IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

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IRB seals fate by approving fake protocol in federal sting

"To say this is just a problem of [some] IRBs is very naïve."

A federal undercover investigation into possible vulnerabilities in the IRB review system has led to the closure of one independent IRB, and has left other IRBs wondering whether the due diligence they exercise is diligent enough.

Coast IRB, based in Colorado Springs, CO, announced in April that it would close its doors as soon as oversight of its protocols was transferred to other IRBs. Coast had been one of the targets of a General Accounting Office (GAO) sting, in which investigators submitted a phony protocol on behalf of a non-existent medical device company.

Two other independent IRBs had rejected the fake study of a post-surgical healing device for women, which had purposely included multiple characteristics of "significant risk" from existing FDA guidance, according to a GAO report on the investigation.[1] Comments from those IRBs had called it "junk" and "the riskiest thing I've ever seen on this board," the report found. However, Coast IRB approved the study, said **Gregory Kutz**, managing director of forensic audits and special investigations for the GAO in Washington, DC.

The GAO investigators provided information to the FDA, which "determined that Coast IRB committed several violations of the laws and regulations intended to protect the rights and welfare of human research subjects in clinical trials and that the company failed to perform the robust review needed to approve a study," according to an FDA statement.

While criticizing the sting operation as illegal and unnecessary, Coast did voluntarily agree to stop accepting new studies and to put in place a number of improvements, including a new board chair, new members and new standard operating procedures. Shortly afterward, however, the company announced it would stop operating.

Kutz says that since the investigation became public, he's received calls from other IRBs asking for help in determining whether they're doing all they can to protect subjects.

"We've done some teleconferencing with IRBs telling them about our

investigation and giving them some advice," he says.

Marjorie Speers, PhD, executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), says the investigation should serve as a wake-up call for all IRBs, not just commercial or independent IRBs.

"I would say, based on looking at the IRBs that come to us for accreditation, there are a number of IRBs that are not functioning at the level they ought to be functioning at," Speers says. "To say that this is just a problem of central or independent IRBs I think is very naïve."

Committee requests investigation

The GAO investigation came at the request of the U.S. House Energy and Commerce Committee, which Kutz says has a long-standing interest in human subjects protection issues.

The GAO actually looked at three aspects of the human subjects protection system – establishing and registering an IRB with the U.S. Department of Health and Human Services (HHS); obtaining a federalwide assurance (FWA) from HHS; and getting protocols passed by IRBs.

To do this, they created a fictitious IRB and medical device company, using phony documents to apply for real certifications. Using these methods, the investigators were able to register their fake IRB with HHS and obtain an FWA for the device company (see accompanying story).

They also used this company to submit a protocol for a fictitious surgical adhesive gel – a protocol rife with problems, Kutz says.

"The study should have raised red flags – there were no animal studies, the chief investigator wasn't licensed to practice medicine," he says. "There were sterility issues. The details of what (the device) did were deliberately confusing."

He says the protocol was submitted to three independent IRBs after searching online for those that had less burdensome paperwork requirements. They submitted fake CVs and a fictitious medical license number for the principal investigator.

Two of the IRBs sent back so many questions and concerns about the protocol that the investigators could not keep up the deception. One asked for documentation of animal testing that the investigators claimed had been conducted on their product. In the end, the two boards refused to approve the study, one voting unanimously to reject the protocol.

Kutz noted that even those IRBs, while recognizing the obvious deficiencies in the study, failed to realize that the company didn't exist and that the medical license number was fraudulent.

"No one caught the fact that it was a bogus study," he says.

IRBs aren't necessarily set up to catch the type of elaborate fraud used in this case, says **Felix A.**

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Khin-Maung-Gyi, PharmD, MBA, CIP, chief executive officer of Chesapeake Research Review Inc., a Columbia, MD, independent IRB that is receiving some of the studies being transferred from Coast.

"That type of scheme is something that was pretty elaborate," he says, "For an IRB to uncover that would have been a stretch of the imagination."

He says the fact that two of the three IRBs approached rejected the protocol out of hand is significant.

"What it says is there was one bad apple," he says. "The system is not perfect but it is working."

Speers says central IRBs accredited by her organization – none of the three IRBs approached in the GAO investigation were AAHRPP-accredited, she says – are supposed to check the credentials of investigators because in many cases those researchers wouldn't be known to the board.

"They actually do a good job of evaluating the credentials of the investigator and they do look at issues around medical licensing," she says. "Some of the central IRBs actually go out and do site visits."

In fact, she says, those central IRBs are often more rigorous about checking the bona fides of investigators than are institutional IRBs, who may make assumptions about investigators based on the fact that they are associated with the hospital or institution.

"An institutional IRB generally does not check credentials of an investigator or research staff – they just assume that if they're part of the institution, they pass muster," she says. "And they shouldn't be making that assumption."

Obvious deficiencies

Speers says the faked protocol in this case had obvious deficiencies that should have been picked up by an IRB.

"For example, there was no data and safety monitoring plan," she says. "It was a fairly short protocol, given that this was going to involve the implantation of a device that involves significant risk."

But she's not confident that all IRBs would have recognized those deficiencies.

"I think there are institutional IRBs that could have done the same thing (Coast did)," Speers says. "AAHRPP knows from looking at hundreds of applications that, for example, IRBs are unclear what they should be looking for in a data and safety monitoring plan, so that could easily be missed."

In his report, Kutz noted that his investigators conducted all their communications with the IRBs by fax or through the Internet.

"As a result, our investigators were never exposed to real-time activities, such as telephone conversations, face-to-face meetings, or site inspections, which would have revealed their lack of expertise, lack of an actual facility, and other fraudulent representations," the report says.

As more IRBs go electronic, Speers says it's important to ensure appropriate oversight. She says that effort is two-fold.

"One is the importance of education upfront, so that investigators and research staff know what they're supposed to do, how to interact with the IRB," she says. "And likewise, the IRB is educated so it knows how to interact with investigators. Through education, you set up a particular culture."

Secondly, she says, it's important to establish post-approval monitoring.

"So if either the investigator or the IRB staff needs to pick up the phone and make a phone call or they need to make a visit, that occurs."

Reference

1. U.S. General Accountability Office: Human Subjects Research: Undercover Tests Show the Institutional Review Board System Is Vulnerable to Unethical Manipulation. GAO-09-448T. Available at: http://www.gao.gov/new.items/d09448t.pdf. ■

HHS also faulted in GAO investigation

Questions raised after fake IRB registered

The General Accounting Office (GAO) report on the IRB system's vulnerabilities doesn't just criticize the individual IRBs targeted by the investigation.

It also faults the U.S. Department of Health and Human Services (HHS), which oversees the registration of IRBs and the issuance of federal-wide assurances (FWAs), both of which investigators were able to obtain fraudulently for a fake IRB and fictitious medical device company.

In his report, **Gregory Kutz**, managing director of forensic audits and special investigations

for the GAO in Washington, DC, described the process of registering the IRB through an online registration form, and then using that fake IRB on its application for a FWA for its medical device company. In neither case did HHS's Office for Human Research Protections (OHRP) verify the information in those applications.

"With an HHS-approved assurance, GAO's device company could have applied for federal funding for human subjects research," Kutz notes in the report.

Investigators created a Web site for their fake IRB and advertised in newspapers and online. They received one request from a real medical research company seeking to get approval to join an ongoing clinical trial.

"Since the transaction involved privately funded human subjects research and did not involve any FDA-regulated drugs or devices, GAO's bogus IRB could have authorized this testing to begin without needing to register with any federal agency," the report states.

In an interview, Kutz says the investigation revealed real vulnerabilities in the system for protecting human subjects.

"We wanted to see if anybody could set up a private IRB, and basically they could," he says. "And a federalwide assurance isn't an assurance of anything – it's just a self-certification process."

OHRP clarifies language

Marjorie Speers, PhD, executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), says the revelations in the report about HHS are of greater concern than the fact that one independent IRB approved a fraudulent protocol.

"Our protection system by both OHRP and the FDA is based on the fact that both regulatory agencies set the regulations and they're supposed to enforce the regulations," Speers says. "This operation shows that an IRB can register with OHRP and that registration doesn't have any meaning."

She notes that OHRP has issued clarifying language on its Web site stating that the fact that an IRB is registered doesn't mean that the IRB has the appropriate expertise to review a particular research study. In addition, it stated that issuance of an FWA doesn't mean that OHRP had determined that the institution complies with federal regulations.

"So if the federalwide assurance doesn't have any meaning, if the IRB registration doesn't have any meaning, then one has to ask how these federal agencies are ensuring the American public that research is conducted safely," Speers says.

OHRP Director **Jerry Menikoff**, MD, JD, says the current IRB registration system was created in response to a previous report by the Office of the Inspector General.

"Basically what that report said was it thought it would be useful to implement a very simple registration system, which would have a list of all the IRBs and you would have some basic contact information about them," Menikoff says.

"We do require that if an IRB is going to be used by one of the institutions under our jurisdiction, that we want them on this list," he says. "Being registered means just that – they've given us the required information."

He notes that FDA is setting up a similar registration to the one currently maintained by OHRP.

Menikoff says an FWA is akin to contractual agreement stating that an institution will abide by 45 CFR 46.

"So obtaining an FWA is a very significant thing, because that's how an institution has committed itself," he says. "It now is in a position that it has to do what those rules require in terms of protecting human subjects."

In the GAO report, HHS officials stated that OHRP does not have resources to verify the information on all of the applications it receives.

Menikoff says OHRP is part of a larger system of research protection, and that funding agencies such as the National Institutes of Health or the Centers for Disease Control and Prevention would be quite likely to catch a fraudulent investigator or organization.

"I suspect it would be a really, really difficult thing for some entity that's fictitious to actually end up going through all of the hoops in a very competitive process and getting federal funding," he says. "The GAO could have tried to create this entity and have it get funding from NIH, for example. And they didn't end up doing that, probably because they, too, recognized the fact that for a fictitious entity to get federal funding is not an easy thing."

He says in addition to releasing the clarifying language about FWAs and IRB registration, OHRP is working with Coast IRB, which is closing as a result of the sting, to ensure protection of human subjects in the Coast protocols that are being transferred to other IRBs.

Menikoff says it would be up to Congress to

consider further policy changes to the current human subjects protection system.

Changing the system?

Trudo Lemmens, DCL, LLM, associate professor of law and medicine at the University of Toronto, has written extensively about human subjects protection. He says the GAO investigation has confirmed many of his fears about the vulnerabilities of the IRB system.

"In my view, you should have a system whereby a regulatory agency decides what IRBs can function for what kind of purpose," Lemmens says. "I would be in favor of a clear authority for particular IRBs in a particular region or for a particular kind of research."

While one alternative mentioned by Menikoff would be making the current voluntary IRB accreditation system mandatory, Speers worries that such a proposal could end up watering down accreditation standards in order to ensure that IRBs can achieve it.

"What I would like to see is voluntary accreditation with strong incentives," she says, noting there are some signs that is beginning to happen already. "For example, Pfizer has said it will only work with AAHRPP-accredited central IRBs in reviewing its research. And that it is encouraging investigative sites to become accredited."

She says having sponsors and even federal agencies give preference to accredited institutions is a better approach.

"That type of carrot rather than a stick is a much better way to drive institutions and companies to seek a higher standard," she says. ■

Get to know GINA: What it does – and doesn't do

Genetic nondiscrimination act shouldn't be oversold

The Genetic Information Nondiscrimination Act (GINA) of 2008 protects Americans against discrimination in employment and health insurance coverage based on genetic information.

It also provides new protection to potential subjects in genetic research. There is hope that GINA's passage last year may make people less fearful of participating in such studies.

But the challenge for IRBs is to explain that new protection without overstating it in the informed consent process, says **Lauren Dame**, JD, MPH, associate director for the Center for Genome Ethics, Law and Policy at Duke University in Durham, NC.

"While IRBs should feel that the risks of informational misuse of genetic information have gone down, it's not zero," Dame says. "So even though GINA has passed, it does not offer absolute protection for what is really quite personal and sensitive information."

The law, which has been in the works for several years, was passed last year, but began to take effect this year, with full protections scheduled to be in place by May 2010.

Earlier this year, the Office for Human Research Protections (OHRP) released guidance on GINA and how it should be interpreted by IRBs and investigators. That guidance recommends that IRBs reviewing research that involves the collection of genetic information should take into account GINA's protections when assessing risk.

The guidance details information protected by GINA:

- An individual's genetic tests, including those conducted as part of a research study;
- Genetic testing of a person's family members, fetuses of pregnant individuals or embryos created through assisted reproductive technology;
- Information collected about an individual's family members who have a disease or disorder;
- Information about participation in clinical research that includes genetic services (including testing, counseling or education).

The law generally forbids health insurers or health plans from requesting or requiring genetic information from an individual or using genetic information for decisions regarding coverage, rates or pre-existing conditions. It prohibits employers of 15 or more employees from using genetic information for hiring, firing or other employment decisions.

At the same time, however, the OHRP guidance points out the limitations of GINA, and urges IRBs not to oversell its benefits in informed consent.

Dame, who has made a presentation to her own IRB on the subject, says the OHRP guidance does a good job of balancing GINA's benefits and limitations.

"It makes two basic points – one is that to the extent that the risks we're concerned about with genetic testing and research are informational rather than a physical risk of some sort, GINA does reduce the risk," she says. "In that regard, it

reduces what has been the major risk of people participating in genetic trials.

"On the other hand, I thought it also did a good job of emphasizing that it doesn't take care of everything."

Limitations

Built into the new law are deadlines for enacting protections: Title I, which covers health coverage, began taking effect in May and will continue rolling out through May 2010, depending on when the health insurer's annual coverage period begins, Dame says. Title II, which covers employment, takes effect Nov. 21.

Even genetic testing conducted before those dates cannot be used once the law takes effect, OHRP guidance points out. But there is the possibility that actions could be taken by insurers or employers before GINA is fully effective, and informed consent documents should make note of that, Dame says.

"I would say in practical terms during this transition period, there would have to be different language (in informed consent)," she says. "Some of the language would be the same – what GINA is, when it was passed. But there probably would have to be some language that all of the protections of GINA do not go into effect until certain dates.

"IRBs are just going to have to deal with a slightly changing template as we approach full coverage."

In addition, GINA does not cover workplaces with fewer than 15 employees, and this would need to be explained in the informed consent.

And Dame notes that GINA protects individuals who may have genetic predisposition to a disease, but not those who already have the disease. It's a fine point, she says, but an important one.

"If you're participating in some kind of research looking at a disease that has a very strong genetic component and you don't have the disease yet, but you do have the genetic component, GINA is protecting that information," Dame says. "but if you're in that study because you have the disease and they're also doing research on your genes, the fact that you have the disease, unless it's protected in other ways by other laws, could cause you to be discriminated against."

Other uses

Dame says one serious limitation of GINA is that it only covers discrimination in health coverage and employment. She says there may be other entities that have an interest in genetic information, and disclosure could still pose certain risks. For example, the OHRP guidance specifically points out that life insurance, disability insurance and long-term care insurance are not covered under GINA.

"I could certainly imagine if somebody was participating in a study about Alzheimer's disease, that's information that a long-term care company might very well want to know," Dame says. "It would be a little misleading to say, 'We're testing your genes for APOE alleles (which are related to an increased risk of Alzheimer's disease) but don't worry, you're covered by GINA.' Because that's not entirely accurate."

Dame notes that it's hard to know right now all the potential risks that may someday exist for the disclosure of genetic information. As a result, IRBs shouldn't attempt to imagine every possible scenario, they should be aware that this is an area of medicine and law that is continuing to change.

"The point I would make is because it's a transition period, they can't expect to come up with one answer that's going to be correct forever – they're going to have to revisit this," she says. "We're theorizing how these problems might arise and trying to deal with them and that makes it difficult. Because it might be that they're going to come up in a way we just didn't think about."

But she notes that in any case, the risks of disclosure are small, and that IRBs will continue to carefully monitor plans for protecting personal health information, including genetic information.

While there's little evidence that discrimination based on genetic information was frequent or widespread, Dame says studies had shown that people were concerned about the possibility, and that it contributed to reluctance to participate in genetic research.

"I think one of the effects of GINA is that it sets a really clear norm for health insurers and employers, which is you can't use genetic information to hurt people," Dame says. "We're just not going to go down that road. And while it doesn't appear that many in those groups were going to go down that road, GINA probably did a good thing by stopping them before anyone got started."

For more information, see the OHRP guidance on GINA at http://www.hhs.gov/ohrp/humansubjects/guidance/gina.html. ■

Crafting informed consent under GINA

OHRP's suggested language is a good place to start

The Office for Human Research Protections (OHRP) recently released guidance for IRBs and investigators on how to deal with the new Genetic Information Nondiscrimination Act (GINA).

The guidance includes suggested template language for informed consent documents:

"A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

• Health insurance companies and group health plans may not request your genetic information that we get from this research.

• Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

• Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

The guidance states that IRBs are free to revise this template to meet certain situations or groups of human subjects.

Lauren Dame, JD, MPH, associate director for the Center for Genome Ethics, Law and Policy at Duke University in Durham, NC, says she thinks the suggested language does a good job of explaining GINA's protections clearly without overselling them.

"It's sort of a careful balance between trying to make it clear and in English, but recognizing that you really have to state certain things to be technically accurate," she says. "It captured the main improvements and the things that still are not covered.

When it comes to determining whether additional language is needed in the informed consent, Dame points out that certain types of research may raise issues because GINA does not cover long-term health insurance, disability insurance or life insurance.

She says that if a genetic research proposal under review is likely to raise issues in these uncovered areas – for example, Alzheimer's disease research – there should be special attention paid to that in the informed consent process.

Dame says IRBs should pay attention as the Equal Employment Opportunity Commission releases the regulations for the employment discrimination provisions of GINA to assist in explaining the law clearly to participants.

"The preamble to the regulations usually does a good job of incorporating examples," Dame says. "Those are really useful things for somebody to read through. They'll give some examples of what GINA does mean and what it doesn't mean in clear English. It may be that as people are devising information to give potential subjects, there may be examples in the preambles that are really useful ways of phrasing things." ■

Save hours on minutes: How to hone the process

No short-cuts, but efficiency possible

There might not be any shortcuts to creating the most accurate and thorough IRB reviews and meeting minutes, but it is possible to make these consistent and accurate with a well-thought-out process.

When the Office of Protocol Research at the University of Texas M.D. Anderson Cancer Center in Houston, TX, worked with IRB chairs to develop protocol review guidelines five years ago, greater consistency was a chief goal.

"We have five IRBs, and we needed consistency in the way the information was being presented," says **Marion Olson**, CIP, supervisor of human subject research regulations in the Office of Protocol Research.

The aim was to help IRB members remember to provide all of the essential information in their protocol presentations and to help IRB coordinators take more accurate and thorough meeting minutes.

The IRB approval process includes having a scientific editor at each IRB meeting. The scientific editor is part of the research regulations editorial staff, says **Martha Matza**, MS, CIP, CIM, director of operations of protocol research in the Office of Protocol Research.

"The scientific editor is focused on the consent document, making sure all risks are included and bringing it down to a sixth or eighth grade reading level," Matza says.

There are 25 to 30 IRB members at each IRB meeting, says **Wanda Quezada**, CIP, manager of human subject research regulations in the Office of Protocol Research.

The support staff attending these meetings includes one IRB meeting coordinator, one IRB coordinator who handles only continuing review discussions, the scientific editor, and Olson, Quezada, and Matza, Quezada says.

"I saw that IRB meeting coordinators were struggling with what exactly needed to be captured," Olson says.

"IRB coordinators in previous years had a lot of IRB experience," she adds. "So when our organization started growing larger, we had more people who had generalized knowledge of the IRB, but who needed specifics."

Likewise, some IRB members, including MDs and PhDs, who present protocols have a great deal of experience, and others are relatively new at the role. IRB chairs assisted with the development of presenter guidelines that would help the newer IRB members in particular.

The Office of Protocol Research staff and IRB meeting coordinators also provide points to consider, helping with the presentation.

For example, if a protocol features an investigational new drug (IND), then the IRB staff would highlight that question in the protocol review guidelines, suggesting that the presenter could focus a little more attention on that issue, Matza says. Also, IRB meeting coordinators might cue the board if a presenter has omitted an important regulatory point.

"I meet with IRB meeting coordinators before the IRB meetings to make suggestions," Olson says.

For example, a study that will enroll a pediatric population will need a pediatric risk assessment, Olson says.

"If the presenter misses bringing that issue to the committee's attention, then the coordinator will whisper to the chair, 'Don't forget about pediatric risk assessment,' and the chair will ask the presenter about it," Olson explains.

The presenter guidelines are part of the institution's strategies for improving both IRB meetings and IRB minutes. **(See story with tips on improving IRB meeting minutes, p. 81.)**

"We started with the IRB presenter guidelines, a template for presenting to the IRB," Quezada says. The guidelines provide the framework for beginning a protocol discussion. For example, the first section of the guidelines contains protocol information with a question about the objectives/purpose of the study.

Breaking down the process

The presenter guidelines feature these main sections:

1. Protocol information: "This section includes objectives, rationale, description, the investigator's brochure, treatment plan, and summary of procedures," Olson says. "They need to let us know if M.D. Anderson is the lead site and whether the study involves a grant that M.D. Anderson applied for."

Protocol information also might cover radioactive materials used and whether the study has been approved by the institution's radioactive safety committee, and whether the protocol uses a new drug or new device, Olson adds.

2. Study population and recruitment practices: Questions for this section include whether the subject selection is equitable and whether the study includes vulnerable subjects and has adequate procedures in place for ensuring their protection.

There also are questions about recruitment practices, including recruitment materials and compensation to study participants.

3. Scientific review process: At M.D. Anderson, the review process is divided into two parts, with the first review being a scientific review made by a separate committee, Olson explains.

"Once they make a determination, it's forwarded on to the IRB," Olson adds.

So this section asks about the important points identified by the scientific review committee, the principal investigator's responses, and how these were resolved. It also addresses any remaining issues and proposed future amendments, and it serves as documentation that the scientific review board did review and approve the protocol.

4. Informed consent document: "The guidelines have questions about consent, risks, side effects, and whether the waiver was appropriate," Olson says. "Also it asks about tissue banking." **(See sample presenter guidelines section on informed**

consent, p. 82.)

5. Recommendation: This last section asks whether the presenter recommends the protocol for IRB approval and/or has any contingencies. If the presenter recommends that the board defer or disapprove the protocol, this section asks that the presenter provide a formal rationale for this position.

The guidelines are not mandatory, but IRB members are encouraged to use them, Olson and Quezada say.

"The reviewer has to give a detailed description of what the protocol is about," Quezada says. "The guidelines give reviewers reminders to touch on all regulatory aspects, including categorizing risk."

Presenters find that the guidelines help them give a detailed presentation, and so some IRB members will type their presentation in advance, giving a copy to the office of protocol research, Quezada says.

"Then that written presentation becomes part of our minutes documentation," she adds.

Not all presenters will have hard copies of their presentation, but when they do it serves as a useful tool for educating the IRB meeting coordinators, Olson notes.

"Our meeting minutes are very good and capture most of what's said," Olson says. "But often there are concepts and ideas you might need to see on paper."

There was no need for obtaining IRB member buy-in on the guidelines since the IRB chairs were involved in creating the guidelines, Quezada says.

"If you get buy-in from the chairs first then the committee members are easy to convince," she says. "The IRB members seem to like these a lot."

While physician and scientist IRB members are experts at research and medicine, they might not be regulatory experts, Quezada says.

"So we give them all of the regulatory information they need," she adds. "The more experienced IRB members can get through our two-page [IRB presenter] template in 10 minutes, but new members might take 20 to 30 minutes to get through the template." ■

Tips for improving writing of IRB meeting minutes

Use "action" verbs actively

IRB staff can greatly improve how the IRB meeting minutes are written by following a few helpful hints, experts say.

For one thing, IRB meeting coordinators need to be able to follow the sometimes disjointed way IRB presenters discuss a protocol. So while a template is useful, it needs to be made very flexible.

"Sometimes a presenter, depending on experience level, may jump from one point to another," says **Marion Olson**, CIP, supervisor of human subject research regulations in the Office of Protocol Research.

For example, a presenter might briefly mention that the sponsor is holding the investigational new drug application and then move to the topic of biochemical blood draws, which might take up the bulk of the meeting discussion, Olson explains.

"So the IRB meeting coordinator takes notes about the issue that the IRB thinks is important," she adds.

Also, Olson meets with meeting coordinators before each IRB meeting to review the protocol and discuss the points that are likely to be most important to the board.

"We want to make sure all the important points are captured," Olson says.

"We put special considerations for each individual protocol in the coordinator's template for that meeting," says **Martha Matza**, MS, CIP, CIM, director of operations of protocol research in the Office of Protocol Research.

The minutes are put in a format that includes the title of the protocol, name of principal investigator, name of protocol presenter, presenter synopsis, committee discussion, final IRB committee motion, and final protocol contingencies/issues.[1]

Another key to improving meeting minutes involves mentoring IRB staff.

"Marion is a great mentor to her staff," says **Wanda Quezada**, CIP, manager of human subject research regulations in the Office of Protocol Research.

"We can develop templates and give them to the staff, but it's really important that the management staff develop a mentoring relationship with their meeting coordinators," Quezada says. "A lot of the coordinators do not have meeting experience when they're hired, so Marion tries to meet with her staff on a weekly basis."

Olson also meets with IRB staff before each IRB meeting to give them a chance to ask her questions or to explain why certain items have to be well documented.

"So they're educated about the protocol," Quezada says. "In the last four years, we've had

the best minutes we've ever had in the IRB office because of the continuous education Marion provides."

Tips for the troops

Quezada, Olson, and Matza also offer these tips on improving IRB meeting minutes:

• **Use action verbs:** "Use action words like 'clarify' and 'justify' in the minutes," Matza says.

Other examples are 'provide,' 'document,' and 'revise.' An example, according to an abstract on the topic is the sentence: "Clarify and provide an assurance of how the data will be collected, reviewed, analyzed, and monitored…"

• **Avoid pronouns and be more formal in capturing the discussion:** Olson teaches meeting coordinators to avoid using "he" and "she." Instead, they need to refer to the speaker by title, such as "IRB chair" or "community member" or "committee member."

"I don't have them use pronouns because it's too confusing," Olson says. "You don't know who the speaker was or who the commentator was."

Also, meeting coordinators use complete sentences and avoid making word-for-word documentation of the discussion.

• **Make the minutes readable:** IRB meeting coordinators should read the minutes out loud to ensure they've accurately captured the discussion. And they need to write the minutes with language that would be clear to people outside of the IRB office, especially focusing on making the IRB's intent clear.[1]

"If we can keep the minutes in layman terms and not put in too much scientific jargon, then it seems to work well, and investigators can respond in a timely manner," Olson says.

• **Use reference materials:** The meeting minutes should include reference materials, including the protocol abstract, informed consent documentation, regulatory guidance, etc.

It's important for IRB directors to train staff on taking meeting minutes because this is not something they will know how to do without specific experience, Olson notes.

"When you bring in individuals who don't have a lot of IRB experience, they don't realize that taking minutes for an IRB meeting is not like taking minutes for a corporate board meeting," Olson says.

"Since doing it this way the minutes have been much more comprehensible," Olson says.

"Say someone wanted to review the minutes because of a critical issue that had been discussed at the meeting," she adds. "They could take the minutes and understand what the IRB was trying to convey to the principal investigator, even if they had not attended the meeting."

Reference

1. Olson M, Quezada WA, Matza MJ. Guidelines for composing institutional review board (IRB) meeting minutes. Poster presented at 2008 PRIM&R Advancing Ethical Research Conference, held Nov. 17-19, 2008, in Orlando, FL. ■

Sample questions from IRB presenter guidelines

Presenters touch on eight main points

The office of protocol research at the University of Texas M.D. Anderson Cancer Center in Houston, TX, has created comprehensive guidelines that IRB members can use as they present their findings and opinions of protocols.

Here is a sample selection from the section on informed consent:

Informed consent document

A. Is the consent document edited to the appropriate grade level?

B. Are all procedures included in the consent document? If not, please clarify which items are missing.

C. Are risks, side effects, and benefits adequately explained to the participant?

D. Are alternative treatments for this patient group described adequately in the consent document?

E. Has an assent section been included within the informed consent document (ICD) for pediatric participants (if needed)?

F. Does the ICD need to be translated into a language, other than English (based on the proposed patient population? Has a non-English ICD already been included with the study?

G. If this protocol has a waiver, is this an appropriate request?

H. Does the ICD include any information about tissue banking? If so, where will the bank be housed and who will have access to the bank? ■

Finding ethical balance on protocol violations

A real world problem

There isn't a black and white answer when an IRB discovers that a human subjects research site has collected some data that is tainted by a protocol violation.

"This is a question of degree," says **Bruce Levin**, PhD, professor and chair in the department of biostatistics at Columbia University's Mailman School of Public Health in New York, NY. Levin spoke about data collected out of compliance at the Columbia University Institutional Review Board Educational Conference, held March 17, 2009, in New York.

It's unrealistic for IRBs to insist that clinical trial sites perform with no protocol violations, Levin notes.

"The real world of doing clinical studies has the ideal of following the protocol, but it's not often possible," Levin says. "Some would say it's not ever possible to follow it exactly to the letter, so the question is 'What is the magnitude, the frequency of protocol violations?'"

Most phase III, randomized, large clinical trials have a mechanism for reporting protocol violations, and most of the time they're not serious and nothing happens as a result of it, he explains.

"Sometimes they're serious and have to be reported to the IRB and data safety monitoring board and regulatory agencies, as well," Levin says. "So it's not easy to give a black and white answer."

One of the ethical challenges is that how an IRB should handle this might depend in some part on how large the study is.

"If one is focusing on small scale studies, the issues become potentially more serious," Levin says.

For instance, if a small study with 20 enrolled participants has a protocol violation that could result in data from four or five subjects being excluded in the analysis, then this would mean throwing out 20 to 25 percent of the sample, Levin says.

"This would be a serious degree of missing data," he adds.

"Of course the dilemma is when you include data that is seriously out of compliance you run the risk of potentially not knowing what experiment you're conducting," Levin says. "The world will understand the experiment according to the protocol."

As a biostatistician, Levin has worked with investigators both during and after studies.

Sometimes it's the investigator's obligation to report two sets of findings: one that includes the data that was impacted by a protocol violation and another that does not include the data that was impacted by a protocol violation, Levin says.

If there is a large amount of noncompliance then that changes the study's results, and investigators will need to admit that this was a failed study and no conclusions can be drawn from it,

CNE/CME Objectives

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

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **apply** the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

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

COMING IN FUTURE MONTHS

- Follow tip on reducing meeting length
- Low-tech, low-cost solution to going paperless
- Check out these training strategies
- Breakthrough software limits access to PHI

CNE/CME *questions*

1. True or False: The fact that an IRB is registered with the U.S. Department of Health and Human Services means that OHRP has verified the IRB's qualifications and deemed it capable of handling clinical research.

2. The employment provisions of the Genetic Information Nondiscrimination Act of 2008 apply to employers of:
   A. Any size
   B. 15 or more employees
   C. Fewer than 15 employees
   D. 30 or more employees

3. Which of the following should be included in guidelines for IRB protocol reviewers?
   A. Study population and recruitment practices
   B. Scientific review process
   C. Informed consent document
   D. All of the above

4. Which of the following questions should not be included in the section on informed consent for guidelines for an IRB protocol presenter?
   A. Is the consent document edited to the appropriate grade level?
   B. Are all procedures included in the consent document?
   C. Is the research a double-blinded case-control study?
   D. Are alternative treatments for this patient group described adequately in the consent document?

Answers: 1. False; 2. B; 3. D; 4. C.

he notes.

IRBs can discuss with investigators all of these scenarios when major protocol violations are discovered.

"In most cases where fraud or intentional malfeasance is found on the part of the investigator, then IRBs take the position that the study may not be published," Levin says.

Most often, IRB members will have more than one opinion on what should be done. ■