IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Dealing with complaints: Listen, investigate, and report findings

Research programs need systems for accepting, addressing concerns

It's a call an IRB office dreads getting — a patient with a complaint about a study or a researcher, or an anonymous caller alleging problems with a clinical trial.

While informed consent documents must list contacts to call if a person has questions or concerns about research, that's only the first step, says **Marjorie Speers**, PhD, executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), a Washington, DC-based accrediting body.

"I think of it in three parts: having a mechanism for concerns to be voiced, investigating [those concerns], and then reporting back on what the findings were and what actions were taken," Speers says.

She says that in the past few years, research institutions have begun to take more proactive steps to ensure that anyone with complaints or concerns can be heard — everything from 24-hour hotlines and web sites to standing committees of research participants set up to advise IRBs. "I think the changes are tied to a number of things," Speers says. "The suspensions of research programs are one thing. Another is just the need to recruit individuals into research, trying to increase subject enrollment, and competing for research studies."

Most institutions she sees that have made the effort to institute a process for dealing with complaints do a good job, she says.

"It's as if institutions fall into two categories. They either have some type of mechanism in place to hear concerns, or they don't," Speers says. "If they do have something in place, then it's usually pretty good."

But one area that she says often needs strengthening is providing a systematic, objective process for investigating every complaint. That process need not necessarily be carried out within the IRB.

"The IRB is very busy doing what it is mandated to do under the regulations, which is to review and approve research," she says. "Also, some of the concerns might actually be raised about the IRB, and so you want individuals who are not sitting on the IRB dealing with concerns

that are expressed about them."

She says the complaints that are most appropriately handled by an IRB are those coming directly from subjects.

At Baylor College of Medicine in Houston, the Office of Assurance and Compliance handles complaints and questions about human research from staff, subjects, and anyone else involved in clinical trials, says **Kathleen Motil**, PhD, MD, associate professor of pediatrics and chair of two of the college's six IRBs.

"The ethicist within an institution may call us, or the nurse coordinator may call us," she says. "In some instances, we may have physician clinicians outside the specific research project who may also raise questions about the nature of the project."

Motil says the office often is seen as a sort of ombudsman, taking all kinds of calls, including those not directly related to the research at hand. As a result, those receiving the calls have to be very knowledgeable about the departments around them and who does what.

According to Speers, a wide variety of questions or concerns can be raised about research, particularly by subjects. "It can be [asking] why were they chosen to be in this study," she says. "Maybe they don't like something about the investigator or the research staff. They want to know what's going to happen to their data. They haven't been paid. There's a whole range of concerns that subjects will raise.

"Very often the people who receive those complaints can just deal with them. If it's a payment issue, for example, you just contact the investigator and find a way to have the subject compensated," Speers adds.

At Baylor, once someone calls, that person then is asked to submit written comments, a step that Motil says often helps clarify the issues involved.

"That doesn't mean to say that we ignore oral complaints, but I think the insistence that somebody commit to writing about their complaint is very important," Motil says. "And quite often people are not shy about putting their complaints in writing." She says she doesn't remember a complaint that was halted because a person didn't want to submit it in writing.

"I think that says something about the people who handle the calls," Motil says. "I think people feel comfortable enough with the voice on the other end and that someone's listening that they really do put their thoughts on paper."

Speers notes that regardless of the form in which the complaint is received, the person making it needs to be able to remain anonymous if he or she chooses. She cites the hypothetical example of a staff person who has a problem with an investigator, but is concerned about losing his job. "There needs to be a message from the institution that we

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Editorial Questions

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Program emphasizes seeking facts, consensus

IRB withholds judgment until review is finished

The Baylor College of Medicine in Houston has a prescribed inquiry process for complaints generated by human subject research at the institution, says **Kathleen Motil**, PhD, MD, associate professor of pediatrics and chair of two of the college's IRBs.

"We purposely do not call it an investigation," Motil says. "The AAMC [Association of American Medical Colleges in Washington, DC] has some very clearly defined guidelines for university investigations, and that's not exactly what we're about."

Motil outlines the steps an inquiry would take, once a person calls with a complaint:

• **A staff member records the facts as the person describes them over the phone, then asks the person to submit their comments in writing.** "The litany that they gave you on the phone may be more or less relevant to what actually gets written on paper," Motil says.

• **A review by senior staff, such as director of assurance and compliance or an IRB chair, is held to determine what to do next.** If safety or medical health is an issue, the person can be referred for medical care. After weighing the merits of the complaint, the IRB chair and assurance staff will convene a subcommittee of the IRB and designate an audit team. That team notifies the principal investigator and research staff that an audit will be conducted.

• **An audit of all documentation surrounding the study in question is conducted.** Staff review the consent forms, adverse event reports, amendment reports, and investigators' brochures or grants.

"We look for ongoing documentation of individual subjects throughout the course of that particular study," Motil says. "So for example, if [the investigator] has been allowed to enroll 25 patients and has 32, we will take note of all of that."

• **Staff and administrators are interviewed as well as the investigator to determine operating procedures.** "If we perceive that there is a problem, we will suspend any further enrollment if we have to," she says. "But what we try to do is follow the judicial system if you will — you're innocent until you're proven guilty."

• **The results of the inquiry are presented to the IRB subcommittee, which can send it back to the audit team for more questions.** Once the subcommittee is satisfied, a letter is sent to the investigator for a response, which the subcommittee again reviews. Before the matter moves any further along through the process, the investigator is invited to meet with the IRB subcommittee to be sure there is no miscommunication of the facts.

• **The subcommittee sends its findings to the fully convened IRB, which does its own deliberations.** "If the full IRB still has questions, then it goes all the way back to the audit team to resolve or if the subcommittee can resolve it in subsequent meetings, then that happens, too. We don't want third-hand gossip; we want it straight from the source," Motil explains.

Consensus reached

• **When the full IRB has had all of its questions answered, its members deliberate and come to a decision about the complaint.**

Motil notes that the Institute of Medicine has recommended that IRBs reach their decisions by consensus, rather than simply a majority of members.

"That's how we operate all the time. We operate in terms of consensus agreement," she says.

The investigator is notified, as are any other departments or agencies that need to become involved. For example, if staffing on a study is an issue, then the departmental chair might be notified, she says.

The IRB reports to the executive vice president and dean of medicine, as well as the vice president and dean of research. Legal counsel receives a report, and may in fact be involved earlier in the inquiry process if there are serious issues of noncompliance, Motil says.

"If we have angst about some things, we will very clearly involve them as early as the subcommittee reviews," she says.

The U.S. Department of Health and Human Services' Office for Human Research Protections (OHRP) is notified if the IRB finds any serious issues of noncompliance.

Motil says the IRB waits until all of the questions have been resolved before involving OHRP. "We are not going to report hearsay to OHRP. Once all the deliberations have been completed and the IRB has been presented the facts, and the vote has been taken, that's when we do our report."

Finally, the person who made the complaint also is notified of the IRB's decision, again at the end of the process, when all of the questions have been resolved. Motil says that process can take years.

In the meantime, she says her office often hears from subjects checking on the progress of their complaints.

"We do hear from subjects again, but we don't make any definitive statements until the facts are settled," she says. ■

want to hear about your concerns and your questions, and if you want to raise them anonymously, we will listen to you," Speers points out. "We think providing that protection is important."

When OHRP gets involved

At Baylor, a complaint triggers a systematic inquiry process that, depending upon the complexity of the case, can take several years to complete, Motil says. **(See related story, p. 39.)**

Once the inquiry is complete, the IRB determines whether to involve the U.S. Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP). Under HHS regulations, all "serious or continuing noncompliance" must be reported to OHRP.

While this type of report from an institution can prompt an oversight investigation by OHRP, the trigger for an investigation is more commonly a complaint from a subject or a whistle-blower alleging noncompliance with human subjects protections, says **Michael Carome**, MD, OHRP associate director for regulatory affairs in Rockville, MD.

An OHRP compliance oversight evaluation can take one to two years, Carome says, and the agency has a full range of tools at its disposal to deal with noncompliance, including possibly restricting or withdrawing an institution's assurance of compliance.

After reaching a peak of 182 open compliance oversight investigations in August 2000, OHRP currently has about 40 open investigations, he says.

Motil says Baylor hasn't seen any increase in complaints in the wake of the highly publicized problems at research programs nationwide. "I think we always have a steady amount," she explains.

She says that in evaluating a complaint, it's important to keep the perspective of the person making the complaint in mind.

"If people think that something has gone wrong, whether it's true or not, it is true in the reality that they see," Motil says. "Sometimes, you have to educate people about the research enterprise, about how the system works. And in those cases, they may say, 'Oh, I didn't know that; I guess this isn't such a big deal after all.' But in many instances, that isn't the case."

However an investigation or inquiry of a complaint turns out, that final contact with the person who lodged it is important, Speers says.

"We find in the more successful programs, where investigators and IRB members are satisfied with the program, that part of that open communication is getting back in touch with the individual," she says. "So that they know the issue was addressed. Changes might have occurred or they might not have, but there is that feedback loop."

A culture of communication

In order to be accredited by AAHRPP, research programs must demonstrate that they have policies in place to allow subjects to raise concerns about research and investigators to raise concerns about the research process, including IRB review.

The goal, Speers says, is "a corporate culture where they're open to communication, where investigators and other research staff, if they have a question or concern, have a mechanism to express it and to have it addressed."

Along those lines, many institutions have instituted toll-free telephone numbers, not only for research subjects to use, but also for employees to use if they want to raise issues anonymously. At larger institutions, Speers says, the lines are staffed around the clock. Web sites geared toward participants also are becoming more common.

Some compliance offices also maintain logs of complaints in an effort to track patterns or problems.

"If there's a particular study and a lot of people are calling in about that study, then the IRB may need to get involved and contact the investigator, or even potentially reevaluate the study if things have changed in some way," she says.

Speers notes that one institution regularly surveys its employees regarding IRB issues — asking whether they are satisfied with the IRB process, with educational training, and with the resources available to support research.

Both Speers and Motil say institutions are moving toward more proactive steps in dealing with complaints — not just reacting to problems, but trying to head them off down the road.

Many institutions have taken steps to more fully involve research subjects in the research process, Speers says.

Some have community advisory groups that are asked to comment on the design of studies. "A couple of places have subject or participant advisory groups," she says. "If they're working in particular communities or doing certain types of research, they'll actually have a standing committee of participants who advise them about research studies."

Speers says that public input can improve the research, by providing insight that can help increase enrollment or keep people in the study longer.

Motil says the key to preempting complaints is "education, education, education," not just in medical proficiency but in communicating with subjects. "It's the way in which you present yourself and the activity you're about to engage in," she says. "How you relate to people. It's about listening skills. Those are the kinds of things that I think minimize the complaints that will be registered.

"Yes, there will be things that go awry that you in your worst nightmare don't want to see happen. That's the human factor in just about everything we do. But the ability to listen, the ability to communicate, to present yourself in a straightforward manner without an attitude problem — those go a long way," Motil adds. ■

Should participants have access to study results?

Some research should include access protocols

As genetics research yields more and more information about individuals' predispositions to disease and illness, researchers are beginning to question whether study participants should have access to the genetic information obtained about them. And should such access be granted to subjects in other types of research?

"It's an evolving issue," says **Rebecca Pentz**, PhD**,** professor of hematology and oncology in research ethics at The Winship Cancer Institute at Emory University in Atlanta. "It used to be that we never returned research results or information obtained about the person back to that person. It just wasn't considered necessary, and no one thought about it."

But as we know more about genetic influences on disease risk and disease processes, early intervention or monitoring could mean the difference between life and death for these people, Pentz notes.

As an ethical matter, researchers and former research participants are questioning the traditional view that information obtained in human studies should be under the sole control of the research entity. Studies have shown that people considering participation in research trials are interested in knowing the information that is gathered about them and its relevance to the purpose of the research, she adds.

"We are just becoming more sensitive to these people and their needs," says Pentz, who frequently works with the parents of children who are participating in oncology studies or who have done so in the past. "Patient advocates have played a huge role in that. They are beginning to say, 'We want to know.' And researchers are saying, 'Well, of course, yes, you should know, but there are a lot of challenges that we face if we are going to provide that information to you.'"

Granting research subjects access to information obtained about them is not as simple as it sounds.

First, research participants are not going to have enough background knowledge to be able to understand the raw results or to be able to put them in context so that the information is relevant to them, say researchers and ethicists. If investigators plan on granting access, they must build education and counseling into the study protocol.

"If they have decided that information is to be provided, the IRB should be sure that the investigator has a plan for how much information will be given, what kind of information will be revealed, how it will be revealed, and whether there will be any substantive counseling available or whether the subjects will be referred to counseling, etc." says **Anna Illtis**, PhD, assistant professor in the Center for Health Care Ethics at St. Louis University. "All of those sorts of structures have to be in place at the outset."

And not all information may be suitable for dissemination.

Researchers and members of the review board have the responsibility to consider what types of information participants can derive some benefit from and what, in fact, may be damaging.

"I think it's important to distinguish between knowledge and information because in some research, you don't necessarily have — at various points in the trial or even at the end — information that is actually going to help the person," notes **Mary Anderlik**, JD, PhD, associate professor in the Institute for Bioethics, Health Policy and the Law at the University of Louisville (KY).

If asked up front, participants may say they want to know any information obtained about them but not have a real context about what that might mean.

"If you participate in a study of genetic factors and heart disease and the end finding is that if

you have a child, that child is at risk for some genetic disorder," she says, "that is not the kind of information you expected from the study. The same would be true of a finding of nonpaternity."

In genetic trials, there also are complex issues of privacy and confidentiality that can be raised, adds Illtis. "With genetic information, that is not just information about you, the participant," she emphasizes. "It is often also information about other family members that could be revealed to you, especially genetics trials that involve families. If one person chooses to know information and others don't want that information revealed, and you reveal to the one person, you have essentially revealed genetic information about an entire family to that one person."

Participants also may not be able to comprehend the true implications such knowledge might have for their future, says Pentz. "Once you have the information, you have it. And with a lot of information about genetic predispositions, even researchers are not really sure what that means. Even if the information is not included in your medical record, if you are filling out an insurance form and it asks whether you have any information that you might be at higher risk for a certain type of disease, you have to decide: Am I going to tell the truth, or am I going to lie about this information? It is difficult situation to be in."

Most genetic trials now require genetic counseling for participants to be built into the overall study protocol. Researchers at Washington University in St. Louis who are studying genetic factors and Alzheimer's disease are requiring that participants go to three sessions with a genetic counselor before the consent process begins, says **Gerard Magill**, PhD, director of the St. Louis University's Center for Health Care Ethics.

"The purpose of these sessions is to inform the individual that he or she is in a family environment and to understand the significance of the information obtained both for themselves and their family, " he explains. "And it is designed to help people understand what the risk-ratios mean. What does a 13% increased risk mean? Or even a 40% increased risk?"

Even with such protections, however, it's still a duty of investigators and IRBs to determine whether access to study results even should be offered. IRBs should be guided by the core ethical principles outlined in the *Belmont Report* — respect for persons and beneficence — as well as recent guidance published in the Health Information Portability and Accessibility Act (HIPAA)[1] and findings issued by the National Institutes of Health, Department of Education (NIH-DOE) Task Force on Genetic Testing[2] and the National Action Plan on Breast Cancer,[3] Anderlik says.

"It's important to make the distinction between therapeutic and nontherapeutic research and also between the findings you expect to generate vs. accidental findings," she continues.

Study protocols should stipulate what types of information the researchers intend to offer participants and how it should be offered.

"Researchers should anticipate and address these issues in their protocols: how they will handle findings related to the purpose of the study and what criteria they will use to determine this (i.e., validity of results)," Anderlik explains. "And they should indicate what they will do with accidental findings, such as a finding of nonpaternity in a medical study or finding of a chromosomal abnormality that may affect reproductive decision making in a study of genetic risk factors for heart disease."

In addition, she notes, if the study involves therapeutic research, HIPAA stipulates that participants have a right of access to any information in their medical record at the conclusion of a clinical trial, subject to certain exceptions.

For example, most research laboratory testing is performed in labs that are not certified under federal Clinical Laboratory Improvement Amendments (CLIA). Labs without such certification cannot give results suitable for clinical diagnosis or use. If testing is performed in this manner and investigators want to offer access to test results, they must have a protocol in place for contacting the participants at the conclusion of a trial and asking if they want to have testing repeated in a CLIA-certified lab.

How beneficial is info to the participant?

IRBs mainly should be involved in evaluating how beneficial the information will be to the participant, Anderlik says.

In an article for an IRB ethics journal, Philip Reilly and colleagues advise review boards to consider three factors:[4]

- the magnitude of the threat posed to the participant that the information reveals;
- the accuracy with which data predict that the threat will be realized;
- the possibility that action can be taken to ameliorate the potential injury.

The NIH-DOE Task Force on Genetic Testing

suggested standards for the use of genetic test results in clinical practice, Anderlik adds. These might be useful criteria for judging whether genetic test results performed as part of a research trial might be useful and relevant for the participants.

Those criteria are as follows:

• **Scientific validity.** Findings independently replicated and subject to peer review.

• **Analytical validity.** Reliably detects analytes (e.g., particular sequence) when they are present in specimens and does not detect analytes when they are absent.

• **Clinical validity.** Data are available related to clinical sensitivity, specificity and predictive value.

"Clinical validation," she notes, "involves establishing several measures of clinical performance including: (1) the probability that the test will be positive in people with the disease [clinical sensitivity]; (2) the probability that the test will be negative in people without the disease [clinical specificity]; (3) the probability that people with positive test results will get the disease [positive predictive value (PPV)] and that people with negative results will not get the disease [negative predictive value].

"Parameters of clinical validity will depend in part on the group or population in which the test will be used," she notes. "For instance, the frequency of disease-related alleles might differ between ethnic groups, making it difficult if not impossible to extrapolate test sensitivity from one group to another."

• **Clinical utility.** Data permit evaluation of the benefits and risks that accrue from both positive and negative results.

Some experts have argued in favor of giving potential study subjects the option of requesting individual results even if nontherapeutic research, as part of the informed consent process, but others argue that there is not clear benefit to the participants and giving individual results runs the risk of making the results seem more accurate than they really are, she notes.

When access is impossible

Of course, information in some research trials is completely "anonymized." The information is stripped of all information linking it to a particular person, making sharing of research results with individual participants an impossibility, note Illtis and Anderlik.

Even in these cases — and in situations where investigators and IRBs determine that no useful information is available — participants should be informed that they will not have access during the informed consent process.

"You should always tell potential participants about the intentions of the investigators concerning the communication of results and inform them if provisions of information will not be possible," Anderlik says. "You might consider a newsletter or some other means of communicating aggregate results to participants."

Obviously, some trials take years, or decades, to complete and contacting participants once relevant information is known would be very difficult, if not impossible, notes Pentz.

However, in some cases, researchers have concluded that the information obtained was so important that they had a duty to contact the people involved, she says. "I worked with Louise Strong at MD Anderson [The University of Texas MD Anderson Cancer Center in Houston] in studies of families with the p53 gene mutation," Pentz says. "When she first started, 20-30 years ago, they didn't know it was the p53 gene [that predisposed people to colon cancer]."

Over time, as the research revealed the genetic link, the researchers were left with a large pool of people that they knew had this mutation. In addition, there is significant benefit to people who know they have this mutation: They can get colonoscopies more frequently, and if detected early, the cancer can be treated.

Researchers worked out a system to contact people who had participated in the study and ask if they wanted to get re-tested at a CLIA-certified lab, she notes."

"These days, if you have something like the HMPCCC gene, we are not going to do a research study on that within a family and not have provisions within the protocol for genetic counseling and then offering of test results," she notes. "We are evolving toward feeling responsible, at least when there is a medical intervention available, to let people know and build that access into the protocol." A newer debate in the field of research ethics is whether participants have a right to request their personal information, whether or not investigators feel that it provides useful information, Pentz adds.

Researchers with the Children's Oncology Group — researchers at different institutions who collaborate on pediatric oncology studies — are exploring ways to build in participant access to information into their protocols.

"Ethically, we believe that if people take the trouble to join a research trial, they are partners in the research; and if they are partners, then we owe them the results," she says. "It is a complicated issue, particularly in oncology, when the results may be seven to nine years later."

The group is currently preparing a study that will involve building information access into the protocols of a few studies on a pilot-testing basis.

Some researchers have balked at the idea of disclosing individual information after the fact, both because of the added costs and the potentially painful information that may be revealed to the parents of children who participate, she notes.

"What if their child was in the arm of the study that proved to be the less-effective treatment?" she asks. "That's going to be true of half the people involved. And maybe their child died."

Some parents may not want to know what role their child played in the research, but some parents will, she says.

"The Patient Advocacy Committee of the Children's Oncology Group is providing feedback to the researchers — these are parents of children who had cancer and who have died," she explains. "They are saying, 'Look, parents aren't as crazy as you make them out to be; we know these things. Some people won't want to know, but you need to have a nonthreatening mechanism for saying: The paper is now ready to be published. You were partners in the research; we will offer you a conversation with your doctor who will explain everything to you.'"

Such an approach also will help the researchers obtain information about long-term effects of some of the treatment regimens, she adds.

"We are getting better at curing cancer, but we now have these long-term effects of aggressive cancer therapy," she says. "So we also need to be able to bring people back in years later and share the new knowledge with them."

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SPOTLIGHT ON COMPLIANCE

FDA issues guidance on use of electronic records

New draft guidance designed to clarify

By **J. Mark Waxman**, JD
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While the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is clearly getting all the headlines and a great deal of attention in the research community, the recent Food and Drug Administration (FDA) *Guidance for Industry on Electronic Records* indicates it is not the only game in town. The purpose of the guidance, issued as a draft, is to address the requirements for use of electronic records to fulfill the record keeping requirements of the Food, Drug and Cosmetic Act; the Public Health Service Act; and FDA regulations.

For some years, the FDA has grappled with the rules to be applied to the acceptance of electronic record and signatures. In early 1997, final regulations were issued [21 CFR Part 11 (Part 11)] to provide the criteria for acceptance of electronic as opposed to paper records. Their goal was to permit and encourage the "widest possible use" of electronic records.

Thereafter, over a period of years, numerous other documents, some in draft guidance form, were issued, as the FDA sought to both seek input from industry and clarify its position on such matters as time stamps, record maintenance, record storage, audit trails, and legacy systems.

Ultimately, the ongoing discussion convinced the FDA that it would need to re-examine its entire approach, leading it to withdraw its prior guidances, while at the same time, issuing new guidance, albeit in draft form, as to how it will approach regulatory enforcement.

Part 11 is designed to address the criteria under which the FDA will consider electronic records adequate to be used in lieu of paper records. This means that electronic records must be "trustworthy, reliable, and generally equivalent" to paper records and signatures. To ensure

this, computer systems, including hardware and software, controls, and the attendant documentation, are subject to FDA inspection.

Under the new draft guidance, this scope is refined to be narrowly interpreted. For example, Part 11 applies to records specifically required to be maintained or submitted, but not to records necessary to meet all the regulated activities. In such cases, the "merely incidental" use of computers would not make them subject to Part 11 requirements. However, where records are required to be maintained and are maintained in electronic format, as well as paper, and the electronic records are relied upon to perform the regulated activities, Part 11 would apply.

As the FDA suggests, the approach to be used for decision making is to create a standard operating procedure (SOP) reflecting an assessment of the organization's business practices. This allows knowledgeable and documented decisions to be made.

Specific requirements

The specific FDA requirements are generally divided into electronic records and electronic signatures. Those records for a closed system — i.e., access controlled by designated employees responsible for the content of records on the system — must meet an extensive series of requirements (21 CFR § 11.10) to create assurance with respect to authenticity, integrity, and, where appropriate, privacy. This requires SOPs in the following areas:

• **Validation**. The guidance points out that there is no specific regulation with respect to validation. Yet, as Part 11 points out, those using electronic record systems will need to have validated systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records. The guidance itself goes on to suggest that the effort made to validate any particular system would vary with the risk assessment and the potential to affect product quality, safety, and record integrity.

• **Audit trails**. Existing regulations actually do require, in some instances, an auditable trail of dates, times, or event sequences. For example, the FDA requires that all data generated during the conduct of nonclinical laboratory study must be dated, signed, and initialed.

If the system is automated, the individual responsible for direct data input must be identified. Finally, if changes are made, the reason, date, and responsible individual must be identified (21 CFR § 58.130). To protect the organization, similar information is desirable, even where not required. As a result, the ability of an electronic record system to maintain an accurate record of a trial through the creation, revision, and even deletion of records is important and should be validated prior to complete reliance.

• **Legacy systems**. One of the critical issues in the ongoing discussion with the FDA over electronic records is related to systems that otherwise met FDA regulations prior to the effective date of the final regulations, Aug. 20, 1997. Based upon the draft guidance, it now appears that assuming any actual FDA regulations were actually met, the use of such systems, although all the specific requirements of Part 11 are not met, will not lead to any regulatory action with respect to such systems.

• **Copies of records**. One of the important elements of any electronic system is the ability to provide copies as well as to simply make the records available for inspections.

The guidance recommends that copies be supplied using common portable formats, applying established conversion methods if necessary to attain this goal. If the existing system allows searches or trending, the same capability is desirable in the provided materials, but only if technically feasible — thereby not requiring that this be achieved.

The guidance does not specifically differentiate between open systems (those systems where access is not controlled by people responsible for record content) and closed systems (those systems that are controlled by those responsible for record content) systems. The Part 11 regulations do, however, address the requirements for such systems separately.

The controls for closed systems form a baseline (21 CFR § 11.10). In addition to validation, maintenance of audit trails, and record protection, they include procedures and controls:

• to limit system access to authorized individuals with a system for authority checks;

• to ensure validity of the source of data input or operational instructions;

• to ensure a determination can be made that people who develop, maintain, or use such systems have the education, training, and experience to perform their assigned tasks;

• to deter record or signature falsification (this specifically regards policies that hold system users accountable and responsible for actions taken based upon their signatures);

• to maintain and control appropriate systems documentation and related revisions.

For an open system environment, the challenge and resulting requirements are enhanced. Accordingly, in addition to the closed system requirements, an open system must employ procedures and controls must focus on authenticity, integrity, and higher levels of confidentiality in the system.

This typically will require processes such as encryption and use of digital signature standards. (21 CFR § 11.30).

Part 11 contains a series of logical requirements for electronic signature (21 CFR § 11.50 et seq). Recognizing that the usual "XX" is inadequate, the regulations require a signing that indicates:

• the printed name and that the related signature is unique to the individual;

• the date and time of signature;

• the purpose or authority of the signer in connection with the document involved.

Systems that use electronic signatures or handwritten signatures must demonstrate reliability with respect to authenticity and integrity (21 CFR § 11.70). There is latitude provided for those signatures based upon biometrics (fingerprint or retina scan) or identification codes in combination with passwords. Such approaches also require appropriate validation and testing to ensure integrity, including loss management procedures.

Finally, the entity must certify to the FDA — in paper form and "signed with a traditional handwritten signature" that the electronic signatures are intended to be as binding as the equivalent handwritten signature. ■

Baylor uses its BRAAN to improve IRB operations

Two years ago, Baylor College of Medicine had a dilemma: double its staff to accommodate the increase in study protocols being submitted to its IRB or find an electronic solution to its problem.

"A strategic decision was made to develop a comprehensive electronic web-based animal- and human-subject protocol system that would provide electronic capabilities to address every aspect of the IRB function," says **Addison Taylor**, MD, PhD, associate dean for clinical research at the Houston-based medical college.

Baylor had downloadable IRB forms on the web for four years and had begun to accept online protocol review comments from IRB members, but the college wanted a system that would provide a more comprehensive compliance solution.

"We could not identify a product at that time that provided more than a document tracking capability," explains Taylor.

Therefore, BRAAN, the Baylor Research and Assurance Network system, was developed by end users. BRAAN is a web-based application that allows investigators and IRB members to do everything from submitting protocols to tracking and reviewing studies on-line to training investigators on human subject protections.

The application is menu driven, providing pull-down selections for users in every aspect of protocol creation, submission and review. From the home page, administrators and investigators can select the appropriate path — animal or human protocol, existing or new protocol — and they then will be directed step-by-step through the program to supply information that must be included in the protocol application.

BRAAN is divided into sections, with each containing questions or prompts designed to gather pertinent information about the protocol. For example, investigators creating a new protocol must answer questions such as "What is the purpose of the protocol?" or "Will research data be tied to individual's names or record number?" They also will be asked to provide specific information on inclusion and inclusion criteria, sample size, potential risks or discomforts, and consent procedures (e.g., who will be recruiting subjects, how research population will be identified, and how consent will be obtained). Investigators can generate a preliminary informed consent form that contains autopopulated information provided in previous answers.

Required fields, such as risk categorization or a series of questions to determine whether a protocol

COMING IN FUTURE MONTHS

- ■ Gauging informed consent of participants
- ■ Training for community board members
- ■ Are IRB members individually liable?
- ■ The impact of patient advocacy groups

qualifies for expedited review, are highlighted in red. The system will not allow investigators to move forward if those fields are left blank. There also is a "Review for Completeness" section that will list areas that require more information before submission.

If investigators would like to use information from an existing study, they can select the study from a drop-down menu, and all pertinent information will autopopulate in upcoming screens. Investigators then may revise or update autopopulated fields as they go along. Additionally, personnel information can be autopopulated with data provided by the human resources department.

IRB administrators can use the program to schedule meetings and report findings using templated memos. IRB board members can access protocols on-line and provide comments that can be viewed later by investigators. "One example of a BRAAN feature that has made life easier is as an investigator, I have access to the protocol and all documents related to the protocol," Taylor says. "These are stored on-line and can be printed for regulatory authorities or clinical monitors wherever needed. Also, as an IRB member, I can now review protocols off-line by downloading them to my laptop for review away from the office. I can access protocols from anywhere in the world as long as there is Internet access."

BRAAN contains education modules on research ethics; investigator responsibility; the role of the IRB; and special topics, such as informed consent and scientific integrity.

"I have evaluated most of the other IRB support products currently available," says Taylor. "BRAAN is the only comprehensive software suite developed by clinical investigators, IRB administrators, IRB board members, and IRB staff that provides a complete electronic IRB solution, form web-based investigator submission to adverse event reporting."

The application won the 2002 Award for Excellence in Human Research Protection given by the Bethesda, MD-based Health Improvement Institute and sponsored by the Office of Human Research Protections.

Baylor so believes in BRAAN that last year the college decided to go public, making the program available to other universities and independent IRBs. The Academic Performance Institute (API) is handling the commercial sale of the application. You can visit the API web site and request more information or access to the BRAAN demo at www.Papi.md/buyers/index.cfm. ■

NEWS BRIEF

VA mandates review of research programs

The Department of Veterans Affairs (VA) last month issued a nationwide ultimatum to its medical centers involved in research to "shape up" or else. The department ordered a 90-day review in its 115 medical centers following a series of accidents, including the death of one patient at an undisclosed location.

The review, outlined in a March 6 memo to VA research personnel, requires individuals who run and oversee medical research to update their training on patient protection.

The VA is responsible for more than 15,000 research studies involving around 150,000 patients each year, according to the agency. As a result of the review process, each hospital involved in research must confirm to VA headquarters that it ensures its ethics procedures and system for catching errors meet widely accepted human research standards. Incidents cited, while not specific because of the ongoing investigation, include:

- falsified individual patient data that contributed to the death of one patient;
- a patient overdose in drug study project at another center;
- an experimental procedure that was conducted without the approval of the IRB;
- a drug study conducted with a researcher

CME instructions

Physicians participate in this CME program by reading the article, using the 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 answer key 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 to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

without clinical privileges permitted to prescribe the study medication;

• failure of a review board to meet even minimally required standards.

Medical directors and chiefs of staff for research will have to attest that the IRB and research and development committees are appropriately constituted and meet on a regular basis to provide timely review and oversight of new and continuing protocols and a review of adverse events and serious adverse events, according to the memo. The review will last until June 6. ■

CME objectives

The 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;
- describe 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;
- explain the potential for conflict of financial interests involving human subject research;
- discuss reporting adverse events during research. ■

CME questions

13. What step is NOT part of Baylor's inquiry process for handling complaints?
    A. face-to-face interview with the person making the complaint to determine credibility
    B. audit of all documents related to the study at the heart of the complaint
    C. interviews with the principal investigator, staff, and administrators to determine operating procedures
    D. review by an IRB subcommittee

14. According to the article, when evaluating study protocols in which participants will be offered access to research results, IRBs should:
    A. consider what types of medical treatment will be provided to participants
    B. consider what type of information will be given to participants, and whether that information will be beneficial to the participants
    C. ensure that study participants have access to anonymized information
    D. all of the above

15. Closed electronic documentation systems must have procedures and controls:
    A. to limit system access to authorized individuals with a system for authority checks
    B. to ensure validity of the source of data input or operational instructions
    C. to ensure a determination can be made that people who develop, maintain or use such systems have the education, training and experience to perform their assigned tasks
    D. all of the above

16. The Department of Veteran Affairs has ordered a 90-day review of VA-sponsored clinical trials because of which of the following:
    A. patient overdose
    B. falsified individual patient data
    C. lack of IRB review
    D. all of the above

Answer Key: 13. A; 14. B; 15. D; 16. D