IRB ADVISOR
Your Practical Guide To Institutional Review Board Management

THOMSON
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Experts on IRB education offer ideas and tips for improving member training

Washington University program wins award

Most IRBs long have provided education and training to IRB members; but in recent years, IRB members' education has become a top priority for some boards.

Education of IRB members is such a priority at Kaiser Foundation Research Institute (KFRI) of Oakland, CA, that KFRI recently published a 150-page book about human subjects protection and informed consent for IRB members, says **Jeffrey Braff**, DrPH, director of KFRI.

IRB education also is an integral part of the human subjects protection program at Washington University School of Medicine in St. Louis, where the human studies committee received a 2002 Award for Excellence in Human Research Protection for its comprehensive education program geared toward IRB members and researchers.

For the past two years, the Washington University program has had a full-time education specialist. "They really wanted to beef up their education program, and that happens to be my background," says **Sarah Frankel**, PhD, education specialist.

Washington University has 14 IRBs, more than 300 IRB members, six new protocol committees, four continuing review committees, four subcommittees, and staff to assist with minimum-risk protocols, Frankel says.

"We have had IRB members here for years, and some others will go through the orientation and realize it's not for them," she says. "We also have a mock IRB that has been held twice and is open to the Washington University community and to people who could become committee members."

Even smaller institutions can stress education among IRB members, especially as federal agencies increasingly see this as an important way to enhance human subjects protection, says **Carole Ehleben**, EDD, senior partner with Consultants for Evaluation and Applied Research in Norcross, GA.

"I do think this is a topic that's going to become more important,"

Ehleben says. "I work with community hospitals, and we have set up a resource of listings that are passed down to IRB members as an introduction packet."

The packet lists web sites for on-line training, web sites for the Office of Human Research Protection, information sheets from the Food and Drug Administration, federal regulations regarding human subjects protection in research, and periodicals about IRBs and human subjects protection, Ehleben says.

The Goodwyn IRB in Cincinnati has IRB members who are geographically spread apart, so education is handled via the Internet, as well as through an annual 2½-day retreat, says **Ellen Holt**, CIP, managing member and administrative vice chair.

"We give ourselves enough time to do it right, and there's a big educational opportunity there," she adds.

Here are some tips on improving an IRB's educational system:

1. Thoroughly train new members and train as you recruit. All IRB members receive a thick book about the process of informed consent at Kaiser Foundation Research Institute, Braff says.

The book, created with funding from the National Institutes of Health (NIH), is provided to the various IRBs as one component of IRB member training and education. Each IRB also may supplement the education in various other ways, Braff says.

At Washington University School of Medicine, new IRB member orientations are held once a month. "Members are introduced to some of the major areas they will have to discuss, and they'll discuss these as if they are at a committee meeting," Frankel explains. "There are three types of committees, including new protocols and subcommittees, and the information new members receive pertains to their own committee."

This gives new members an opportunity to gain insight into the process of sending protocols through a committee review, she says.

The institution also has started an orientation for people who are new to research or new to submitting a protocol, Frankel says. "It's a basic workshop that lets them know how to check on a protocol, which ones to renew, and what happens during the year. Researchers may also attend a workshop for IRB members because they want to see the other perspective."

Washington University holds a mock IRB meeting for potential IRB committee members. "It's like a new-member orientation for people who are not committee members, and they can be taken through the process for submitting a protocol," Frankel says.

The mock protocols are based on real protocols that have been changed and reprinted with the permission of the researchers.

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Editorial Questions

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Call **Alison Allen** at (404) 262-5431.

Ehleben has a template for IRB member education, and it includes an IRB submission booklet that includes references to regulations.

Along with IRB chairpersons, Ehleben will sit down with each new IRB member to answer questions and explain the packet's information.

2. Educate in a variety of ways. Washington University varies educational sessions, using some special half-day sessions, conferences, web site education, and other ways to give IRB members information. The basic topics covered include the following:

- expedited and exempt protocols and whether studies are minimal risk;
- all informed consent issues;
- data monitoring;
- regulations and guidelines;
- vulnerable populations, including prisoners and minors;
- use of autopsy materials;
- participant screening;
- literature summaries;
- ethical discussions;
- third parties' interest in research.

"We do a monthly inservice for staff, and it could be on professional development, providing them with information so they can help people submitting protocols," Frankel says. "Once the staff become more knowledgeable, then we have them do education as well."

Each KFRI IRB may devote up to 30 minutes to education at each meeting, Braff says.

"We have a portion of the IRB meeting that is devoted to the education on salient topics and is left to discussion by the IRB chair and the administration at each of the IRBs," Braff reports. "There are nine IRB meetings in eight regions, and each has a biomedical and health services panel."

Small hospital-based IRBs can provide educational information through the Internet, as well as at meetings through the introduction of 15-minute topics for discussion, Ehleben says.

Members of Goodwyn IRB will receive updates and reminders about federal regulations as part of their materials distributed with protocols, Holt says.

"We put together pieces of information that address various items, such as what are the considerations of these regulations or of these populations," she explains.

Whenever there is a change or new event on the human subjects protection horizon, Goodwyn IRB members will receive up-to-date information about it, Holt adds.

3. Use educational conferences or forums. KFRI holds an annual IRB leadership conference where IRB administrators and chairs come together to discuss issues of interest and importance, changes in rules, regulations, and specific events that have impacted the IRB community within the previous year, Braff says.

For an IRB that has members who live in various parts of the country, an annual, weekend educational retreat is the most efficient and easiest way to update members on human subjects protection, Holt says.

Washington University holds a conference each year, sometimes hosting national conferences that include information on regulatory agencies or regional conferences that are cosponsored by research organizations. Topics may include research and privacy regulations and compliance topics, Frankel says.

The institution also makes good use of forums. "Forums are very instructional and help the reviewer know what to look for in protocols," she says.

IRB chairs are sent to human subjects protection conferences sponsored by other organizations, and they are expected to bring the information back for the benefit of fellow IRB members, Frankel adds.

4. Provide opportunities for questions and answers. Making time for questions and answers also is an important part of educating IRB members. When someone asks Frankel or an IRB chairperson a question, they will provide answers to both the individual and the entire IRB, when this is appropriate.

"I attend the committee meeting and talk about specific issues," Frankel says. "What I might do is talk about how to assess risk, and we go through some examples of what would be greater than minimal risk."

The IRB members would discuss a particular protocol and use examples from it to discuss and identify greater than minimal risk.

It will encourage IRB members to ask questions when educational sessions are kept small — with fewer than 30 attendees, Frankel adds.

The goal is to make the educational session conducive to question-asking, and this means paying attention to the time of day that the session is held and making sure it's a convenient time for members, Frankel says.

"We found that if we have a longer session, people like it to be on Friday afternoon," Frankel says. "Also, early mornings are very good if they're held before people go into their office."

The worst time is in the middle of the day, and don't worry about providing a meal or snacks because food does not attract attendees, Frankel notes. ■

Accreditation is not for the faint of heart

IRBs give lowdown on what to expect

With the first non-Veterans Affairs (VA)-affiliated IRBs now achieving accreditation, IRB coordinators may have their clearest look so far at how the process has worked and what might be gained from jumping into the accreditation waters.

The Association for the Accreditation of Human Research Protection Programs Inc. (AAHRPP) of Washington, DC, announced late spring the names of three research organizations that were the first to be accredited. These were the Western Institutional Review Board (WIRB) of Olympia, WA, the University of Iowa in Iowa City, and the New England Institutional Review Board in Wellesley, MA.

The Partnership for Human Research Protection, which is a partnership between the Joint Commission on Accreditation of Healthcare Organizations of Oakbrook Terrace, IL, and the National Committee for Quality Assurance of Washington, DC, has begun the process of accrediting IRBs, but no announcements were made as of early August.

According to the people who gathered information, organized changes, and met with AAHRPP site visitors during the accreditation process, there are two words that aptly describe what IRBs seeking accreditation might expect: enormous undertaking.

"Other IRBs applying for accreditation should be aware that it is an enormous undertaking, and planning appropriate resources is critical," says **Erin Thacker**, MS, CIP, lead administrator for the New England IRB.

Nearly a year before becoming accredited, the University of Iowa hired a full-time IRB co-chair, whose job entailed putting together the AAHRPP application, reports **Trish Wasek**, CIP, director of the human subjects office.

At WIRB, an accreditation task force, consisting of the director of human resources, the chief financial officer, and a senior vice president led a team that spent several months preparing the accreditation application, says **Angela Bowen**, MD, president.

Here is an inside look at how these institutions prepared and succeeded in achieving full accreditation:

• **Completing the application and preparing for site visit.** The application process is time-consuming and requires a heavy load of files to be sent to AAHRPP. "We had sent in six copies of almost everything," Bowen says.

Besides putting one person in charge of completing the application, the University of Iowa held a major administrative meeting of the institution's two IRBs. "We told all of the IRB members a little bit about AAHRPP, and we gave everyone electronically a copy of the application we had submitted," Wasek says.

"We went through a preliminary version of the site visit schedule and told people that certain IRB members would be interviewed, although we didn't know who would be selected by site visitors," she says.

"Also, we gave them some background information and gave them a rough outline of what to expect during the visit," Wasek adds. "I think people had a lot of confidence in what we were doing."

The institution sent the accreditation application electronically and in a paper version, and the application included a thick set of additional documents, including IRB meeting minutes from the previous year, the institution's standard operating procedures, a list of currently active protocols, consent application templates, monitoring reports, memos to IRB members, approval letters and memos to investigators, and just about anything else that was documented by the IRB office, she says.

IRB staff also assessed whether any of its current processes and policies needed updating or changing, and they decided that they could enhance the information that's available for participants in research, Wasek says.

"We added a good deal of information on our web site for the public," she says. "We also developed a brochure with general information about participating in research, and we placed it in public locations all over campus, including the library," Wasek says.

Once the application was complete, it was about six weeks before the IRB heard from AAHRPP, and then the organization worked with the IRB to schedule a site visit for January 2003, she adds.

Since the University of Iowa IRB staff knew that the accreditation site visitors also would interview researchers, they sent a mass mailing to about 1,000 principal investigators, telling them about the accreditation application, Wasek says.

"We told them it was possible they'd be selected as one of the researchers the site visit team would interview on a rather short notice," she explains.

• **Surviving the site visit.** The site visit included four accreditation officials plus the deputy director of AAHRP, Wasek says.

The site visitors gave the IRB staff a list of active protocols that they wanted to review, she says.

"Half a day of the site visit was spent reviewing files," Wasek adds.

"I met with them for about 45 minutes, and the accreditation team split into two teams, so there were simultaneous interviews going on," she explains. "We had a very pleasant interview, talking about how our office operates and about the similarities between how we process biomedical applications and behavioral research applications."

It was clear to Wasek that the site visitors had reviewed the volumes of information sent with the application, and she says she felt her role was to explain everything in more detail, including how certain aspects of the IRB review process works.

For example, the University of Iowa IRBs hold two full board meetings per month on continuing review applications. Other institutions may do this differently, so Wasek explained to the site visitors specific details of how the IRBs handle continuing reviews.

Six accreditation site visitors spent four days at WIRB, reviewing files and interviewing department heads, Bowen says.

During Bowen's interview, the site visitors asked about her career and how she manages the business affairs, Bowen recalls.

They were particularly interested in the types of systems she uses to manage WIRB. "They were asking, 'How do you keep up with whether there's a quorum at the board?'" she says. "They asked how the board members are performing, how the staff are performing, and how I make sure everything is done within the regulations."

Most of the 100 or so WIRB members were interviewed by the site visitors, although some of the members who are located in Canada and California were interviewed by teleconference, Bowen notes.

WIRB had notified investigators and sponsors in advance that they might be interviewed as part of the accreditation process, so everyone who was contacted knew what to expect. Although the site visit interview is a time-consuming and intrusive process, all of the people who were interviewed responded very well to it, she says.

• **Debriefing IRB members and staff.** The New England IRB held an informal debriefing session with IRB members and staff after the site visit was completed, Thacker says.

"The outcome of the survey was discussed, as well as everyone's opinion of the overall process, including the site visit and member interviews," she says. "Everyone felt as though they had learned from the process, including increasing their own personal knowledge base, as well as learning about AAHRPP's mission and how it has helped to improve our organization."

IRB members expressed satisfaction with how they had done, and they were not surprised to learn that the IRB had excelled in most areas examined during the accreditation process, Thacker says. "Everyone concurred that the level of review provided by NEIRB reflects our commitment to the protection of human research subjects."

As a part of the New England IRB's commitment to continuous quality improvement, the IRB recently has developed a national site visiting program and an investigator self-training CD, as well as having expanded its quality assurance and quality improvement program, she adds.

• **Reaping accreditation rewards.** After receiving word at the end of April 2003, of the board receiving full accreditation, WIRB staff and board members celebrated with a big cake and coffee, Bowen says.

Also, Bowen gave each staff person and board member a plaque that announced that person's contribution to the pursuit of accreditation.

Better yet, the Washington state legislature gave WIRB a proclamation, stating support of the IRB's having received accreditation, Bowen notes.

Achieving full accreditation has resulted in other benefits, as well. For example, some of WIRB's research sponsors have been willing to accept the IRB's accreditation as sufficient evidence of the IRB being in full compliance, and so they have not conducted audits as they had in previous years, she says.

"We do some portion in or in some cases all of the IRB work for some 80 institutions, and it was quite reassuring for the institutions for us to have public evidence of our adherence to proper process," Bowen reports.

When the New England IRB received word of

full accreditation on May 30, 2003, the IRB held a small celebration and issued a press release announcing the good news, Thacker says.

"Many [of the staff] also expressed pride that our organization had decided to pursue the voluntary accreditation, as the accreditation provides NEIRB with a sense of distinction," she says. "For those directly involved with putting together the application, there was a feeling of relief as well as of fulfillment." ■

Now the real work begins: Maintaining accreditation

IRBs describe how they plan to stay accredited

Preparing for an accreditation site visit is difficult enough, but the hard work doesn't end after an IRB receives a letter announcing that it has been fully accredited, according to the first IRBs to receive full accreditation from the Association for the Accreditation of Human Research Protection Programs Inc. (AAHRPP) of Washington, DC.

"I would advise others to be aware that the accreditation is an ongoing process and that resources are needed for the implementation of new policies and procedures, and for educating members of the organizations of these new policies," says **Erin Thacker**, MS, CIP, lead administrator for the New England Institutional Review Board (NEIRB) of Wellesley, MA.

The hard work also doesn't end with the site visit. The four-day visit typically has an exit interview and is followed by a letter sent to the IRB in which AAHRPP details suggestions for improvements in the IRB's processes and policies.

Following the New England IRB's site visit, AAHRPP wrote the IRB, detailing recommendations and findings that had first been discussed during the exit interview, Thacker says.

"None of the changes requested by AAHRPP were unexpected, and the exit interview had prepped NEIRB to begin to develop strategies to comply with AAHRPP's recommendations," she says.

One change, for example, was recommendation that NEIRB address the reporting of unanticipated problems that may occur during a clinical trial, Thacker recalls.

"In order to address this, NEIRB created a definition of an unanticipated problem and developed examples of what might constitute an unanticipated problem," she says. "SOPs were developed for the reporting, tracking, and handling of these reports."

IRB staff also notified investigators, staff, and members about the new reporting requirement, she adds.

"AAHRPP's recommendations also included suggestions that resulted in further development of our policy regarding exculpatory language in the consent form and for monitoring the consent process," she says.

For instance, NEIRB staff further developed the policy about exculpatory language to provide examples of language that is considered exculpatory and, therefore, would not be allowed in a consent document, Thacker says.

"NEIRB's policy regarding monitoring or witnessing of the consent process was further developed to address situations in which NEIRB may decide to witness the process and the mechanisms for conducting the observation, as well as any corrective actions that might need to occur," she reports.

After AAHRPP site visitors spent four days at the University of Iowa in Iowa City, reviewing IRB records and interviewing IRB staff and members, AAHRPP sent the institution an initial report to which the IRB staff could respond within 30 days, says **Trish Wasek**, CIP, director of the human subjects office.

"They went through all of the criteria in that report, and they made comments and wanted us to correct any factual errors," she says. "And if there were any recommended changes, we could respond with our plans for implementing those changes."

Any changes the IRB made within those 30 days would be included in AAHRPP's consideration for the final determination on accreditation, Wasek says. "Nothing in the draft report was a surprise because we had a detailed exit interview in which the leader of the accreditation team went through, point by point, all of the standards with us."

All of the suggestions were minor items, such as suggestions for adding more questions about the consent process to the protocol application form, she notes. "We did make a change in the way we conduct our continuing review."

"We felt we had a very strong program going into this, so the suggestions were not a problem for us," Wasek adds.

Once an institution receives full accreditation,

the IRB must submit an annual report for each of the three years that the accreditation is valid, and at the renewal time, the IRB must submit an updated version of the initial application to AAHRPP and schedule another site visit, Thacker says.

"The most important program that NEIRB has implemented in order to remain prepared for the next survey is an expanded internal quality assurance and quality improvement program," she adds.

The program enables NEIRB to continuously examine its policies and procedures, improve areas of weakness, and fine-tune any areas that need improvement, Thacker says.

"In addition, NEIRB's educational program for staff and members has been expanded," Thacker adds.

For instance, staff members who are particularly knowledgeable in certain areas have been encouraged to develop inservice programs for the rest of the staff, Thacker explains.

"In order to be prepared for our annual report, NEIRB continuously tracks areas in which new policies are being implemented and records the implementation of the new policies," Thacker says. "This compilation will allow NEIRB to have a solid framework for the submission of our annual report, requiring less resources to be utilized at the time of the submission of the annual report." ■

SPOTLIGHT ON COMPLIANCE

The VA's handbook for IRBs is good reference

By **J. Mark Waxman**, JD
General Counsel
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A handbook for IRB members sets forth the policies of the IRB, and serves as a reference and working guide for members as they review protocols and carry on their work. Those looking for a guide or benchmark for such a handbook should review the Veterans Health Administrative Handbook published July 15, 2003. Although parts of the handbook relate specifically to Veterans Affairs (VA) formats and structures, the approach, definitions, and processes provide important reference points and valuable guidance.

This article provides an introduction to the Handbook and highlights several of the important comments and processes in the handbook:

• **IRB composition.** IRB composition is the subject of general regulatory rules (38 CFR § 16.107). The handbook identifies a process for appointment, which the regulations do not address. First, IRB members and Research & Development Committee members may forward names to the Medical Center Director. If others have recommendations, they must nevertheless forward them through the IRB or R&D Committee. Second, members are appointed by the Director for a period of three years, and may be appointed indefinitely. Finally, the Director appoints the Chair for a term of one year, who may also be reappointed indefinitely.

• **IRB authority and review criteria.** The handbook carefully sets forth the rules and requirements regarding IRB authority and review criteria. Several elements of the process are noteworthy. First, in determining the reasonable risk benefit ratio, the IRB is directed to consider the risks and benefits related to both biomedical research and nonbiomedical research. On the other hand, the IRB is directed not to consider "possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research or public policy) as among those research risks that fall within the purview of its responsibility."

Second, the handbook states that the IRB, as opposed to some other Institutional official, is to ensure that steps relative to either potential or real conflicts of interest have been taken.

Finally, the handbook specifically addresses the IRB duty with respect to the principal investigator, the investigator educational requirements, and necessary certification. The IRB must affirmatively determine that the investigator(s) is / are qualified through education, training, and experience to conduct the research. To meaningfully perform this task, the IRB submission would, of course, need to specifically require this information, as well as an assessment of actual experience in the area to be researched.

• **IRB processes and procedures.** The handbook addresses a series of important process topics

including initiation of the research, communications with investigators, the written processes for ongoing IRB operations, audits, quorum requirements, ongoing project monitoring processes, and the procedures with respect to IRB records.

The handbook requires the following:

— If research is approved contingent on modifications or clarifications to the protocol, or the informed consent, the approval of the research must not and cannot occur until the subsequent IRB review.

— If approval is contingent on "specific minor conditions" (a term it might be helpful for the IRB itself to define further), the research may not begin until those conditions are met.

— The listing of necessary written IRB procedures, including procedures for reporting changes in research activity, reporting noncompliant activity, ensuring that education requirements for the IRB are met, and for suspension or termination of IRB approvals.

— Quorum requirements, and the clear statement that all IRB votes require the presence of a quorum. The handbook, however, does allow teleconferencing or video conferencing member participation.

— If continuing review does not occur within the required timeframe, the research is automatically suspended. This means new enrollments are not permitted and the research itself can only continue if there is a specific finding by the IRB or its Chair that it is in the "best interests" of the subjects to continue their participation for suspended research to resume, full IRB review and re-approval is required;

— IRB minutes must be completed within three weeks of a meeting date. The minutes must, in addition to documenting attendance on required findings, contain a summary of "controversial issues" and their resolution.

• **Surrogate consent and vulnerable populations.** The handbook notes that "under appropriate conditions," consent may be obtained from a legally authorized representative. The handbook authorizes patient appointed "health care agents" pursuant to a Durable Power of Attorney, with appointed guardians or next of kin in a defined order of priority, unless otherwise specified by state law: spouse, adult child (defined as 18 or older), parent, adult sibling, grandparent, or adult grandchild.

The process to determine when surrogate consent may be obtained is also set forth. The handbook also provides that if it is feasible, the attempt must be made to explain the proposed research to the subject. If the subject then refuses to participate, the research may not proceed with that subject.

Of course separate requirements exist when vulnerable populations are involved. The handbook addresses such populations in a specific Appendix, which contains its own set of definitions.

• **Payment for subjects.** The handbook addresses payment for subjects, initially mandating that no payments may be made to participate in research when the research is integrated into the patient's care and make no "special demands." Payment may, however, be made if there is no direct subject benefit and the standard in affiliated non-VA institutions is to make a payment; others in multi-institutional studies are being paid; in other comparable situations, payment is appropriate; and it is appropriate to compensate for transportation costs.

In every case, the amounts must be substantiated as fair, and do not represent undue pressure or influence.

• **Investigational services and drugs.** The handbook details the rules applicable to investigational devices and drugs. A readable discussion of the applicable rules is presented, with concise definitions of both an investigational drug and an investigational device. The FDA regulations to the general requirements for informed consent to use an investigational drug are set forth as:

— a life-threatening situation, necessitating the use, when effective consent cannot be obtained, and there is no available alternative likely to save the life of the subject [21 CFR § 50.23 (a)];

— if immediate care is required to preserve the subject's life and the time available is not adequate to obtain an independent determination [21 CFR § 50.23 (b)].

The IRB must be notified within five working days when an emergency exemption is used. Where devices are involved, similar requirements must be met.

Devices differ from drugs in that they must be evaluated at the outset to determine whether they represent a "significant risk." Where the study of the device is not exempt, then those devices posing significant risk must be fully compliant with the FDA's Investigational Device (IDE) regulations (21 CFR Part 812). It is noteworthy that for IRB approval purposes, all significant risk studies are considered by the FDA to pose greater than minimal risk. ■

Study finds conflicts of interest pollute science

Widespread financial ties permeate field

With nearly two-thirds of biomedical research funded by industry, it is perhaps not surprising that there are financial conflicts of interest between companies, investigators, and universities. A study published in the *Journal of the American Medical Association* in January quantifies it and discusses its impact.[1] The results: There is more than we would like, with more influence than is good.

In some respects, the influx of private money into biomedical research has been great, note the authors — there have been medical advances and impetus for further research. However, many studies, they say, have indicated that close ties between scientists and industry may compromise the integrity of research.

The article included 37 studies that looked at the extent and impact of financial relationships. Eleven of them determined that industry-sponsored research tends to yield pro-industry conclusions.

The lead author, **Justin Bekelman**, MD, an intern at Johns Hopkins Hospital in Baltimore, says that there could be many reasons for this. "Some suggest that publication bias in the literature — positive studies are published more often — contributes to this finding."

Part of the publication issue is that pharmaceutical companies that experience negative results don't send in those studies for publication, says the former editor of the *New England Journal of Medicine*, **Jerome Kassirer**, MD, a distinguished professor at the Tufts University School of Medicine and an adjunct professor at Yale's medical school. But the critical question with any study sent for publication isn't whether it's positive or negative, but whether it will make a difference.

"If a study says that the treatment with a new and unused drug doesn't work, why publish it?" he asks. "What you care about is whether a study changes practice." Recent studies on hormone replacement therapy can certainly be construed as negative, yet because they changed the practice of medicine, Kassirer says, there was no question that they would be published.

But positive results can't only be the result of publication bias. "We have found evidence of a funding effect," says **Sheldon Krimsky**, PhD, a professor in environmental and urban planning and policy at Tufts University who has written extensively on financial conflicts of interest in science. "That means that on a population scale, not on a one-to-one determinative scale, we see that privately funded research tends toward the values and interests of the funder."

Take any group of studies on the same topic, and as a group, those that are funded privately would be more positive toward the people providing the money than those that don't rely on that money.

Bekelman also notes the impact of industry on trial design, and four of the studies analyzed in his article look at that topic. "We found that industry tends to sponsor trial designs that favor pro-industry results," he says. For example, in one analysis of multiple myeloma trials, industry-sponsored studies were substantially more likely to use placebo controls than were nonindustry-sponsored studies. "The authors of this study also found that the use of placebo controls increased the likelihood of positive study results. One of the fundamental ethical principles of medical research is that there needs to be uncertainty about which treatment is better. Otherwise, it's not fair to ask patients to volunteer for studies if you already know that one treatment is inferior."

Another issue raised in Bekelman's article involves financial conflicts of interest between researchers and sponsoring companies. One of the studies looked at how institutions dealt with financial conflicts of interest and found that among 250 institutions, management of conflicts and penalties for nondisclosure were almost universally discretionary. Only one of 10 research-oriented medical schools prohibited investigators from having equity, consulting agreements, or decision-making positions in a company sponsoring their research.

In 2001, a series of articles in the *Seattle Times* about the Fred Hutchinson Cancer Research Center (the Hutch) in Seattle pointed to some serious conflicts of interest in several patient protocols that may or may not have clouded the judgment of researchers and harmed patients. But the Hutch was hardly alone.

"It would be very rare now for a researcher, particularly the most senior of them, not to have their foot in the corporate door," says **John Pesando**, MD, PhD, a medical consultant and former researcher at the Hutch who was one of the whistle-blowers in the case. "It is a very large and weakly controlled issue."

In part due to the investigational reports in the

media, Fred Hutchinson executives made some changes to the center's financial disclosure policies. It now prohibits ownership of stock or receipt of royalty payments on patents by a researcher directly and significantly related to a clinical trial in which a researcher is involved. Scientists involved in the conduct of human subjects' trials are also now required to disclose to patients and in scientific publications any financial interest that they have in the for-profit company sponsoring the trial in which they are involved.

Purity of science is paramount

Medical research is a matter of life and death, says Bekelman. "The guidance and medicine that patients receive from their doctors relies upon valid scientific evidence," he notes. "While industry sponsorship of medical research has led to considerable scientific progress over the past few decades, it is imperative to ensure that the integrity of the scientific process and the safety of research participants is never jeopardized."

The funny thing, Bekelman says, is that pharmaceutical companies and medical device manufacturers have a greater interest in valid scientific research than positive findings.

Kassirer says he would like to see clinical trials staff simply be more aware of the financial conflicts that are there. "Who is a consultant for the company? Who is on their speakers' bureau? Who has stock? It's not that it has to impact whether the science is good, but we have no idea."

In an ideal world, no one with a financial interest in the sponsoring company would do any medical research, says Kassirer, who just finished writing a book on the subject of industry's infiltration into medicine. The potential for a bias is simply too great. "But as a start, I would like to see more disclosures of the relationship between researchers and companies — the amount and type of involvement."

Academic and industry collaboration has been fundamental to many advances in medical care, says Bekelman. "Our findings demonstrate that such collaboration is extensive and may have an impact on trial outcome. The question is not whether to prohibit collaboration but instead how to manage collaboration appropriately. Researchers need to be cognizant of the fact that industry sponsorship is associated with study bias, publication delay, and data withholding. Then they should design their collaborations in such ways as to minimize these unintended consequences."

Additional resources

- Kassirer JP. Financial conflict of interest: An unresolved ethical frontier. *Am J Law Med* 2001; 27(2-3):149-62.
- Krimsky S. *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* Lanham, MD: Rowman & Littlefield Publishers Inc.; 2003.
- Moses H III, Braunwald E, Martin JB, et al. Collaborating with industry — choices for the academic medical center. *N Engl J Med* 2002; 347(17):1,371-1,375.

A lot of people have interesting ideas on how to do that, he continues, citing Harvard researchers as being "pretty close to getting it."

Bekelman thinks part of the answer is that guidelines must be adopted and practiced by medical journal editors and medial professional societies. "We also suggest a comprehensive clinical trials registry so that the results of all trials will be available with any financial interests of the investigators."

Something has to change, says Krimsky. "Imagine if you are in a courtroom and a judge, before meting out a sentence on a felon, stands up and says, 'Before I issue this sentence, I want to disclose that I will be sending this person for the rest of his life to a for-profit prison in which I have a financial interest.' Most people would cringe at the idea, that the judge, who has disclosed his interest, has this interest in the first place. But we have become acclimated to the fact that scientists make these disclosures all the time. That's just the way things are."

Some value systems — such as that of universities and industry — just shouldn't be blended, Krimsky says. Perhaps, over time, they will become less enmeshed as the policies Bekelman mentioned at journals and in institutions are created.

But a policy or rule won't be enough, says Pesando. "We have some great rules out there that are designed to protect patients. But you have to have enforcement. Otherwise, it's like having speed limits but no police to enforce them. You won't control anyone that way."

Reference

1. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: A systematic review. *JAMA* 2003; 289:454-465. ■

Reader Question

HIPAA changes retro data research rules

By **Paul W. Goebel Jr.**
Vice president
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Question: Is informed consent needed for retrospective data research? Under what circumstances can informed consent be waived?

Answer: Retrospective data include stored physical samples or data, resulting from either earlier studies or nonresearch activities such as the practice of medicine. There are two sets of regulations to consider, the Common Rule and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The Common Rule generally applies only when the project is federally funded, although its requirements are often extended to cover all applicable research. HIPAA generally applies only when the research site is a covered entity.

The two rules provide protections for two different activities: 1) The purpose of the Common Rule is protection of the rights and welfare of the human subjects of research. 2) The purpose of HIPAA is to prevent inappropriate use or disclosure of protected health information (PHI). PHI is information through which the individual patient can be identified.

Much low-risk or no-risk research involving interviews or surveys is exempt from the Common Rule. A nonexempt retrospective review project is eligible for waiver of the Common Rule informed consent requirement if it involves no more than minimal risk to the subjects.

A project is exempt from HIPAA if the information is de-identified, with all 18 identifiers removed, that is the information is recorded so that the subjects cannot be identified, either directly or through identifiers linked to the subjects.

Although the HIPAA Privacy Rule applies only to covered entities, its authorization agreement elements are rapidly becoming the standard for all research projects.

• **Informed consent vs. authorization agreement.** Under HIPAA, the PHI now belongs to the individuals and the hospitals and researchers are its custodians. The medical staff have unrestricted access to the information for treatment, payment for health care, or for health-related operations (TPO). Research is not included in TPO, so the use or disclosure of the PHI for the specific research activity must follow specific procedures, usually either an authorization or a waiver of authorization. Before HIPAA, sponsors and investigators often collected and stored specimens without revealing to the study subjects the intended future uses for these samples. HIPAA now requires the uses to be specifically outlined in the authorization agreement. Although they can be combined into one document, the authorization agreement and the informed consent document serve different purposes and both may be required.

• **Consent at the time of collection.** Many biomedical studies include in the consent document permission to collect tissue or blood to be stored for future research. The intended use of this human biological material (HBM), the length of time it will be stored and whether it will be stored as identifiable should be outlined in the consent. The current guidance is that consent should be obtained for all HBM at the time the material is collected. HIPAA requires a research subject to sign an authorization agreement for all prospective uses or disclosures of PHI including unspecified future research, unless it is not practicable to do so.

• **Use of stored samples for which consent was not obtained.** Many of the stored samples and data sets were either collected without explicit written permission of the study subject

COMING IN FUTURE MONTHS

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to use them for research or else the consents have been lost. Still others were collected with general consents that do not address research as one of the purposes for which the samples may be used. HIPAA allows data/samples to be de-identified and re-identified with a code before the repository provides them to the researcher.

The confidentiality can be maintained while still providing the researcher with donor-specific medical information by having a gatekeeper at the repository hold the identifiers. The gatekeeper would forward samples and relevant medical data in a form that is anonymous to the researcher. If the researcher needs additional medical data, they could be obtained from the gatekeeper, which would maintain the anonymity of the donors.

With respect to the oversight of genetic tests, the Secretary's Advisory Committee for Genetic Testing has stated that informed consent must be obtained from all subjects participating in such research.[1]

Reference

1. *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT*: http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.htm. ■

CE/CME*questions*

Physicians, nurses, and others participate in this continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. 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 in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

9. When establishing educational plans for IRB members, which of the following is a good strategy for both educating IRB members and recruiting new IRB members?
A. Publish a manual that details IRB duties, regulations, policies, and procedures
B. Hold a public mock IRB session
C. Hold an educational conference or seminar focusing on a particular topic of interest to IRB members
D. All of the above

10. In preparing for an accreditation site visit, IRB staff may want to let which people know that the site visitors could interview them?
A. IRB members
B. Principal investigators
C. Sponsors
D. All of the above

11. The VA Handbook addresses which of the following process topics:
A. Initiation of the research
B. Communications with investigators
C. Ongoing project monitoring processes
D. All of the above

12. What percentage of biomedical research is industry-sponsored?
A. Two-thirds
B. One-third
C. One-half
D. None of the above

Answers: 9-D; 10-D; 11-D; 12-A.