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IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

In This Issue

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IOM's recommendations call for new name and more focused role for IRBs

Informed consent should be process, not ending point

The Institute of Medicine (IOM) of the National Academies in Washington, DC, has called for some major changes in IRBs and research, including suggestions that research grants and sponsors, as well as research institutions, put more money into the process of protecting human subjects.

In a report titled "Responsible Research: A Systems Approach to Protecting Research Participants," the Committee on Assessing the System for Protecting Human Research Participants has outlined the legislative, regulatory, and institutional changes that are needed in order to gain public trust in the ethics of human subjects research.

One of the major changes promoted in the report is that federal legislation be passed requiring human subjects protection for all research projects involving human volunteers, regardless of funding source or research setting, and for institutions engaging in research to establish human research participant protection programs (HRPPP).

The report's emphasis on this change has support in two bills introduced in Congress this year. One bill, introduced Oct. 4, 2002, by Sen. Edward M. Kennedy (D-MA), is the Research Revitalization Act of 2002 (S.3060), and the other is the Human Research Subject Protections Act of 2002 (HR 4697), introduced May 9, 2002, by Rep. Diana DeGette (l-CO). Both bills would require all research to follow human subjects protection regulations.

The Senate bill would require accreditation for all IRBs, establish rules for financial conflict of interest for IRB members, and allow IRB expenses to be charged as direct costs on federal grants. Conflicts-of-interest rules would be strengthened, and regulations would be written to create a model ethics-training program for investigators.

The House bill would require informed consent and require all human subject research to be conducted in accordance with the common rule and the vulnerable-population rules.

The House bill was referred May 17, 2002, to the House subcommittee on health, and the Senate bill was referred Oct. 4, 2002, to the Senate committee on health, education, labor, and pensions.

These programs would send the message to staff, researchers, and the public that high ethical research standards are a top consideration from the institutional CEO on down, says **Daniel D. Federman**, MD, chair of the committee that wrote the IOM report. Federman is the senior dean for alumni relations and clinical teaching and the Carl W. Walter distinguished professor of medicine and medical education at Harvard Medical School in Boston.

"That sounds like nothing new, but it is," he says. "To have a CEO on record insisting on high standards is not universal."

The key point of the IOM report is that human research protection must take place within an entire system so that institutions are actively involved in overseeing the process, says **Timothy Stoltzfus Jost**, JD, who is on the committee and is the Robert L. Willett Family Professor of Law at the Washington and Lee University School of Law in Lexington, VA.

"There was a concern of the committee and of people who talked with us that IRBs are overloaded, overstressed, and are asked to do too many things," Jost says. "Because of that, they are losing the most important and original focus on research human protection and making sure research is conducted ethically."

IRB members and others interviewed by the committee often reported having too many responsibilities and too few resources, Federman says.

Some IRBs, consisting of eight to 10 people, have 3,000 protocols to handle, and that seems a stretch, Federman notes.

With an HRPPP in place, an institution would then need to provide the financial and personnel resources necessary for IRBs to adequately monitor human subjects protection, and different boards should handle some of the IRB's other responsibilities, the report says.

Increased resources could be sought from both the institution and from the funding sources of the proposed research, Jost says.

"One of the most important messages of our report is that if an institution asks for a research grant and the sponsor says, 'We'll give you the grant, but we're not going to give you any indirect costs,' then the institution should say, 'No, we have to cover our costs if we do research,'" he says. "If the sponsor isn't willing to pay for IRB protection, then the research shouldn't be done because the ultimate consequence of it not happening is we'll continue to have scandal after scandal and perhaps death after death — although those are rare events — and other injuries as well."

Some might argue that if sponsors and funding

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sources are forced to pay for the IRB and other indirect costs then the total funds available for research will be more limited, Federman says.

However, no one has a comprehensive idea about the total amount of research that is under way, and no one knows how many people are experiencing harm as a result of the research, he notes.

"Absent that information, I recommend that enhanced support, including financial support for human subject protection, is a good idea now, and the government should be collecting comprehensive data on the total amount of research and harm to subjects," Federman says.

One way to reduce the work overload of IRBs would be for the institution to put the responsibility for full scientific review and conflicts of interest into the hands of separate committees that would then share their findings with the IRB as part of the review process.

Soon after the report was issued in October, critics, including the Alliance for Human Research Protection (AHRP) in New York charged that this proposition was flawed because it suggested that institutions be responsible for self-monitoring their conflicts of interest, which critics claim is one of the major problems with the current system of research review and protection **(see related story, p. 130)**.

"Conflicts of interest are at the root of most of the ethical/legal violations in medical research," according to a statement issued Oct. 3 by AHRP in response to the IOM report. "There are high financial stakes to speed up clinical trials — but there are neither effective enforcement mechanisms nor meaningful penalties."

Federman says the committee could see no reason institutions couldn't handle reviews of individual conflicts of interest, which include instances when an investigator holds stock in a company for which he or she is conducting research. However, institutional conflicts of interest should be handled by a group of senior faculty, investigators, and ethics and community participants, he says.

"We think it's mandatory that institutional conflicts-of-interest committees have not only outside members, but, to a degree, an outside board," Federman explains. "I know we've already received some criticism that this is not tough enough."

But there probably isn't a practical way to have conflict-of-interest committees that are completely outside the research institution, he adds.

Another chief recommendation in the report is that IRBs be given a new name that reflects their more focused role in protecting human subjects. The report suggests IRBs be called Research Ethics Review Board or Research ERB.

The Research ERB's objective should be to obtain consensus in approving research protocols, rather than majority control, the report says.

With a stronger mandate and more time and resources to focus on ethics and protecting human subjects, the Research ERB should make certain that investigators obtain informed consent as an ongoing process, rather than merely obtaining signatures on a form that often is bloated with language designed to insulate the institution from liability, the report states.

"Informed consent needs to be a dialogue between participant and investigator," says **Daniel L. Azarnoff**, MD, president of D.L. Azarnoff Associates and senior vice president of clinical and regulatory affairs at Cellegy Pharmaceuticals in South San Francisco, CA.

"The dialogue should be about a variety of things related to potential risks and benefits of the trial or the procedures that they're asking the participant to undergo," he says. "And the dialogue shouldn't stop because as the trial proceeds, new information becomes available that may require continuing the discussion with the participant."

For example, if during a trial there is an increase in a particular adverse event, then this needs to be discussed with enrolled volunteers, he says.

"It needs to be discussed with all subjects about whether the new risk warrants their wanting to continue with trial participation," Azarnoff explains. ■

Special Series: Assessing Risks/Benefits

Risks and benefits must be evaluated separately

Risks and benefits are not parallel, experts point out

(Editor's note: In this issue of IRB Advisor *is the second part of a series on how IRBs can assess potential risks and benefits. Included are stories on the ASSERT statement, how to give potential benefits equal consideration, and past research mistakes involving an imbalance in risks and benefits.)*

Rather than treat the risk of harm and potential for benefit as two weights on opposite sides of a scale, IRBs and researchers should fully explore and express the potentials of each, say

research ethics experts.

Too often, IRBs and researchers misunderstand a study's goals with regard to benefits, and this can cause confusion on the part of subjects, as well as those involved with the research.

"Some IRBs may say that if an investigator does a lot of research with patient subjects, then benefiting subjects directly is a primary goal, and this is a misunderstanding," says **Nancy M.P. King**, JD, a professor of social medicine at the University of North Carolina-Chapel Hill.

"But IRBs should look at societal benefit and make certain the risks have been minimized and the research is going somewhere that has value," she says.

For instance, suppose an IRB is presented with a proposed drug study that will treat a disorder that already has a dozen viable and approved drugs available. Suppose that the research protocol anticipates that the drug, if successful, will work as well as the other similar drugs on the market, King says.

Some IRBs may not approve such a protocol, saying that the drug doesn't provide enough of a societal benefit since there already is an adequate number of useful medication treatments on the market, she explains.

"They might say they don't see the need to approve another compound that does the same thing as twelve other compounds," King says. "But other IRBs may say that another useful version of this drug is good because it gives patients more choices in the future."

The bottom line is that it's up to the IRB to make the call on societal benefit, and it's permissible for different IRBs to have different opinions on this issue, she adds.

One of the obstacles to both investigators and IRBs adequately assessing potential benefits of a study is that those involved with the research and those reviewing the research may assume that good intentions equal good benefit outcomes.

"One of the problems is that people think they're going to do the right thing because they're good people," says **Dale Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota Medical School in Minneapolis. Hammerschmidt is an IRB member and has chaired IRBs.

The way to prevent assumptions from replacing a thorough and methodical examination of potential benefits is to define benefits in an organized way and assess each protocol according to one of the definitions below.

King divides possible benefits into three types:[1]

- **Direct** benefit to subjects, which is when the volunteer subject receives a benefit that results from the intervention being studied.
- **Collateral** benefit to subjects, also called indirect benefit, is when a volunteer subject receives a benefit even when he or she did not receive the experimental intervention. This could include free medical care.
- **Aspirational** benefit, which is a benefit to society and future patients, resulting from the research.

Each proposed study needs to be evaluated according to these potential benefits, and each informed consent should discuss them in detail, rather than leave research volunteers with a vague idea that their participation may result in some benefits for themselves and/or others, the experts say.

Taking the analysis a step further, investigators and IRBs should examine the probability and magnitude of each benefit, another concept that King and other researchers have promoted, says **Paul B. Gold**, PhD, an assistant professor of psychiatry at the Medical University of South Carolina in Charleston. Gold has conducted human subjects research and is an IRB member.

For example, in a short-term, diabetes clinical trial that involves testing new drugs for treating diabetes Type II, what would be the probability and magnitude of the three types of benefits? Gold offers these simple assessments of each:

- **Very low probability and magnitude of direct benefit:** "If an IRB is reviewing a two-group study with a placebo-control group, and the study is a Phase I, II, or early Phase III study in which effective drug dosing has yet to be determined, then investigators need to be extremely conservative in conveying any impression of direct benefit to volunteers," Gold says. "This is because the placebo-group volunteers will not benefit, and most of the volunteers in the active group will not receive an effective dose of the drug."
- **Low-to-moderate probability and magnitude of collateral benefit:** There is a greater probability and magnitude associated with collateral benefit because the research participants will be given a blood sugar monitor that will allow them to check their own glucose levels at home, and they will receive education and frequent medical exams during the course of the study.

For example, researchers will examine how the subject's blood sugar levels fluctuate over the course of days while the person is enrolled in the

study. "Not only does that generate information about the effectiveness of the drug, but people learn how to monitor their own blood sugar levels so they can take their own actions to prevent disease complications and to promote healthier behavior, even when the study is over," Gold explains. "They can learn how to keep their blood sugar levels from going too high or too low through diet control, taking medications at appropriate times, and monitoring their own blood sugar levels."

• **Moderate-to-high probability and magnitude of societal or aspirational benefit:** The probability and magnitude of a societal benefit likely would be the highest of the three benefits in this example because if the drug works as well as the study's investigators expect then it would provide the large population of people with Type II diabetes with another effective treatment, Gold says.

In King's research about benefits and clinical trials, she found examples of how little investigators and study participants discuss and understand potential benefits.

"In our study, we interviewed investigators, study coordinators, and subjects involved in gene research," King says.

There were two types of responses that appeared to be universal, she says. These were:

• For some diseases, such as genetic diseases that may affect the participant or the participant's family, investigators will say people volunteered for the study for altruistic reasons, King explains.

• "The other response from investigators is to say that "no matter what we tell them, they're always going to hope," she says.

"I think investigators believe this, and it seems to be true," King adds. "But the notion of being more explicit about potential benefits doesn't devalue that at all."

For study participants to hold out hope that they may receive a personal benefit from a particular trial in which the odds of that direct benefit are very low is similar to the hope people have each time they buy a lottery ticket, and it's no less legitimate, she explains.

However, while investigators may believe that they have fairly and thoroughly communicated potential risks and benefits to participants and that despite what they've said that subjects will continue to hold out hope, the truth may be that they haven't done as good a job communicating these as they think, King says.

"It remains to be seen whether this belief in hope that subjects are said to have is irrational and flies in the face of evidence, or whether it comes from ambiguities in the way these issues have been discussed with them," King says.

Reference

1. King NMP. Defining and describing benefit appropriately in clinical trials. *J Law Med Ethics* 2000; 28:332-343. ■

Special Series: Assessing Risks/Benefits

ASSERT statement offers guidance in trial design

Checklist aids in ethical evaluation

IRBs and investigators who would like an organized checklist of steps to take to ensure human subject protection and the highest ethical standards in designing clinical trials could look no further than the ASSERT statement.

Based on existing ethical requirements and guidelines, including the CONSORT (Consolidated Standards of Reporting Trials) statement, published in *The Lancet* in April 2001, the ASSERT statement, which stands for A Standard for the Scientific and Ethical Review of Trials, was created by **Howard Mann**, MD, program associate of the division of medical ethics at the University of Utah School of Medicine in Salt Lake City. Mann also is a radiologist at the University Hospital and Clinics in Salt Lake City.

"I was prompted to develop the ASSERT statement and the associated checklist after becoming aware of the CONSORT statement that addresses the reporting of clinical trials," Mann says. "Important items in the CONSORT checklist are included in the ASSERT's checklist."

The ASSERT statement addresses important, but neglected, aspects of randomized clinical trials, he adds.

Mann suggests that IRBs include ASSERT's requirements in their applications for research, but to keep in mind that ASSERT alone is insufficient guidance for IRBs in evaluating clinical research proposals. Here's a brief look at the ASSERT statement and the issues it raises:

• **Checklist table:** The on-line checklist provides links to longer explanations of an application section. **(See "ASSERT Checklist Table," p. 126.)**

(Continued on page 127)

ASSERT Checklist Table

Application Section	Item	Description
Social and scientific value — Background	1	Exposition of scientific background, rationale, and relevance. This should be referenced to a Systematic Review whenever feasible.
Trial registration	2	Details about trial registration and International Standard Randomized Controlled Trial Number.
Public dissemination of trial results	3	Plans for public dissemination of results; name(s) and affiliation of individuals responsible for results dissemination, including contact information.
Scientific validity — (items 4-12 are from the CONSORT statement) Participants	4	Eligibility criteria for participants.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, methods used to enhance the quality of measurements.
Sample size	7	How sample size was determined.
Randomization — Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).
Randomization — Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Randomization — Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, subgroup analyses, and adjusted analyses.
Fair subject selection — Recruitment of participants	13	Description of the populations from which participants will be recruited, including details concerning location, age groups, gender, ethnicity, and whether participants will be recruited from vulnerable groups.
Favorable risk-benefit ratio — Interventions offering the prospect of health-related benefit	14	Ordered enumeration and explication of research interventions offering the prospect of direct health-related benefits.
Interventions performed solely to answer the research question	15	Ordered enumeration and justification of interventions (invasive; measurement; data collection; surveys, etc.) performed solely to answer the research question and generate generalizable knowledge.
Clinical equipoise	16	Description and justification of control and experimental arms, including modes and dosages of drug administration. Reference the claim of clinical equipoise to an applicable Systematic Review whenever pertinent.
Respect for potential and enrolled subjects — Trial monitoring plan	17	Description and justification of a formal trial monitoring (safety and efficacy) plan. Details concerning a DSMB (if applicable), including names/affiliations of members and details concerning the stopping guidelines for the trial, and how they were chosen.
Communication of protocol changes and trial monitoring results	18	Details concerning the method and timing of transmission of protocol changes and trial monitoring results to research ethics committees.

• **Systemic reviews:** Referencing the Declaration of Helsinki, the statement supports systemic reviews in order to determine a proposed clinical trial's relevance, avoidance of duplication, and prevention of exposing human subjects to interventions that lack therapeutic efficacy.

The four main parts of a systematic review, according to the statement, are:

1. assessment of clinical value and relevance;
2. assurance of clinical equipoise;
3. assessment of significance of interim results analysis;
4. contextual reporting of results.

Also, systemic reviews may reference existing reviews found in the Cochrane Library or a review performed by an investigator involved in the trial, the ASSERT statement adds.

• **Outcomes and social value:** All members of an IRB are responsible for assessing a potential trial's social value, including relevant outcomes, according to ASSERT.

"Investigators may not evaluate pertinent and scientifically-relevant outcomes," Mann says. "An example is the inappropriate choice of surrogate outcome measures."

Important insights into social value may be gleaned from the input of consumers, patients, and laypersons, he says.

Also, a study's specified outcomes may not represent those that matter to patients, which is why it's important to have patient/consumer involvement in planning trials, Mann adds.

"Thus, IRBs should request investigators to justify their choice of outcome measures," he says. "A formal trial monitoring plan should indicate the manner in which outcomes will be assessed during the trial."

Often, trial protocols do not contain an assessable monitoring plan, Mann notes.

• **Disseminating trial results:** The public release of a study's results is a final step in the research process, and when investigators fail to disseminate scientific research results, this can have an adverse effect on published results of other trials, and investigators who fail to report their results are considered to have engaged in misconduct, the ASSERT statement says.

The statement identifies these precise ethical imperatives for the public dissemination of research:

— a judgment that the research meets the requirement of scientific and social value presupposes the public dissemination of results;

— justification for the inclusion of nontherapeutic interventions designed to answer the research question;

— avoidance of publication bias, which adversely affects clinical decision making and the utility of systemic reviews and meta-analyses of the published literature;

— honoring the altruistic motivations of patient-subjects who agree to participate in a clinical trial;

— entitling participants to know the results of the research their enrollment made possible;

— consistent dissemination with the duty to share new knowledge with colleagues, commonly found in professional codes of conduct.

• **Risk-benefit ratio:** ASSERT states that the design of a research protocol should maximize benefits and minimize risks to participants, and to do so requires IRBs and research ethics committees to conduct a systematic, nonarbitrary assessment of risks and benefits associated with the protocol.

In doing so, an IRB should make a distinction between therapeutic and nontherapeutic interventions, Mann says.

"The regulatory criterion of minimal risk, when applicable, should be applied to the nontherapeutic interventions," Mann says. "An IRB should be rigorous in ascertaining that clinical equipoise is present."

Quoting the Declaration of Helsinki, principle 29, ASSERT states: The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.

"Clinicians should consider the nature, magnitude, likelihood, reversibility, and timing of potential harms, when designing and evaluating research proposals," he explains.

(Editor's note: To see the entire ASSERT statement and checklist, visit the following web site: www.assert-statement.org/.) ■

Special Series: Assessing Risks/Benefits

Recent clinical trial deaths suggest imbalances

Troubles point to assessment problems

There have been some high-profile deaths of research participants in the past decade that have led to federal scrutiny of IRBs and their roles in protecting human research subjects.

Some of the studies in which people died clearly

show some problems with informed consent and an assessment of potential risks and possible benefits. Here's a thumbnail sketch of some of these cases:

• **Tony LaMadrid:** According to testimony given Sept. 18, 1997, at a meeting of the human subjects subcommittee of the National Bioethics Advisory Commission of Silver Spring, MD, LaMadrid died in 1991 after jumping off an engineering building. LaMadrid had been a participant in a schizophrenia research project at the University of California-Los Angeles (UCLA) in which a large percentage of participants suffered worsened symptoms a year into the study.

A father to another participant in the UCLA schizophrenia study testified that his own son lost intellectual functioning and became violent during participation in the same study. These negative outcomes were never discussed or revealed by researchers. "The researchers told us at that time that Greg might not even have to take antipsychotics medication, and it was recommended that he participate in the crossover and withdrawal protocol," testified **Robert Aller**, the father of research participant Gregory Aller.

Aller further stated that the study's consent forms were ambiguous, misleading, and contained no ranking or assessment of risks.

• **Kathryn Hamilton:** 48-year-old Hamilton chose to participate in a clinical trial, called Protocol 681, involving an experimental drug that she had hoped would help her survive a recurrence of breast cancer. The research was conducted at the Fred Hutchinson Cancer Research Center in Seattle.

However, in 1993, Hamilton became one of four study participants who died from the high-dose experimental treatment, according to media reports.

Hamilton's family told reporters that she had never been given adequate informed consent, including information regarding a change in how the drug was to be administered and disclosure that the drug already had caused one woman's death.

• **Gage Stevens:** A 3-month-old infant suffering from reflux, Stevens was enrolled in a clinical trial for Propulsid, a heartburn medicine that had only been approved for adults and had already been linked to heart problems and adult deaths. After being given Propulsid for four months, Gage died in 1999, according to media reports.

The physician who encouraged the baby's parents to enroll him in the Propulsid study did not disclose the potential risks or the deaths associated with the drug, and the consent form erroneously said the drug had been approved for use in infants, according to news articles. Hundreds of people have died from heart problems associated with Propulsid use, and the drug has been taken off the market.

• **Jesse Gelsinger:** Suffering from a rare genetic defect in the liver, ornithine transcarbamylase disorder, Gelsinger was enrolled in an experimental gene therapy at the University of Pennsylvania in Philadelphia. Gelsinger had not expected to receive any personal benefit from the therapy, but he volunteered so that future babies might receive a cure. The therapy resulted in the 18-year-old's death following a coma in 1999, according to news reports.

Gelsinger's parents say the young man had not been adequately informed of the health risks and that he had not been told of two previous volunteers who suffered from temporary liver toxicity, news reports say.

• **Ellen Roche:** A healthy volunteer in a Johns Hopkins University research study of asthma, Roche died in 2001 as a result of her research participation, according to a public statement by **Edward D. Miller**, MD, of Johns Hopkins.

A July 19, 2001, letter addressed to Baltimore-based Johns Hopkins, by the Office for Human Research Protections (OHRP), states that the study had used a toxic chemical called hexamethonium that is not approved by the Food and Drug Administration for use in humans and that the IRB did not ask investigators for any information about the pharmacology and toxicity of the inhaled hexamethonium.

The OHRP letter also says that investigators changed the research protocol without obtaining IRB approval and that the informed consent document, which was approved by the IRB, failed to adequately describe the research procedures. The informed consent even referred to hexamethonium as a medication, and the consent document did not adequately describe the research risks.

• **Nicole Wan:** A University of Rochester in New York student, Wan volunteered to participate in a research project that involved performing bronchoscopy on healthy individuals, according to a report from the State of New York Department of Health in Albany.

Wan died two days after the bronchoscopy from lidocaine toxicity, and blood level tests taken at the time she was brought into the emergency room indicated that she apparently had received four times the amount of lidocaine during the procedure than the maximum dosages established in previous research protocols, the

New York Department of Health states.

In addition, the research protocol had no mechanism in place to limit the amount of lidocaine available during the procedure, and there was no documentation of the amount of lidocaine administered, all suggesting that IRBs should take an active role in ensuring researcher compliance with regulations and laws involving human subject protection, the report says. ■

SPOTLIGHT ON COMPLIANCE

Improved clinical care or medical research?

Defining research comes under court scrutiny

By **J. Mark Waxman**, JD
General Counsel
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A key issue in determining whether IRB review is necessary is whether the program in question is, in fact, research. While at least one federal regulation defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge" [45 C.F.R. §46.102(d)], the application of the definition provided by the regulation is not always clear.

One recent appellate case, *Ancheff v. Hartford Hospital,* [260 Conn. 785, 799 A 2d 1067 (2002)], illustrates how tricky the challenge of determining whether a program to simply improve medical care is ongoing clinical activity or medical research can be.

In *Ancheff,* a plaintiff alleged that Hartford Hospital's program of administering gentamicin could be considered research and therefore should have undergone IRB review, which would have included the informed consent process that would have outlined the risks, benefits and alternatives. The fact that the program did not undergo IRB review violated the applicable standard of care for research activities, the plaintiff alleges.

The facts regarding the gentamicin program in question were presented by the plaintiff as follows:

1. The program administered a dosage that had not previously been tested on humans and departed from the conventional dosage approved by the Food and Drug Administration.
2. At the time of the treatment in this case, the hospital was the only hospital in the country that prescribed the dosage involved to entire classes of patients.
3. The method of administration was not conventional.
4. The data collected on each patient were maintained apart from what was kept on the medical record.
5. The program was advertised as a "radical change" from standard dosage and administration of the drug.
6. The physicians responsible for enacting the program lectured to the medical community on their findings from the program.

In response, the defendant, Hartford Hospital, pointed out that:

1. The program had been widely studied for many years.
2. The program was approved by the appropriate hospital departments (e.g., infectious diseases, pharmacy, therapeutics committee, and the hospital's medical executive committee prior to its initiation).

Based upon these facts, the ultimate issue in the case was what was the appropriate standard of care, and did the hospital follow it. Resolution of this turned on the issue of whether the hospital was required to secure a written consent from the plaintiff because the gentamicin program of administering the medication constituted medical research. The jury found for the hospital — thereby concluding that the program was not a research program, a decision affirmed by the appellate court.

In supporting the jury's conclusion, the court was seemingly persuaded by several factors. First, it viewed its mission as primarily to determine whether there was adequate evidence to support the court rulings and the jury verdict. Given that expert testimony declared that the program was not research, there was ample evidence in the record. Inherent in this approach was the conclusion that whether the program fit within the definition of medical research was a fact-based question, and not a legal conclusion to be determined by the court. This also meant it was a determination for lay individuals to make, and not solely by experts or the hospital's administration.

Second, in reviewing the evidence presented at the trial, the Court noted that the evidence

submitted by the hospital "tended to prove" that the program did not constitute medical research. In its recitation of the facts, several appeared to be critical and may have been perceived by the jury as ensuring adequate patient protection, even without the IRB-related processes. Specifically, the Court referenced the hospital departments, committees, and physicians who, based on voluminous data, determined that clinical improvement, and not medical research, was the goal of the program.

Third, again in highlighting the facts presented by the hospital, the Court noted that the program was not implemented to test the drug's safety, but directly to improve patient outcomes, and was "at least as safe and more effective than daily dosing."

Finally, it appears that the fact that standard research processes such as control groups, randomization, and blinding were not employed was also an important factor in the outcome. There was no specific analysis, however, of the implications of data collection and retention separate and apart from the patient's own medical record, and the ongoing and public dissemination of the program's results. Each of these factors could well have been interpreted to provide ample evidence of systemization of the process with the goal of contributions to generalized knowledge, but the jury apparently was not convinced that these elements made the gentamicin program research. Similarly, it is quite possible to visualize situations where the interest of the physicians is to do research, but avoid the perceived costs, burdens, and insight, and delay of the IRB process that must be the subject of the patient protection framework.

Whether the same result would obtain in similar cases is hard to predict. The case does, however, reaffirm that:

1. Every new procedure or advanced treatment program implemented by a hospital is not automatically research.
2. The fact that the results of these efforts will be publicized to others to advance medical treatment will not in and of themselves make such efforts automatically subject to the IRB processes.
3. The hospital may be significantly protected from liability exposure where nonresearch new or advanced programs or procedures are implemented as the product of an in-depth record of decision making by qualified physicians and hospital committees. ■

IRB review may include financial connections

IOM report says ethics demand IRB involvement

The Research Revitalization Act of 2001 introduced by Sen. Edward Kennedy (D-MA) in October addresses among other things financial conflicts of interest involving researchers. Though there are no federal laws that mandate that IRBs collect and evaluate the potential impact that financial conflicts of interests may have, the bill Sen. Kennedy introduced and a recent Institute of Medicine (IOM) report recommend that such an evaluation become a critical element in ethics and human subject protection.

"A central tenet in the protection of research participants is the independent review of research protocols to assess their scientific merit and ethical acceptability. It is also critical to consider whether conflicts of interest on the part of the investigator, the Research ERB [Research Ethics Review Board — IOM's proposed new name for IRBs], or the institution place research participants at undue risk," the report states.

Specifically, the IOM report advocates that IRBs be aware of financial connections between principal investigators and sponsors or institutions and sponsors so that they can evaluate: 1) whether the connection has the potential to impact participants; and 2) whether the connection should be disclosed to participants.

According to the U.S. Public Health Service (PHS), "a conflict of interest exists when a significant financial interest could directly and indirectly affect the design, conduct, or reporting of research."

Not everyone is anxious to take on this role, as some IRB members believe they are already overextended. Says **Erica Heath**, MBA, CIP, president of IRC, an independent IRB in San Anselmo, CA, "As the IOM noted in its lengthy report, many jobs have been given to IRBs, many of which the parent institution is better equipped to handle.

"Most institutions have organizationwide policies and protections in place and separate committees to review potential conflicts," she points out.

Given the two bills introduced in Congress this year — Kennedy's bill and the Human Research Subject Protections Act of 2002 (HR 4697), introduced in May by Rep. Diana DeGette (D-CO), IRBs may want to go ahead and develop a protocol for assessing financial conflicts of interest. To ensure that financial connections do not impact

how a study is conducted or results reported, PHS recommends that IRBs do the following:

• Obtain information on financial interests held by the institution and/or investigators involved in the study. **(See "Questions to Assist in Evaluating Financial Conflicts of Interest," right.)**

"Under current regulations, research institutions are formally responsible for developing and communicating a process for reviewing, authorizing and monitoring arrangements that prevent conflicts of interest," **Robin N. Fiore**, PhD, assistant professor of philosophy at Florida Atlantic University in Boca Raton, points out. "However, the specifics have been left up to each institution, and vary widely."

Fiore cites a 2001 General Accounting Office (GAO) review of conflict-of-interest disclosure and management policies and procedures at major universities receiving substantial funding from NIH [National Institutes of Health] for biomedical research and having a high degree of technology transfer activity. "The GAO was critical of the degree of variation and laxity permitted by the current discretionary approach, finding that the ability of institutions to perform the requisite oversight is subverted by institutions own commercial relationships," she says. "Under the new HHS [U.S. Department of Health and Human Services] guidance, such information is to be formally shared with the IRB, and the IRB is now responsible for evaluating its relevance for the protection of human subject-participants and for considering changes to protocols and consent documents."

• Disclose financial interests held by IRB members.

"In addition to disclosing financial conflicts of interests, IRBs should have written policies regarding recusal and the IRB chair, members and staff should recuse themselves accordingly," Fiore says. "The most effective means of protecting the integrity of the IRB process is to have the broadest possible participation of members from outside the institution to assure its independence."

• Make financial conflicts of interest part of any educational programs that exist to train participants in human research protections.

"Education on how to assess and to mitigate the impact of financial interests is essential responsible conduct of research training for all who are involved in the research enterprise: investigators, staff, institutional officials, IRB members, vendors and contractors," says Fiore. "There are a number of initiatives aimed at making the training available at major academic research centers available to others on a cost-effective cooperative basis." *(Editor's note: CITI, the University of Miami's Collaborative IRB Training Initiative, is one such program.See* IRB Advisor, June 2002, p. 67.)

• Ensure that financial interests are disclosed in the informed consent document.

"Without complete information about the risks of participation, including the possibility that financial interests of the investigator might influence their clinical judgment, robustly ethical

Questions to Assist in Evaluating Financial Conflicts of Interest

- Who is the sponsor?
- Who designed the clinical trial?
- Who will analyze the safety and efficacy data?
- Is there a Data Safety Monitoring Board?
- What are the financial relationships between the clinical investigator and the commercial sponsor?
- Is there any compensation that is affected by the study outcome?
- Does the investigator have equity interest in the company — publicly held company or nonpublicly held company?
- Does the investigator receive significant payments of other sorts (e.g., grants, compensation in the form of equipment, retainers for ongoing consultation, and honoraria)?
- What are the specific arrangements for payment?
- Where does the payment go? To the institution? To the investigator?
- What is the payment per participant? Are there other arrangements?

Source: Office of Human Research Protections, Washington, DC.

COMING IN FUTURE MONTHS

- Controversy arises over smallpox vaccination and IRBs' roles in approving use
- Council for International Organizations of Medical Sciences (CIOMS) issues its revised guidelines
- A comparison of IOM and CIOMS recommendations for IRBs
- The role of Data Safety Monitoring Boards

consent is unobtainable," Fiore says. "Some argue that disclosure merely confuses or disturbs subject-participants and that efforts ought to be aimed at reducing or eliminating the conflicts themselves." ■

CE/CME objectives

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

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

CME*questions*

17. Which of the following points is not one of the recommendations of the Institutes of Medicine's *"Responsible Research . . ."* report issued in 2002?
A. All human subjects research, regardless of funding source, should be required to meet human subjects protection regulations.
B. Conflicts of interest review should be handled by an entirely outside board that has the authority to reject proposed research based on its findings.
C. IRBs should have their names changed to Research Ethics Review Boards.
D. Informed consent should be an ongoing process and dialogue between human participants and investigators.

18. The ASSERT statement, which is an organized checklist of steps to take to ensure human subject protection and the highest ethical standards and which was created by Howard Mann, MD, identifies which of the following ethical imperatives for public dissemination of research:
A. A judgment that the research meets the requirement of scientific and social value pre supposes the public dissemination of results.
B. Justification for the inclusion of nontherapeutic interventions designed to answer the research question.
C. Avoidance of publication bias, which adversely affects clinical decision making and the utility of Systemic Reviews and Meta-Analyses of the published literature.
D. All of the above

19. In the case *Ancheff v. Hartford Hospital* referenced in Spotlight on Compliance, which of the following was affirmed by the court's decision?
A. Every new procedure or advance treatment program implemented by a hospital is not automatically research.
B. The method of administration was not conventional, which, in effect, turned the treatment program into research.
C. The program departed from the conventional dosage approved by the FDA, which, in effect, made the protocol research.
D. None of the above

20. PHS recommends that IRBs do the following to ensure that financial connections do not impact how a study is conducted or results reported:
A. Disclose financial interests held by IRB members.
B. Obtain information on financial interests held by the institution and/or investigators involved in the study.
C. Ensure that financial interests are disclosed in the informed-consent document.
D. All of the above