, with no agreement for following up or giving information back to the community.

In one particularly troublesome case, Pullman relates, researchers went to several different communities, rented hotel rooms, persuaded residents to come to the rooms, undergo electrocardiograms, provide blood samples and, in some cases, copies of medical records.

Repeated occurrences left provincial officials concerned that residents were being exploited — their genetic information used to further medical science or enrich pharmaceutical research — then abandoned.

They began exploring establishing a provincial research ethics board (REB), similar to an institutional review board, which would have oversight over genetic research conducted in the province or involving province residents. That mechanism, they felt, would better enable authorities to ensure subjects were given adequate informed consent and protection from harm, Pullman says.

However, ethicists also are interested in something more — whether the residents who are agreeing to allow their DNA to be studied should be able to share in the benefits of the research.

Putting a price on DNA

Discussions of benefit sharing — the view that commercial sponsors should return a portion of the profits or other in-kind benefits that accrue from this research to those who made the research possible in the first place or to humankind in general — have become more common in the spheres of human genetic research, Pullman explains.

"Historically, industry sponsors, like the pharmaceutical industry, for example, have not paid a direct benefit to subjects of clinical trials and so forth, the idea being that the market will take care of everything. If they develop a drug that is going to be beneficial to society, then everyone will benefit," he notes. "And that is the response you often get from industry representatives when you talk to them about benefit sharing. 'What's different about genetics?' Our answer is, it is one thing to take out a patent on a drug. It is another to take out a patent on a gene, or a particular string of DNA."

Human DNA, in a sense, belongs to no one and to everyone at the same time, he says. "Even if a company has a patent on genes that may come from me, but they also are in a certain sense your genes, as well, because they are part of the human genome."

Benefit sharing largely has been discussed in relation to large-scale, population-based genetic studies, but little consideration has been given to smaller genetic studies, particularly the add-on studies so common in modern pharmaceutical research, says Pullman.

He and a colleague, **Andrew Latus**, PhD, also at Memorial University, recently published a paper on possible benefit-sharing arrangements in these smaller contexts.

They propose that commercial sponsors who wish to come into a community and study the genes of its population work out a separate benefit-sharing arrangement before being allowed to submit a proposal.

"Of course, our model is built around the idea of health care as a public and not a private good," he notes. "The rationale here is that the people of our entire province bear the burden of disease and illness. We all pay taxes to support the health care system. Any benefits that come from commercial research should go back to the community, not to individuals per se."

Pullman and Latus do not propose that a person or family with a particular genetic disorder receive direct compensation from the commercial sponsors, for example. Because the entire community bears the burden of the family's health care, the community should benefit.

But they do say that perhaps sponsors could agree to help fund a project at a local university or center to study diseases in the population and help find treatments.

The sponsor would then have the right to present study proposals to the provincial REB, or a university REB, for consideration.

Under their model, consideration of the benefit-sharing agreement should be separate from the REB consideration and monitoring of specific studies, he says.

Avoiding conflicts

"It just comes down to, frankly, the potential for conflicts of interest," he says. "If there is a situation where you know there is a research ethics board for an institution is looking at a protocol and, at the same time, knows that this particular pharmaceutical company is willing to provide the institution with a new gene sequencer, then we might be more inclined to say, 'Yeah, let's go ahead with that one.'"

In addition to community-based benefit-sharing arrangements, Pullman points out that some smaller, subject-based agreements may be appropriate in some circumstances.

For example, in the province, a particular family

has a genetic disorder that leaves them chronically insensitive to pain.

"There is a real interest, of course, in finding out what the genetic problem is that makes them insensitive to pain," he notes. "But the interest isn't in determining whether they can help people with this condition, so that they can become sensitive to pain. The interest is in finding the genetic link — which may have all kinds of implications for developing analgesics, etc. But none of the benefits of the specific research would ever go to this family. But they are interesting research subjects because of this."

In that case, it might be appropriate for a study sponsor to work out some sort of benefit-sharing arrangement with this particular family.

Of course, care must be taken to ensure that the benefit did not serve as an inducement to participate or continue participation in a research protocol, he adds.

"We are wide open on the application of this, but the general principle is not that it will be individual people negotiating on their own, but community negotiators to take care of the community in a way that is most appropriate," he says. "Whatever benefit comes back into the system gets dispersed to the community — either to some people who are carrying a tremendous burden and will get very little benefit from the results of the research — or to the community as a whole."

Reference

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Institutional, QI projects may require IRB review

Institutions should have policies in place

As awareness of IRBs and human subjects research protection increases among the public and staff at institutions, IRB members sometimes are asked to consider new gray areas regarding studies that typically haven't made it to the IRB's radar screen.

For instance, do certain types of surveys conducted at colleges or hospitals qualify as research, or are they exempt from consideration by an IRB?

The short answer is that if a study contributes to generalizable knowledge, then it's subject to an IRB review and federal regulations, says **Dale Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota Medical School in Minneapolis. Hammerschmidt is a member of an IRB and has chaired IRBs for 10 years.

But this simplistic approach creates some problems, including the question of who makes the decision that it doesn't meet the regulatory definition of contributing to generalizable knowledge, he notes.

"Most institutions don't have a very clear policy on this," Hammerschmidt says. "Federal assurances require an institution to have a system for designating when research is exempt."

However, these regulations apply to studies that already meet the definition of qualified research and also meet one of the categories of research that is so low-risk that it doesn't need an IRB review, he explains.

"And most commonly the mechanism is to have a screening for exempt status done through the IRB office," Hammerschmidt says. "But if the study doesn't even meet the threshold for research, then institutions usually don't have specific policies, and people get confused."

In the process of updating information about its IRB and research guidelines, members of the Institutional Review Board: Human Subjects and Research at Colby College in Waterville, ME, came across the issue of institutional research, says **Bob McArthur**, chair of the IRB.

Traditionally, research at Colby College has been behavioral research, and the projects come from the psychology, education, sociology, and political science departments, he says.

"Our institutional research office, which is relatively new, does research of the standard kind on our student population," McArthur says. "So the question that has developed within our IRB is whether or not such projects should be themselves come before the IRB for review, and what sort of authority the IRB would have over such projects."

Charting new territory

IRBs may not have grappled with these questions before because certain types of studies and data collection were never sent to IRBs for consideration or review, notes **Lawrence H. Muhlbaier**, PhD, assistant research professor at the department of biostatistics and bioinformatics in the Duke University School of Medicine in Durham, NC.

For example, there are lots of activities in medical centers that use the scientific method, but are

not considered research, such as quality assurance activities that include collecting data from charts about infections, he says.

"Our hospital and many hospitals are expected to survey their patients about satisfaction with their care, and that's also not considered research," Muhlbaier adds. "The report goes through the hospital to help us do a better job, but it never is published, and I think very few IRBs or institutions would consider it research."

Most quality improvement activities are not submitted to an IRB unless the staff person involved in the project is considering publishing the information, he notes.

"I think that's typical of many academic medical centers," Muhlbaier says. "And just as a note, a lot of QI activities are done by staff rather than faculty who would typically be considered researchers because it is a hospital activity rather than a school of medicine activity."

However, it may be an issue with IRBs when institutions conduct studies and quality improvement services that don't meet the federal definition of research, but carry the same sort of risks for research, Hammerschmidt says.

"Institutions have different ways of handling this," he adds. "It seems that someone should be looking out for loose cannons."

When is QI really research?

Some quality improvement activities can create risk that is comparable to research, says Hammerschmidt. "If you look at hospice patients sent home to die, they're every bit as inconvenienced by telephone calls at home where someone calls to see how happy they were with their hospital stay as they would be if someone called them for an outcome study," he explains. "One would be under the IRB, and one would not."

Likewise, studies conducted by colleges and institutions for the purposes of understanding client problems and issues can pose risks that are comparable to research studies.

For example, suppose the institutional research office or a dean of students' office at a college is engaged in a project to understand alcohol use among students, including underage students, McArthur says. "The activity being researched is an illegal activity at some level, so there are major privacy and confidentiality concerns that the institution has and that individuals who are subjects have."

The exact same study could be proposed by the college's psychology department, and there would be no question that it would be subject to an IRB review, so should it be reviewed by an IRB when it's conducted by the institution for institutional purposes only, he poses.

"If the nature of the study is essentially the same, with the same instruments, the same population, then should there be an exemption just because the source is different," McArthur says. "The faculty is doing the research in one case while the institutional research office is doing research in the other, and we'd just say that because the source is different, it's not clear to us that the ethical concerns are any different."

In fact, some aspects of the research would appear to pose a greater risk to subjects if the institution rather than a psychology department does it. For instance, the institution that is conducting the research is a college that may have a responsibility to report crimes when these are detected, and students have privacy concerns, particularly with regard to their college, he says.

"This kind of study in the climate of understanding undergraduate alcohol use is going on all across the country," McArthur says. "And it's the sort that could easily transgress the concerns we have about privacy and confidentiality."

If an IRB were to review this study, IRB members would want to know who has access to the identify of the subjects and what would be the standard protections afforded the subjects, he adds.

"We would be very concerned that the identities of subjects of research would not be available, and we would be worried even if the director of research knew the identities," McArthur says. "But we also would be worried about anyone else having access to the identities."

Hammerschmidt suggests that a solution to these sorts of problems would be to have an institutional policy that states that any quality assurance or institutional research is reviewed by some board.

"It would be better for it not to be the IRB in some cases because IRBs are already overburdened, and in a lot of circumstances, the federal regulations would not have to apply," he says. "On the other hand, the board would need a member who knows what an IRB review is so that studies that really are research could be punted to the IRB."

The real problem is that an institution's staff may not be aware of the IRB's role in protecting human subjects of research, and so these gray areas may

never come under discussion when studies are conducted that entail some risk but do not meet the federal definition of what is considered research.

An IRB is passive in the sense that it receives proposals for review and does not solicit them, so often there is no general education of staff about what constitutes research and human subjects protection, McArthur says.

"If the nature of a study raises ethical questions regarding human subjects, then our IRB's question is whether or not the content is a trigger for an IRB review," he says.

"Our IRB is looking at this issue," McArthur adds. "And we're collecting information and are having a discussion about it with the college administration, and we hope to make a recommendation to the administration by the end of the year." ■

Secondary subjects still need IRB consideration

Are you asking PIs the right questions?

It has been five years since a complaint from the father of a study subject was lodged about a longitudinal study at Virginia Commonwealth University (VCU) in Richmond — a complaint that precipitated a shutdown of all research involving human subjects. But five years has not been long enough to answer all the questions about secondary subjects the case raised.

It was the summer of 1998 when the father of a girl in a long-running twin study opened a thick envelope from the university and found a questionnaire that included queries about the girl's parents and twin. The father complained, saying the rest of the family was essentially participating in research without having consented to it, and the complaint was upheld. After the Office of Human Research Protections investigated the complaint and found the university's response lacking, the Food and Drug Administration suspended all human research. More than a thousand studies were impacted, and it wasn't until the spring of 2001 that the last of the restrictions on human research at VCU were removed.

"This was a real wake-up call to for IRBs," says **Dale Hammerschmidt**, MD, associate professor in the department of medicine and director of education in human subjects' protection at the University of Minnesota in Minneapolis. "A lot of people disagree that the man was a research subject because the information the questionnaire asked for was hearsay."

Regulators felt differently, though, and Hammerschmidt still wonders how much of a damper that could put on "any study based on medical records where family medical history enables you to identify close relatives. I think a lot of people are still running scared on this topic."

The problem grows perhaps more convoluted in an era where a lot of research involves genetic information, he adds. "You are studying Timmy because he has some bizarre disease, but you have DNA from all the first-order relatives. Now you know that Ralph and Fred and Joan are all carriers. With this decision, they all become study subjects, and you have to get informed consent from them."

The pragmatic response is that IRBs must ask every single time whether the issue of secondary subjects — and potential secondary subjects — is being addressed, and being addressed adequately, Hammerschmidt says.

Get consent if required; otherwise, work on a waiver, and do so explicitly. "If the research contains no greater than minimal risk, state it," he says. "If consent for all potential secondary subjects is impracticable, state it. If the rights and welfare of the potential secondary subject won't be compromised if you don't get consent, state it."

In the past, the University of Minnesota never used to do a formal finding of a waiver. It was implied. "Since the VCU case, we always do," says Hammerschmidt.

"If you look hard enough, you're going to find a secondary subject," says **Cynthia Dunn**, MD, formerly with Western Institutional Review Board (WIRB) and now owner and president of a consultancy, Clinical Monitoring and Development Advisor (CMD), in Pittsford, NY. "If you take a medical history, you are disclosing information that is identifiable, private health information. The issue then becomes context. If it is for patient care, people look the other way, but in research, it becomes more of an issue."

Dunn says it's a "judgment call for an IRB because there are no hard and fast rules. The same IRB will come up with different determinations on the same issue on two different days. It depends on how they figure out what the risk is to the secondary subject. Can it cause psychological distress? Affect insurability? Do damage to social standing?"

If the information is potentially damaging, be cautious, she says. Red flags include genetic studies, and those looking at genetic markers. "That's an

area where you would be well advised to look into the potential consequences of the information being disclosed if it gets into the wrong hands," she notes.

One problem, says Dunn, is that there is so much emphasis on benefits of research, and not enough on the risk. "That part of the equation has to come more to the fore. We have to think about this more, watch for the red flags; and if you have an issue with risk, get informed consent."

Maybe this is more about common courtesy than anything else, says **Marianne M. Elliott**, MS, CIP, the director of the office of research administration at the Naval Medical Research Center in Silver Spring, MD.

"Before you do something to or about someone, maybe you want to ask, 'May I please,'" says Elliott, who used to work with the Office of Human Research Protections. "Even if it's something awful, if you ask them, they may say yes. I think the father in the VCU case was more incensed that he wasn't personally asked his permission than anything else."

Still, Elliott says she understands that you can't ask everyone everything all the time. "The IRB's responsibility is to ask whether a reasonable person would want to be asked if information could be collected about them," she says. "Most people want to help and won't say no most of the time, provided you keep the information confidential. Then you have to look at the potential harm if there was inadvertent disclosure. Would it be stigmatizing or embarrassing? Could it cost someone his or her job?"

IRBs should then look at what measures or strategies for minimizing harm are included in the study proposal, says Elliott. And if an investigator doesn't address the issue — either because he or she forgot or because it isn't an issue — send the proposal back. "They have to be explicit in the potential for harm and how such harm, should it occur, would be remedied."

IRBs also should make sure researchers aren't going fishing for information in their questionnaires. "Look at what the investigator is collecting and for what purpose," she suggests. "If you are doing a study about ice cream eating habits, why do you need a question about bicycle riding in there?"

Another kind of secondary subject

Along with potential secondary subjects due to the use of identifiable information, there is another group of people that can become secondary subjects: those whose health can be impacted by studies not being done on them directly.

Hammerschmidt has a couple of examples. Two decades ago, a study was done on whether those getting bone marrow transplants would have improved outcomes if they got blood transfusions from people who had never had cytomegalovirus (CMV). "In order to do the study, one had to randomize whether study subjects would get blood according to ordinary screening or get blood exclusively from those with no CMV antibodies," he explains. "The problem is that it would use almost all of the CMV-negative blood in a community. It was altering the blood supply in that area. Every transfusion recipient in the area would have had a research-related risk, even if they weren't participants."

Either the study would have to meet the strict criteria for a waiver of consent, or the investigators would have to get consent from every transfusion recipient in the community. In the end, they were able to meet waiver criteria by finding communities that had very low incidence of CMV in the population.

Another example is a study done on cocaine metabolism in addicts vs. nonaddicts. "The research was done at a medical research center, and the issues of having cocaine addicts in a medical care setting led to concerns about safety for other people in the area," he says. These were addressed by having extra guards on site during the study, thus minimizing the risk to potential secondary subjects.

A more current example involves new vaccines being tested with live viruses, like for HIV and smallpox. "There is a chance with these that contacts of the patients can acquire the virus," says Hammerschmidt.

Dunn says that with potential risk to physical harm, there has been a problem with regulation not progressing as fast as science. Consider the ongoing discussions about using diluted live virus vaccines of smallpox on children. "In this, there is not only a potential risk to the subject, but to family members, other close contacts, health care providers, and the community at large," says Dunn. "That whole area hasn't received a whole lot of thought and consideration yet."

Despite the real concern for secondary subjects, Elliott warns against getting stuck on the issue. "You have to consider it. Don't stop when you realize there is no potential physical harm. Think of psychological or dignitary harm. But don't brood on it. A proposal from an investigator should include statements on the risks, how big they are, and whether the potential risk or harm is so small

that the study can be done without consent from secondary subjects," she says. "Understand that there are extremes in any research. A death to a subject is bad. A headache for a subject isn't bad. A headache for every single subject is something you might want to tell people about and get their consent for." ■

Reader Question

IRB members should be knowledgeable, diverse

By **John Isidor**, JD
CEO
Schulman Associates IRB
Cincinnati

Question: Does the Food and Drug Administration require that an IRB have a certain number of members?

Answer: The minimum number of members required is five (21 CFR 56.107; 45 CFR 46.107). The IRB must have one member whose primary concern is scientific and one member whose primary concern is nonscientific. The regulations do not define the terms "scientific" or "nonscientific." However, an IRB that regularly reviews biomedical research should have at least one physician at each meeting. Additionally, the IRB must have one person who is not affiliated with the institution.

IRBs should be diverse culturally, ethnically, racially, and in gender. The regulations also require members who are knowledgeable regarding institutional policies and procedures, applicable law, regulations and standards of professional conduct and practice, seemingly necessitating the presence of an attorney and a professional knowledgeable in the subject area of the research. If the IRB does not have such members, the regulations allow the IRB to use nonvoting consultants.

IRBs that regularly review research involving vulnerable subjects such as children, prisoners, or pregnant women should consider including members knowledgeable about the special concerns arising from participation of such subjects.

Finally, no IRB member who has a conflict of interest should participate in the review of research, except to provide information requested by the IRB. ■

NEWS BRIEF

Biotech ethics focus of President's Council

A document exploring the implications of using biotechnical powers for reasons beyond therapy takes up controversial issues — such as the prospect of creating designer babies — and questions whether such scientific advances are possible and ethical.

Billed as an educational piece, the 310-page ethical inquiry, which also discusses topics such as mood-altering drugs, was written by President Bush's 18-member bioethics council. Chaired by Leon Kass, a professor at the University of Chicago, the President's Council on Bioethics is made up of professors, scientists, theologians, lawyers, and humanists.

Titled "Beyond Therapy: Biotechnology and the Pursuit of Happiness," the document's preface describes it as an inquiry into the potential implications of using biotechnology beyond therapy in order to try to satisfy deep and familiar human desires: better children, superior performance, ageless bodies, and happy souls.

The document concedes that many of the potential uses of biotechnology designed to satisfy some of those desires are clearly well

COMING IN FUTURE MONTHS

- Research involving fetal tissue raises new ethical considerations
- NIH develops road map to the newest direction for research
- Proposed legislation could impact how IRBs do their jobs
- OHRP on stand-alone HIPAA authorizations

off in the future. Nevertheless, they are worthy of discussion because of the challenges and choices they would present.

As technology advances, the authors consider the purpose of biotechnology, i.e., is it to give us perfect babies, bigger muscles, rid people of illness and disease, or make us happy?

On the latter, the authors take up the widespread use of mood-altering drugs, or selective serotonin reuptake inhibitors (SSRIs) such as Prozac, Paxil, or Zoloft. The report cites a recent poll that said one in eight Americans use SSRIs, mostly as treatments for diagnosed illnesses (depression, anxiety).

From an ethical standpoint, the document asks, "Why shouldn't a patient use such a drug if he feels unfulfilled or steadily blue?"

While there are many positive uses of SSRIs, the document says memory- and mood-altering drugs pose a fundamental danger to the pursuit of happiness.

"In the process of satisfying our genuine desires for peace of mind, a cheerful outlook, unclouded self-esteem, and intense pleasure, they may impair our capacity to satisfy the desires that by nature make us happiest," the document said. The entire report can be viewed at www.bioethics.gov. ■

CE/CME *questions*

Physicians, nurses, and others participate in this continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **The semester ends with this issue.** You must complete the evaluation form provided and return it in the reply envelope provided in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

21. The Secretary's Advisory Committee on Human Research Protections was created with a charter to review regulations pertaining to which of the following specific populations?
A. Neonates and children, prisoners, and the decisionally impaired
B. Pregnant women, embryos, and fetuses
C. Individuals and populations in international studies
D. All of the above

22. Minimal risk needs to be thoroughly examined from all angles, including physical, psychological, and social-behavioral.
A. True
B. False

23. The issue of secondary subjects should be addressed in each study, and investigators should be prepared to obtain:
A. Consent from potential secondary subject
B. Waiver for consent from IRB
C. Both A and B
D. Neither A nor B

24. How many IRB members does the FDA require?
A. 3
B. 5
C. 7
D. 9

Answers: 21-D; 22-A; 23-C; 24-B.

IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

2003 Index

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