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Statement of Financial Disclosure:

Editor Suzanne Koziatek, Editor Melinda Young, Editorial Group Head Lee Landenberger, Managing Editor Alison Allen, Nurse Planner Kay Ball, and Physician Reviewer Alan Sugar, MD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies related to the content in this CE/CME activity.

MAY 2006

VOL. 6, NO. 5 • (pages 49-60)

Clinical trial problems in England raise ethical questions in US

Could IRBs require more information from protocols?

Three weeks after a phase I clinical trial ended terribly wrong, four of the six London, England, volunteers remained hospitalized, and one patient remained in critical condition. No one could have predicted such an outcome for the first trial for a drug to treat cancer and autoimmune diseases.

"I've never heard of anything like this before," says **Greg Koski, MD**, a senior scientist with the Institute for Health Policy at Massachusetts General Hospital, Partners HealthCare System, and an associate professor of anesthesia at Harvard Medical School in Boston, MA. Koski is the former director of OHRP.

TeGenero AG of Wurzburg, Germany, had been studying a humanized agonistic anti-CD28 monoclonal antibody, called TGN1412. TeGenero contracted with Parexel International of Boston to conduct a phase I clinical trial, which involved eight volunteers at the Parexel unit of Northwick Park Hospital in London. Early on Monday, March 13, 2006, six young and healthy volunteers were injected with TGN1412, and two volunteers were given a placebo. According to media reports, the six men given the compound almost immediately suffered serious symptoms, including inflammation, vomiting, severe pain, swollen heads, and unconsciousness. The two men receiving placebos were fine.

The sick men were transferred to critical care at Northwick Park Hospital, where they received organ support, and it was two weeks before the first two of the six men were discharged from the hospital.

The dramatic events of the clinical trial immediately raised questions among clinical trial and IRB experts about what could have been done to prevent the problem. Some say the six volunteers should not have been given the drug at the same time.

"Nothing in the regulations say you can't give six people the drug at once, but one has to ask why would you want to, apart from the notion of being expeditious in the testing," Koski says. "If one seriously accepts that we need to put the interest of volunteers first and foremost, then the argument for expediency or efficiency doesn't really

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hold up because the risk is obviously greater when you do several volunteers at once.”

It’s not uncommon for phase I clinical trials of a drug that demonstrated low risk for toxicities in pre-clinical studies to use a design in which a cohort of eight people are simultaneously given the drug and placebo, says **George “Trey”**

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), \$389. Outside U.S., add \$30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. **Back issues**, when available, are \$65 each. (GST registration number R128870672.)

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Editorial Questions

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Turner, III, RPh, MA, RAC, an assistant clinical professor in the Clinical Research Management Program at Duke University School of Nursing. However, other trials are designed in a way that the drug is administered a week apart.

In the first week, one person would receive a placebo and two would receive the study drug; and in the next week the same would happen, says **Anthony T. Dren, PhD**, a consulting professor with the Duke University School of Nursing at Durham, NC.

How the doses are divided up is not a detail typically included in the protocol that is submitted to IRBs, but that may soon change as a result of the U.K. clinical trial disaster, Koski says. “I think that’s the take-home message here,” he says. “If there had been one person taking the drug, then there’d be one person in the intensive care unit instead of six persons there.”

Giving the drug to all six volunteers at once is not the way most people think these studies should be done, Koski notes.

IRBs might become more involved with clinical trial design issues, partly as a result of the disaster and partly as the continuation of a current trend, Turner says.

“For small single site studies, like phase I trials, IRBs that review those studies might require that there be more phase I expertise sitting on the review board,” Turner says.

Also there might be closer scrutiny of phase I trials, especially in the United Kingdom, Turner says.

“I wouldn’t be at all surprised if IRBs start asking for detailed information about these designs now,” Koski says. “With every incident where we see a tragedy, the closer we look we find out there are things we could have done better, and that’s what is likely to come out of this.”

“I think there is closer scrutiny of phase I studies in the U.S. now than 10 to 15 years ago, but it’s somewhat still different than phase II or III studies,” Dren says.

However, the England trial disaster is such a rare event that it probably will not have as large of an impact on IRBs and trials as it might first appear, Dren notes.

Compensation questions

Another issue raised as a result of the clinical trial disaster was participant compensation. The volunteers of the TGN1412 trial were paid about \$3,500, according to media reports, and some IRB

officials might find compensation a little too high.

"As people look at the web site for the trials there likely will be criticism for the ways in which it was advertised as having free food, a pool table, and digital TV," Koski says.

Participation in a study is not the same as attending a resort for the weekend and receiving \$3,500, he notes. "That's a lot for participating in a study, and that's certainly an inducement for taking risks," Koski says. "For people who are needy and who may not have a steady income that may be an amount that's excessive."

Koski believes U.S. guidelines would have prevented a similar inducement. However, it's also likely that the England incident will highlight similar practices in the United States, some say.

"The U.K. subjects were going to be involved in a two-week study, and I have seen studies in the U.S. for around \$2,000 for the same type of study," Turner says. "The \$3,500 is a little bit high, but it's not hugely exorbitant."

The compensation would seem very high if the subjects were expected to receive one dose of the drug, but if they were expected to participate for a number of weeks, then it probably wasn't excessive, Dren says.

In the United States, subjects who enroll in phase I clinical trials often are professional research subjects who participate for a living, Turner notes.

While that in itself may raise ethical questions, it also provides an additional layer of protection to the subjects since they are experienced enough to understand informed consent forms and to know when they are willing to accept certain trial risks, Turner says.

When follow-up care is needed

Another issue that should concern IRBs is the medical care for the participants who fell ill, Koski says. "Who's going to pay for the medical care for these individuals and for others who are really injured in clinical trials?"

This may be more of an issue in the United States than in a country with socialized medicine, but it does raise the question of how legitimate it is to have clinical trial companies and pharmaceutical companies provide themselves an exemption to long-term medical care when their trial and product are responsible for a volunteer's illness.

"The form may say something to the effect that if you need immediate medical care it will

be provided, but it doesn't say who will pay for it," Koski says. "And most put the burden for paying for medical care back on the individual and the individual's private insurance company."

When disasters occur, it underscores the huge need for an appropriate safety net for the clinical trial process, Koski says.

"We should have some sort of no fault indemnification that uses a trust fund or another mechanism established by industry or the government to provide the appropriate care for people harmed in clinical trials," Koski says. "When people participate in clinical trials and believe it is a way to get access to medical care without having insurance and then when the drugs you take in the clinical trial make you sicker, you have a real problem because who's going to pay for that?"

The United States' current patchwork system of conducting clinical trials provide an inadequate safety net, and this is something that IRBs and research industry entities will need to reconsider, Koski adds.

"If we want to get serious about it and do it right, we have to find the proper way to put resources into it and try to build an interconnected system," Koski says. "We need a system that works properly, efficiently, and safely." ■

Research is changing IRB views about PTSD studies

Risks of harm may be less than previously believed

In the past, IRBs considering protocols that sought to survey or interview trauma victims had to essentially follow their gut when pondering the question: Would answering questions harm participants by causing them to relive their painful experiences?

In the past several years, many trauma researchers have honed in on the specific issue of trauma research participation, interviewing participants after the fact to see how the research affected them.¹⁻³ The results could be illuminating for IRBs.

In general, their studies have shown that most participants did not feel they had been harmed by the experience. Even many who described themselves as being very upset during the study thought such research was valuable; only a small number reported regretting their participation.

And in some cases, people reported feeling a personal benefit from having discussed a past trauma.

As more information becomes available about which trauma victims have more potential for harm, IRBs will have even more useful information with which to review such protocols, researchers say. It can help researchers draft more precise consent forms and underscore the benefit of strategies such as debriefings that may direct participants who need further help.

"Seven years ago, if I look back at my old consents, I think the language was much stronger, implying that people would feel upset," says **Anne DePrince**, PhD, an assistant professor of psychology at the University of Denver in Colorado. "And now, as we get a better handle on the literature, we can say, 'A minority of people may feel this way,' or 'Some people feel X, some people feel Y.' Empirically we're starting to delineate that. I think it's very exciting, the research that's coming out, how it will help us down the road use really accurate and informative text in our consent forms."

Elana Newman, PhD, an associate professor of clinical psychology at the University of Tulsa in Oklahoma, says her work looking at the risks and benefits of participation in trauma-related research appears to be making an impact at the IRB level already.

"My stuff on research risk is probably the least cited and the most requested," she says with a laugh. "I get e-mails several times a month saying, 'Would you send me this information, I need to send it to my IRB' or 'Help me — I'm trying to do this study and my IRB doesn't understand.' I think having evidence is compelling to many IRBs."

Distressing but useful

Some of the social-behavioral researchers who have focused on this area were prompted by their own difficulties getting IRB approval for projects involving trauma victims. For example, Newman says that a plan she proposed in the late 1990s to interview children who had been sexually abused was eventually turned down by her IRB.

"It became very clear to me in this engagement that people were making lots of faulty assumptions about what worked and what didn't in the name of trying to protect adults and children," she says. "I came to it with this view that we really do need to protect people if they need protection but we don't know anything."

Newman has written extensively on the subject, including a 2004 paper for the *Journal of Traumatic Stress*. The studies looked at trauma victims ranging from battered women to children hospitalized after traffic accidents to Vietnam veterans, Bosnian refugees and New York City residents in the aftermath of the Sept. 11, 2001, terrorist attacks.

Many participants in the various studies reported strong, even unexpectedly distressing feelings during their assessments. For example, a 2003 study of female survivors of domestic violence showed that 41% felt strong feelings during the assessment, and 2% were highly distressed while taking a paper and pencil questionnaire. Five percent of the total reported an unwillingness to be similarly assessed again.

But at the same time, many people reported (in surveys where the question was asked) that they saw usefulness to the questions and were glad they participated. Newman herself was one of the authors of such a study, which looked at more than 200 injured children and their parents. Using a Reactions to Research Participation Questionnaire (RRPQ) she and her colleagues developed for children and their parents, the authors found that 77.3% of children and 90% of parents interviewed felt "good about helping other people by being in this study." Fifty-two percent of children and 74% of their parents reported they were glad they had participated.

Jennifer Freyd, PhD, a professor of psychology at the University of Oregon in Eugene, studies victims' memories of "betrayal trauma," such as childhood physical or sexual abuse. She says that victims of personal traumatic events such as those are more likely to experience distress in a research setting than victims of a large scale natural disaster or terrorist attack.

"For one thing, most people who experience shared events do have an opportunity to talk about it," she says. "And I think IRB members and researchers have a reasonable gut feeling that it's not as big a deal to talk about it as it could potentially be to talk about something that you've never talked about before."

Freyd says that while it may not matter how long ago the trauma occurred, a person is less likely to be upset if they have already had a chance to talk about it, in therapy or some other forum.

"Something could have happened 30 years ago and really not been dealt with and so it can be a crisis for people," she says. "What's interesting is

that for a lot of people it's a kind of welcome crisis, in a sense. If they hadn't gotten the chance to talk about it and they get asked and they're in a position where they're strong enough, it often leads to positive change for people," she says. "They're relieved to finally get to talk about it and they seek other people — whether it's friends or therapists to continue to process it. It's not necessarily unwelcome even to get agitated about it."

One study Freyd has done with college students suggests that questions about personal trauma weren't seen as any more troublesome than other highly personal questions, such as a student's GPA, SAT score or personal body image.

"The students didn't find questions about say, sexual abuse, more problematic than those other kinds of questions," she says. "And furthermore, they said it was more important that we ask them."

In fact, Freyd and others say that *not* asking about traumas such as child abuse may carry its own costs, at a personal and societal level. "It communicates that material is not speakable or not important," she says. "It seems an awful lot like the general problem we have of silence around these events that seems to contribute to their occurrence."

Freyd says she'd like to see IRBs look at protocols with an eye toward what is not being asked, as well as what is. "If they're working in domains where it might be natural [to ask trauma-related questions], then why is this being left out? And what impact is this having on the participants?"

IRB's understanding changes

Juliana Kyrk, IRB program officer for the University of Oregon, says her IRB has benefited from a close working relationship with Freyd. She says that when Freyd and other researchers first began submitting proposals for post-traumatic stress research, the board always gave it full review.

"We looked at it like, 'Oh my goodness, think of what happened to these poor women, and we're bringing up all these issues,' so we always full-reviewed it," Kyrk says.

But as Freyd's research progressed, and members began to deal with the related issues more often, they became more comfortable with them. "We ended up putting her on the committee and as a result, we started getting more interaction with her and her ideas," Kyrk says. "We benefited from that because she heard our concerns and we heard hers. She could hear what we were

concerned about — we were very clear that these participants needed to be debriefed appropriately, and that they always leave these sessions feeling as good about themselves as when they came into them," she says.

Kyrk says that when the committee saw feedback from women about how they felt about the sensitivity of the questions, members began feeling comfortable giving studies like Freyd's expedited review.

She says some issues still raise red flags that a study should have a full review. For example, studies that involve an intervention or manipulation of participants would go before the full board, as opposed to research where participants are simply filling out a survey. Studies that target a potentially vulnerable population would receive closer scrutiny as well, Kyrk says.

After her early difficulties getting her studies through an IRB, Newman went on to become a member of the board. Even before that, she says, she made a point of going to the IRB to educate them about her work. "We sort of collaborated," she says. "I sort of educated them some, and they educated me as well."

Kyrk describes a similar process. Kyrk says an IRB seeking to understand this issue better should invite researchers to sit in on the meetings where the board discusses their concerns. "You can understand the skills and the knowledge of the researcher and what they consider the risks to be," she says. "When the IRB may be totally naïve regarding that type of research, then at least it gives them some information that helps them understand how that works."

Kyrk notes that Freyd would give the members articles as new information came out about the risks of trauma research, and adjusted her own studies to gather more information about those risks to help address IRB concerns.

"In the end, it elevated her research in that regard because she presented both sides of the situation." ■

References

1. Newman E, Kaloupek DG. The risks and benefits of participating in trauma-focused research studies. *J Trauma Stress* 2004; 17(5): 383-394.
2. Kassam-Adams N, Newman E. Child and parent reactions to participation in clinical research. *Gen Hosp Psychiatry* 2005; 27(1):29-35.
3. Becker-Bease KA, Freyd JJ. Research participants telling the truth about their lives: The ethics of asking and not asking about abuse. *American Psychologist*. Publication pending, April 2006.

Consent, confidentiality key in PTSD research

Spell out what will be asked, and who will see it

While recent studies have shown that interviews with trauma victims may not cause serious harm, and in fact can be beneficial, there still are serious issues surrounding asking people about such sensitive, personal experiences.

Those who deal with this type of research say IRBs should pay close attention to key issues surrounding what participants are told about the research and its confidentiality:

- **Detailed consent forms.** Always prepare participants. Consent forms should spell out explicitly what types of questions will be asked so that participants aren't confronted with anything unexpected.

"They have to be told that they're going to be asked very sensitive and personal questions about their personal life," says **Juliana Kyrk**, IRB program officer for the University of Oregon in Eugene. She notes that questions about sexual trauma, such as rape or child sexual abuse, should specifically state that the questions will not only be personal, but of a sexual nature.

Many IRBs require language in the consent form stating that a participant may find the questions upsetting. Researchers say that as more information becomes available about participants' reactions, they should strive to include more information in consent forms.

For example, in her research with victims of post-traumatic stress disorder, **Elana Newman**, PhD, an associate professor of clinical psychology at the University of Tulsa in Oklahoma, found that some participants were more distressed by the research than they had expected to be. So she often puts that in her consent forms: "We have found that many people underestimate how distressing this might be."

She still hesitates to suggest in consent forms that the participant might benefit personally from discussing his or her past trauma, but she says she talks to the participant about that possibility.

"After they read the consent, I say there are a couple of things that we know so far," Newman says. "We know that people who have post-traumatic stress disorder may underestimate how emotionally taxing this is. And that a lot of people find that talking about this stuff is very beneficial, but you need to make that decision."

- **Confidentiality.** Researchers say it's vital that victims of trauma understand under what precise circumstances their information will be revealed.

In many states, researchers are bound by law to report to authorities when they learn of an instance of child abuse or other ongoing danger. This makes promises of confidentiality tricky. For example, if an adult describes past sexual abuse in a household where there is another child at risk, what does the researcher do?

What's key, says **Jennifer Freyd**, PhD, a professor of psychology at the University of Oregon, is that the participant understands what will trigger a mandated report, and what won't.

"You can err in either direction," she says. "You can lead participants to feel they have complete confidentiality and then turn around and tell somebody [or] participants can feel that they're telling you something, and you are going to do something about it. You also have to make clear when you're *not* going to tell somebody."

Freyd handles that issue in her debriefings, giving participants information about where they can go to report a crime or seek further help. She says this isn't just an issue in trauma research. Many psychological studies employ a standard tool for assessing depression that asks about suicidality.

"Let's say a participant writes down that they're very suicidal. What's the researcher then going to do? Are they going to break confidentiality or not?" Freyd says. "You can justify either one, but what you need to do is warn the participant before the fact which way it's going to go."

- **Staff training.** Freyd says the graduate students who run most of the studies involving the University of Oregon's psychology student pool get training through local community organizations that manage people in crisis, including a battered women's shelter and a sexual assault services organization.

"They offer very good training," she says. "And our graduate students are often in the clinical psychology program, so they're getting training in being therapists."

Freyd says she's never had a research subject suffer a severe reaction during a study. "We have had some people who have hung around afterwards and clearly needed to talk to somebody, but we've never had a case where somebody just fell apart," she says.

Ironically, it has happened to her a number of times while teaching — a student has broken

down while discussing the topic of trauma or viewing a film. In those cases, she says, she makes sure the student is physically walked to a counseling center to get help.

She says that the issue of staff training becomes even more important if the study involves any kind of feedback to a person talking about trauma.

"I do think if it's an interview format, an IRB should look closely at this," Freyd says. "You *could* really do some harm by giving negative feedback. If somebody says they were raped and the interviewer says, 'Oh well, it was long ago, you should be over it by now,' it obviously could do damage."

- **Debriefing to assess distress.** At the University of Oregon, any study involving the student psychology pool must provide a debriefing afterward that asks students about their

research participation and provides them with resources in case they need counseling or other follow-up help.

Newman, who also uses debriefings in her work, says she would hesitate to recommend that an IRB require it of all trauma studies. But she does note that there are certain subsets of participants who may be more likely to be highly distressed by research participation — very old and very young people, those with multiple traumas or special vulnerabilities.

"If there's a real, founded concern about exceeding minimal risk, then that might be a good compromise to recommend as a way of assessing and facilitating research," she says.

"I'm wary of saying they should require it. But I also see that as a good compromise when it's unknown." ■

SPOTLIGHT ON COMPLIANCE

The FDA launches guidance initiative

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Mr. Waxman reports no financial relationships with companies related to the content in this CE/CME activity.

To keep IRBs informed on current FDA thinking, the agency has created the Good Guidance Practices (GGPs) program. This is a process whereby dated and obsolete guidance is replaced by new information sheets on a variety of topics, along with the opportunity to comment.

Recently, the FDA announced a series of new or updated guidance documents. It must be noted that these documents are not binding. They do, however, represent the FDA current thinking on the topics covered. What follows are comments on several of these guidance documents.

- **Waiver of IRB Requirements for Drug and Biological Product Studies.** This guidance represents an updating of its September 1998 predecessor. It addresses a series of issues related to when IRB requirements may be waived by the

FDA. While the FDA may waive any IRB requirement in specific cases or classes of research, it will do so only when "alternative mechanisms" for patient safety protection exist. Three important circumstances are discussed:

- For the conduct of a foreign clinical trial under an IND. Here, receipt of a waiver will require an independent ethics committee which operates in accordance with good clinical practices. The guidance notes that such waivers are not available for medical devices (under §520(g) of the FDCA)¹ because IRB review is a statutory requirement;

- Emergencies requiring use of a test article, provided the necessary report is made within five working days following use, and subsequent cases are approved by an IRB; and

- Local IRB review may be waived when a centralized IRB process is used. (21 CFR § 56.114).

- **IRB Inspections.** In another update of a 1998 guidance, the FDA addresses issues related to IRB Inspections. This guidance again provides an accessible guide to elements that might be reviewed by an internal audit or compliance process to prevent issues arising during the course of either a surveillance or directed (i.e., focused on a specific trial or group of trials) inspection.

IRBs should keep in mind that:

- Records of IRB membership, procedures and guidelines, meeting minutes and study documents will be copied; and

- The failure to meet operational requirements may result in significant sanctions, including study terminations.

• **Frequently Asked Questions (FAQs) About Medical Devices.** This update of a 1998 guidance takes the reader through a broad series of questions regarding the relationship between the IRB and trials involving medical devices. Beginning with the definition of what is a medical device (“...instrument, apparatus ... continuance ... intended for use in the diagnosis...or in the cure, mitigation ... or prevention of disease, in man or other animals...and which does not achieve its primary intended purpose through chemical action ... and which is not dependent upon being metabolized...”) through this classification system, and into the IRB responsibilities.

One interesting element of the discussion relates to humanitarian use devices — devices intended to benefit patients with conditions manifested in less than 4000 individuals in the United States per year. A humanitarian device exemption allows a request to be made that authorizes marketing of an HUD, without a full blown pre-market approval, provided the FDA is satisfied with the risk/benefit analysis. Once an HDE is granted, there are specific rules applicable to IRB processes, including that it may approve the use of the device “as it sees fit,” for up to one year.

The guidance goes on to discuss the fact that given the HDE, use of the HUD does not constitute research or an investigation that would require informed consent from study subjects. The FDA does caution, however, about off-label uses, suggesting that approval from the FDA under its compassionate use policy be pursued.

• **Significant Risk and Non-significant Risk Medical Device Studies.** The FAQ guidance discusses in general terms the Investigational Device Exemption (IDE) and the nature of those studies that may be exempt from the IDE regulation (21 CFR § 812) — a non-significant risk (NSR) device study. This guidance addresses, in some detail, the difference between the significant risk (SR) and NSR devices, and the different responsibilities the IRB has in each case.

While defining each, an important part of the guidance is its focus on the factors to consider, and the recommendation for the IRB to write its decision into its minutes. Those factors are:

- The basis for the risk determinations;
- The nature of the potential resulting harm;
- and
- Will the subject need to undergo an additional procedure as part of the study.

The guidance documents do not raise new or controversial issues. The guidance they provide

is both accessible and of real educational value for IRB Board members, PIs, research staff and administration.

• **Inspections of clinical investigators.** This is another update of 1998 guidance and seeks to address inspections under the FDA’s Bioresearch Monitoring Program (BIMO). An investigator will seek to verify:

- Who actually implemented the various steps in the protocol, from obtaining informed consent to collecting adverse event data;
- Where specific aspects of the investigation were performed; and
- The activities of the monitor; from communications to evaluations of progress.

A warning is also worth noting: inspectors may review medical records of participation subjects to verify the diagnosis and ensure eligibility criteria were met prior to enrollment, as well as to ascertain whether post-operative or implant care and monitoring called for was actually provided. ■

Reference

1. The Food, Drug and Cosmetic Act (“FDCA”) citation is 21 U.S.C. § 360; (g)(3)(A).

Liaison efforts can improve compliance

Survey director worked at IRB

Compliance in research oversight has become a more prevalent concept in recent years, and this has led IRBs and research institutions to search for new ways to improve compliance communication and policies.

An IRB and the Institute for Social Research, both at the University of Michigan in Ann Arbor, have forged a new type of relationship with the common goal of improving the environment for conducting ethical research.

“We wanted to do more than improve compliance,” says **Steven G. Pennell**, survey director for the Survey Research Center of the Institute for Social Research (ISR) at the University of Michigan. ISR is the world’s largest academic survey research organization and has been in existence for 20 years, conducting thousands of interviews every year with youths and adults.

“I like to think that we are improving commitment to the underlying ethical principles,” Pennell says. “The idea is not to have people just do what

they think the IRB wants them to do, in a rote way, but to think about the underlying ethical principles and proceed from there.”

The IRB’s role in improving this commitment was to invite Pennell to work with the IRB, attending staff meetings and full board meetings for a couple of years.

“Over the course of that period, I spent at least half of my time here and half at ISR, Pennell says. He reviewed applications to identify areas that were not compliant with regulations, and he would work with investigators to find ways in which they could bring their applications into compliance.

“The IRB helped him have the insider’s view of why certain types of social science applications seemed to face difficulty within the IRB,” says **Judith Marie Birk**, administrative manager of IRB Health/Behavioral Sciences at the University of Michigan.

Having Pennell as a liaison helped IRB members understand what ISR researchers knew about the IRB process and compliance. The IRB staff could then target areas in which researchers needed extra information and education, Birk says.

The IRB has had guidance documents available on line, but investigators probably did not refer to those when they needed help interpreting IRB comments, she notes. So investigators would be perplexed about some IRB requests. For example, when the IRB would ask for more information about research design, investigators would fail to see why that was relevant to the IRB, Birk says.

“If the IRB is just there for human subject protection, why would we be interested in the design of the study?” she says. “So we’d get a short, non-descriptive response to that question.”

While working for the IRB, Pennell observed investigators’ responses, and he understood why the IRB was frustrated with the answers, so he worked at improving researchers’ knowledge of how the IRB process worked, Birk says. “Steve was able to be our interpreter. When the IRB says this is what they mean, he was able to help us spread the message.”

Pennell improved the web site educational information that was available about the IRB process, including information that was specific to ISR. For example, one of the common reasons why research applications are returned to investigators is that one or more elements of informed consent are missing, Pennell says.

“The regulations are straightforward about

what is required, and the IRB resources are available for people to review,” Pennell says.

To bring the information closer to home, he worked on a guidance document that reviews best practices and informed consent practice, reminding researchers of what to do, step by step, he says.

“A lot of guidance documents were disseminated through a written internal newsletter originally, and then they were posted on an internal Intranet site that all staff could access,” Pennell explains. “So they could go to the Intranet site and review information on best practices, informed consent forms, and look at large numbers of frequently asked questions.”

Pennell also has provided direct application assistance to researchers. “I also had the opportunity to review an application before it was sent to the IRB, and so I could catch problems that way.”

Many IRBs would benefit from having a liaison or experienced IRB staff person look at research protocols before they’re submitted to the IRB for review, Birk notes. “They can look at things with a critical eye and say, ‘You may want to fix this, change this,’” Birk says.

“During the time I was a guest at the IRB, I identified various problems and approval of applications,” Pennell says. “And we distributed the guidance documents through various communications we have at the institute, and we created the intranet site that included these guidance documents, as well as other areas that would help researchers better understand federal regulations.”

There also were a series of brown bag lunch presentations on how federal regulations apply to social research, Pennell adds.

Having a liaison has improved outcomes because Pennell was able to contact the IRB office and discuss proposals that he had reviewed before they were submitted, Birk adds.

Pennell continues to provide this pre-submission review on an informal basis, at researchers’ requests, he says.

“One of the other things I did here while at the IRB is look at a lot of outcome data,” Pennell says. “The creation of an application and review and approval of it creates enormous data, and we could look at the outcomes and establish some benchmarks of what the problems are, what issues resulted in an application being returned, and how long it took to approve an application.”

By reviewing data, it was possible to compare the length of time it took to approve an application that didn’t have to be returned to the investigator

versus the length of time to approve an application when the application had to be returned once or twice before all issues were adequately resolved, Pennell explains.

After changes were made as a result of the liaison relationship between ISR and the IRB, the percentage of expedited review process applications approved within two weeks or less increased, Pennell says.

The data show an increase from 56% in the Jan. 2003 to June 2004 time period to 78% in the Jan. 2005 to May 2005 period.

The data review showed that the most common area in which investigators make mistakes is with informed consent, Pennell notes.

ISR investigators use complex and innovative survey designs to address measurement and coverage issues, Pennell says. "Human subjects elements often have cost implications," he says.

"For example, will we be asked to obtain consent, documentation from parents in order to speak with children at a school?"

It's because of these cost issues that investigators need to know before submitting an IRB application how the IRB will address design issues that have human subject implications, Pennell explains.

Also, with survey research, there needed to be an acceptable and feasible consent process, so the IRB office and Pennell worked with investigators to try to craft language that contains the required elements of consent, but did so in a concise and cohesive way, he says.

These types of studies are low risk, Birk says. "We do a lot of research over the telephone, randomly, and speak with an adult in the household where we need to explain the nature of the study and eventually conduct a consent process," Pennell explains. "On the telephone the consent has to be quicker, so we worked with researchers to make sure they were meeting regulatory requirements, but also doing it in a way that minimized the likelihood that somebody would just hang up." ■

Upcoming Conference:

The annual one day subject protection conference, sponsored by the University of Cincinnati, the University of Kentucky, and Schulman Associates IRB, will be held September 22, 2006 at the Northern Kentucky Convention Center in Covington, KY. Registration for the conference, titled "Human Subject Protection: Is It Getting Better All The Time?" is \$125. For more information, contact Lisa Valentine at Lvalentine@sairb.com or (513) 761-4100.

Guest Column

Different disciplines, similar challenges

Biomedical vs. social science

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Dr. Speers reports no financial relationships with companies related to the content in this CE/CME activity.

On the surface, it seems that individuals who oversee biomedical research face challenges that are very different from those encountered by their peers in behavioral and social science research.

This perception is understandable, but not entirely accurate. Granted, there are few similarities in the questions and methodologies used by both disciplines. There also is widespread sentiment on the part of investigators and IRBs that regulations governing human research protections were written primarily with biomedical research in mind and, therefore, are not easily applied to non-biomedical research. Dig a little deeper, however, and these differences seem far less significant than what the two research areas have in common. Take as an example the analysis of risk of harm.

For both biomedical and behavioral/social science research, the range of risks is the same: dignitary, economic, legal, physical, psychological, and social. The responsibility also is the same: to minimize risks, to identify and justify those risks that are unavoidable, and to monitor the research to safeguard participants.

Identifying all applicable types of risk is a challenge in every biomedical research protocol and in every behavioral/social science protocol. The temptation is to focus more on the risks most likely to apply to a particular research discipline, but, in fact, those are the risks least likely to be overlooked.

For example, biomedical investigators typically are aware of the higher probability of physical harm in their studies and, therefore, respond with vigilance. They may be less attuned to the psychological, social, legal, economic, or dignitary risks to research participants and, as a result, may find it more difficult to identify and address them.

Behavioral and social science researchers face similar challenges, albeit regarding different categories of risks. Except in certain types of protocols, physical risks tend to be rare. Psychological or social harms are more common than physical risks but still relatively uncommon. Far more common are dignitary harms, particularly if the research involves sensitive information. Although behavioral and social science researchers must be especially alert to dignitary risk, they are equally accountable for identifying all other risk types.

Legal and economic harms are uncommon in either biomedical or behavioral/social science research. Here again, the low probability of occurrence does not relieve investigators and IRBs of their responsibility. The complete range of risks must be considered in every research study, without exception.

Moreover, investigators should perform the initial assessment, and the results of these assessments should be included in the protocol descriptions that are provided to the IRBs. Such information can be invaluable to IRBs as they identify, analyze, and justify the risks involved in research, particularly in behavioral/science research, where the investigator is often in the best position to recognize potential harms.

Criteria for approval

To comply with federal regulations, the IRB must determine that “risks are minimized” and that “risks are reasonable in relation to the anticipated benefits, if any, to participants and to the importance of the knowledge that may reasonably be expected to result.” Both biomedical and behavioral/social science protocols must be evaluated in light of these criteria. (Note: There are other approval criteria, but they are not germane to this discussion.)

Frequently in biomedical research, and even more often in behavioral/social science research, there are no anticipated benefits to participants. In such cases, the IRB evaluation weighs the risks against the importance of the knowledge that is likely to be gained. For each risk, the evaluation must involve both probability and magnitude.

In many research studies, the probability of risk — regardless of severity — is low. Even in the aggregate, very often the overall risk involved in a particular study is deemed to be no more than minimal. Many contend that this is the case for most behavioral/social science research. While that might be true, it doesn’t relieve IRBs or investigators from their responsibility to identify, analyze, and justify each risk.

Once the risks are evaluated, the focus shifts to ensuring that they are minimized. Because this judgment must be based on the use of sound scientific or scholarly methods and procedures — and the IRB’s understanding of these procedures — the composition and expertise of the IRB are important factors. Social scientists often express concern that the IRB does not have the expertise or, even, access to the expertise. This does not exempt the IRB from its obligations under the federal regulations. Instead, the IRB must take whatever steps necessary to acquire the expertise.

Also common to biomedical and behavioral/social research is the risk that a study presents beyond the research participant: to families, friends, or communities. This risk is not addressed by the federal regulations for protecting human subjects or the Belmont Report, whose ethical principles have guided investigators and IRBs for more than 25 years. Yet, this risk should not be ignored, especially since it could apply to a broad range of studies: on genetics, infectious diseases, caregiving, quality of life, violence and abuse, communication patterns between parents and children, cognitive development in children, divorce, aggression, and myriad other possibilities.

Ignoring risk to others has the potential both to harm individuals and to weaken the research itself, either because of poor research design or inadequate enrollment. Furthermore, if such risks are not considered during the initial review, they may surface as unanticipated problems later in the research process.

It seems a far better strategy — in biomedical *and* behavioral/social science research — to acknowledge and manage these risks up front, when they are least disruptive to the study and before they can result in unintended harm. ■

COMING IN FUTURE MONTHS

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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;
- **apply** the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, 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.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE/CME questions

18. Regarding problems experienced during a clinical trial conducted in London, England in March, what practice did the clinical trial organization use that some critics say made the situation worse than it might have been?
 - A. The same dosage, based on weight, was administered to all six subjects.
 - B. All six subjects received the study drug at the same time.
 - C. The subjects were paid a higher-than-standard fee for participating.
 - D. None of the above.
19. In many states, researchers are bound by law to report to authorities when they learn of an instance of child abuse or other ongoing danger.
 - A. True
 - B. False
20. Which of the following is **not** true of recent studies into the effects of participation in trauma research?
 - A. Some participants have reported strong and distressing feelings after participating in surveys of past traumatic experiences.
 - B. In one survey more than half of children and parents interviewed after treatment in a hospital reported feeling good about helping others through the research and were glad they had participated.
 - C. More than half of participants in recent trauma studies regretted their participation.
 - D. All of the statements are true.

Answers: 18. B; 19. A; 20. C

Clarification

Question 11 in the March issue should have read: Which of the following is part of a good strategy for ensuring optimal informed consent during research trials conducted in developing nations? The answer is D.